High dose treatment for hematologic malignancies From Rituals to Evidence Based Practice

Arno Mank

View-Master is de merknaam van een systeem voor stereofoto's. Het systeem werd in 1938 uitgevonden door de Amerikaanse Duitser William Gruber en in productie genomen door Sawyer's, een fabriekje in Grubers woonplaats Portland (Oregon). In 1966 werd Sawyer's overgenomen door General Anilin and Film Corporation (GAF). De stereofoto's van View-Master bevinden zich in ronde kartonnen schijven met elk zeven stereofoto's (veertien beeldjes). Deze schijven passen in een stereoscoop of diaprojector. In de oorlog werd het systeem voor opleidingen gebruikt door het Amerikaanse ministerie van defensie. Na de oorlog werd View-Master bij het algemene publiek populair. In het medisch onderwijs werd het View Master-systeem regelmatig gebruikt als toevoeging bij boeken die belangrijke structuren in 3D moesten uitleggen, zoals anatomie en de uitleg van chirurgische ingrepen.
In dit opzicht zou de viewmaster gezien kunnen worden als de voorloper van de CD-rom. Deze geeft ook inzicht in structuren en de verschillend aspecten van de intensieve zorg rondom de hematologische patiënt. Zoals de patiëntenvoorlichting, chemotherapie, infectiepreventie, voeding, mondzorg en opname en ontslagbeleid.

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High dose treatment for haematologic malignancies From Rituals to Evidence Based Practice

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Met respect en bewondering voor degene over wie dit proefschrift gaat.

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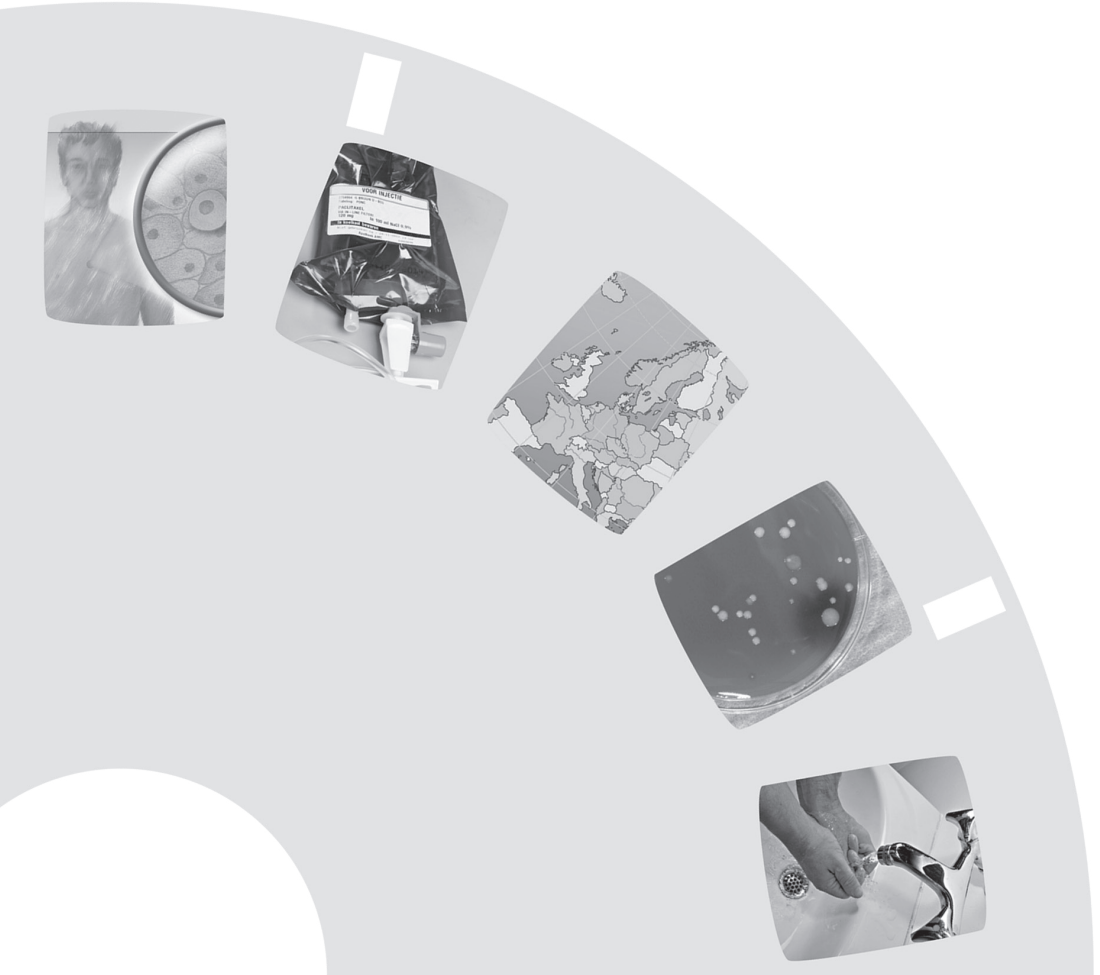
Chapter 1

Introduction and outline of the thesis



Introduction

Hematologic malignancies account for approximately 7% of all new malignant tumors in Europe, with 7500 new cases in 2010 in the Netherlands (1). The most common diagnoses are lymphoma, multiple myeloma and leukemia. The development of hematology as a discipline and its treatment options are closely linked to the history of the discovery and development of chemotherapy.
In 1942 Louis Goodman and Alfred Gilman used nitrogen mustard to treat a patient with non-Hodgkin's lymphoma and for the first time demonstrated that chemotherapy could induce tumour regression (2).
Nowadays in younger patients aggressive hematologic malignancies such as acute leukemia and multiple myeloma in first line, and lymphoma at relapse, are treated with high dose chemotherapy, often followed by autologous or even allogeneic stem cell transplantation (SCT). Whereas autologous SCT is merely intended to be used as salvage treatment to make high dose treatment possible, allogeneic SCT offers additional advantages such as the possibility of a graft versus tumor effect. The development of SCT, now considered to be standard treatment in certain phases of many hematologic malignancies has increased overall survival in acute leukemia and chronic myeloid leukemia (3). However SCT is also associated with considerable transplant related mortality and long term morbidity. The use of non-myeloablative conditioning has made this treatment approach also feasible in patients up to the age of 65-70.
In the past decade several novel treatment options for hematological malignancies have been developed such as monoclonal antibodies and tyrosine kinase inhibitors, which are targeted drugs and considerably less toxic as to induction of mucositis and myelosuppression. Thus, their use is another approach to decrease treatment-related mortality and morbidity. However, as of 2012 chemotherapy still is a key element of treatment in hemato-oncology.
Some of the most serious consequences of high dose chemotherapy are drug-induced neutropenia and mucositis, which are significant risk factors for life- threatening infections (4). During the hospitalization period, the main aim is to provide optimal supportive care for the patient in order to minimize these risks and thus to improve quality of life and survival (5).
Since the 1970's, the overall mortality rate from bacterial infections has decreased from 21% to 7% (6). This was a result of several developments, such as the use of colony-stimulating factors to decrease the duration of

neutropenia (7,8), the widespread use of fluoroquinolones as selective oral antimicrobial prophylaxis to reduce bacterial colonization (9,10), the use of antifungal prophylaxis to reduce the risk of invasive fungal infections (11, 12) and empiric treatment with broad spectrum antibiotics in patients with neutropenic fever. Also, it was believed that protective isolation, the ingestion of low bacterial diet and keeping patients hospitalized during the complete neutropenic period would decrease the risk of bacterial infection. Some of these procedures and traditions, such as protective isolation, oral care and food restriction however seem to be based on routines, 'rituals', adopted by the health care professionals, and lack empirical foundation (13). Even between hospitals in the Netherlands there are huge differences in practice between hospitals. As part of the multidisciplinary hematology team, hematologists and nurses are ideally positioned to play a key role in the identification, management, and (ideally) prevention of hematologic adverse events caused by high dose chemotherapy.
As the founder of modern nursing, Florence Nightingale (1820-1910) already mentioned in her famous *Notes on Nursing* regarding observation of the sick: *"What you want are facts not opinions"* (14).
Evidence- based practice is the conscientious, explicit, and judicious use of current best practice in making decisions about the care of individual patients (15). Thus it is essential for this vulnerable group of patients to develop evidence based guidelines, with the potential to improve care for patients by promoting interventions of proven benefit, and by discouraging ineffective interventions.

Aim and outline of the thesis

The main objective of the research presented in this thesis was to gather evidence for the development of measures to improve the quality of care in the vulnerable patient group of patients receiving high dose treatment for hematologic malignancies. For this purpose both clinical studies, carried out at the nursing ward of the department of hematology at the AMC, and systematic reviews of the literature were performed, all examining the effectiveness and level of evidence of a number of procedures performed by nurses and doctors in their daily practice of caring for patients treated with high dose chemotherapy.

Hyperhydration is an important measure to prevent renal toxicity during nephrotoxic chemotherapy. To prevent fluid overload, it is important to check

fluid balance during hyperhydration. Measuring fluid intake/output is often unreliable, complex, and labor-intensive and leads to occupational hazards for nurses and other health-care workers handling cytotoxic fluids or body excretions. In a prospective clinical guideline study, described in **chapter 2,** we determined the concordance between bodyweight and fluid intake/output, and examined the clinical consequences with respect to the safety of selecting only the bodyweight measurement as a parameter for fluid overload. The results of this study were subsequently used in a retrospective study looking at barriers and facilitators influencing implementation and long-term adherence to new guidelines (**chapter 3)**. Adherence to the guidelines was checked against the data from patient files, and derived from focus group interviews of nurses, oncologists and hematologists.

In **chapter 4** an inventory was performed of international guidelines on the management of neutropenic patients, focusing on the role of protective isolation, in addition to an analysis of potential sources of infection. Furthermore, a follow-up study was performed on the incidence of febrile neutropenia, infections, use of systemic antibiotics and antifungals, comparing two 3-year periods with and without protective isolation.

Regular oral care before and during chemotherapy has been shown to be the most effective intervention to prevent oral mucositis. The availability of practical guidelines and training of nurses is essential, providing that nurses have sufficient knowledge and skills to perform oral care correctly. An intervention study (**chapter 5**) was performed consisting of a baseline test on the knowledge and skills of nurses of hematology wards of two different hospitals. Oral care education sessions were given in one hospital only, and follow-up tests were performed in both hospitals. Knowledge and skills before and after education were compared.

It has been argued that the use of a low bacterial diet (LBD) (i.e. food and drinks with low levels of bacteria), which has been common practice for many years, can prevent the occurrence of food related infections in patients receiving high dose chemotherapy. Nearly all hematology clinics in the United States recommended dietary restrictions to their patients (16). In **chapter 6** a detailed survey is described examining the use of LBD in Europe focusing on criteria such as when to start and when to stop the dietary restrictions, and conditions regarding the use of specific dietary products. Subsequently, a systematic Cochrane review was performed of randomized controlled trials comparing a LBD with a normal hospital diet for adults as well as children, which is described in **chapter 7.**

It can be challenging to give patients the right amount of information about their diagnosis, treatment options and possible side effects. Under these

circumstances, patients may find it difficult to completely understand and retain the information given. As a supplement to standard oral and written information, we developed an interactive CD-Rom with information on high dose chemotherapy and SCT. In addition, patient interviews on the several phases of this treatment are available on the CD-Rom. A major advantage of this tool is that it can be utilized according to the patient's individual preferences. In a descriptive study **(chapter 8)** the acceptability of the interactive CD-Rom by patients was evaluated.
Expanded treatment options, the focus on improved outcomes and economic reforms have created a drive to shift treatments from hospital to an outpatient setting. Chapter 9 and 10 are divided to studies on identification and evaluation ambulatory treatment. In **chapter 9** we described a prospective analysis to identify which patient groups would be eligible for ambulatory care, and which clinical variables are important for safe early discharge. The results have been used to develop an ambulatory care program. In **chapter 10** a six year prospective, non randomized clinical study is described in which patients were discharged into ambulatory care the day after either the last chemotherapy administration or the day after reinfusion of stem cells. They were seen at the ambulatory care unit 3 times a week. In addition to the medical and nursing parameters on safety, the financial aspects and patient's preference were measured as well.
Finally, in **chapter 11,** summary and a general discussion on the results of the studies in this thesis is presented.

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Chapter 2

ORIGINAL ARTICLE

Monitoring hyperhydration during high doses chemotherapy: Bodyweight or fluid balance?

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Piet Bakker and Rien de Vos

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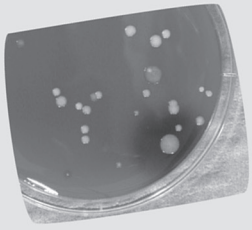

Abstract

Introduction: Usually bodyweight as well as fluid intake/output as parameters for checking the fluid balance are monitored in case of intravenous hyperhydration during treatment with nephrotoxic chemotherapy. The reliability of measuring fluid intake/output is uncertain and redundant. Moreover it is complex, labour-intensive and gives an occupational hazard for nurses and other health-care workers handling fluids or body excreta.

Method: In a prospective cohort study we determined the concordance between bodyweight and fluid intake/output. We also examined the clinical consequences with respect to safety of selecting only bodyweight measurement as parameter for fluid overload.

Results: A total of 591 combined observations of fluid balances and bodyweights were collected. We observed a higher increase in bodyweight than in fluid balance. The Pearson correlation between fluid balance and bodyweight was relatively low ($r = 0.28$). With regard to safety of measuring bodyweight only we found 4 cases (0.6%) which potentially would not have received furosemide if the fluid intake/output would no longer have been registered without clinical consequences.

Conclusion: After standardisation bodyweight can safely be used as the only parameter for monitoring fluid retention in case of hyperhydration during chemotherapy.

Introduction

Registration of both bodyweight and fluid intake/output in order to prevent congestive heart failure during intravenous hyperhydration in a course of treatment with high doses chemotherapy seems to be a 'ritual' act. There is no scientific basis for it and no effectiveness rationale.
Hyperhydration with large amounts of fluid like saline is mainly used in nephrotoxic cytostatic treatments e.g. cisplatin and methotrexate will cause immediate damage to the proximal and distal tubular cells of the kidneys [1, 2]. Cyclophosphamide and ifosfamide may cause damage haemorrhagic cystitis to the bladder [3]. This nephrotoxicity and bladder-damage can be prevented by forced diuresis with 4-5 liters of saline administered intravenously every 24 hours and a minimal diuresis 100 milliliters per hour is adhered [4-7]. It is therefore clear that careful monitoring of the fluid balance is necessary because of the risk of fluid overload with consequence congestive heart failure.
In oncology it is customary to register fluid intake/output as well as bodyweight simultaneously in order to monitor the fluid balance. These controls preferably take place several times within each 24-hour period in order to be able to timely observe unwanted changes in fluid balance and to be able to intervene, if necessary. Fluid intake/output and bodyweight are registered cumulatively during the entire period of hyperhydration. Above a certain cut-off value a diuretic as furosemide is administered.
There are a several objections to this labour-intensive registration. First, it is very likely that these cut-off values are based on experience and opinion since there is no evidence in the literature to support them. Secondly, it is not clear how (possibly) divergent fluid balance and bodyweight values should be interpreted. Thirdly the validity of the measurements is also under discussion: there are different views with regard to the registration of fluid intake/output [8]. It is for instance not clear whether and how the intake of soup, fruit, ice cubes, or the occurrence of diarrhea and vomiting should be registered. Finally there are doubts about the reliability: measurements of fluid intake/output are not always performed accurately. Volumes, for instance, frequently need to be estimated and cannot be measured. Since both fluid intake/output and bodyweight are registered cumulatively, the size of the error can increase by time.
Another argument for critically looking at fluid output is that handling cytotoxic urine of cancer patients is an occupational hazard for nurses. Studies showed an association between handling cytotoxic drugs and fetal

loss and/or systemic drug absorption by the health care provider [9, 10]. Therefore, every possibility to avoid handlings with fluids and body excreta should be utilised.
Bodyweight measurement also has inherent difficulties, but to a lesser degree. The variation in execution, such as time of measurement, type of scales used, clothing worn by the patient and whether or not the patient has urinated prior to the measurement are aspects that needs to be considered using logistical changes and protocols [11]. A quality assurance project analyzed the routine practice of chemotherapy administration and the role performance of nurses. One of the conclusions was the need of standardization of procedure of measuring bodyweight [12].
The sparse literature on this subject does not indicate whether it is really necessary to register both fluid balance parameters, and which parameter would be best in terms of measurement error sensitivity and execution simplicity. In 1979, Plaum et al. investigated the concordance between fluid balance and bodyweight but failed to find a correlation [13]. The Dutch Institute for Healthcare Improvement has based its guideline "Sense and nonsense of the fluid balance", for lack of literature, on consensus and only recommends the use of fluid intake/output measurements if it is supported by strong arguments [14].
In light of the uncertainty regarding the policy to be pursued, we determined the concordance between bodyweight and fluid balance as parameters of fluid overload to indicate that bodyweight and fluid balance are supplementary. Next, we determined the clinical consequences with respect to safety of selecting the simplest and most reliable parameter, bodyweight measurement.

Patients and Methods

Between March and June 2000, all patients that were treated with cytostatics and in whom hyperhydration was used were included in a prospective cohort study. Patients undergoing high doses of chemotherapy were screened on co-morbidity on the out-patient clinic before starting this intensive treatment. Patients were recruited at the Academic Medical Centre (AMC) Amsterdam on the departments of pulmonary disease, gynaecology, and hematology/oncology. Consent from the medical ethics committee was not necessary and informed consent was not required since no changes in the current policy were implemented.

Present situation

The AMC employs international and national treatment protocols. The duration of administration in these protocols varies from one to five days and each treatment course is followed by the next with a resting period of at least one week. Fluid intake/output and bodyweights are registered during the administration of the hyperhydration fluid (4 to 5 litres in each 24-hour period) and measured simultaneously three times per 24 hours. In case of a cumulative fluid balance > 2 liters and/or a cumulative bodyweight increase > 2 kg from the start of treatment 5 mg. of furosemide is administered.

Standardization

In order to have these measurements performed for the study as precisely and reliably as possible, standardization of "bodyweight measurement" and "fluid balance measurement" took place prior to data collection. Special attention was paid to standardization of the weight scales (type and use) and standardization of the circumstances under which the bodyweight measurements were performed, e.g. moment in time and frequency, clothing and shoes worn and prior urination. The results of a recently completed investigation into bodyweight measurement policy have led to a relatively new protocol within the AMC on how to weigh all patients in a standardized way. This protocol was used for the standardization [15]. Standardization of the fluid balance measurement, e.g. agreement on parameters that should or should not be considered relevant, was done with the co-operation of dieticians and other nutritionists.

Data collection

During the study period registration of all fluid intake/output and bodyweight measurements took place in patients who were admitted for a course of treatment with cytostatics involving hyperhydration. Both medical and nursing patient files were used and data collection was performed per patient and per course of treatment.
At the start of each course of treatment, sex, age, specialism, co-morbidity and data on the treatment (type of cytostatics, treatment) were registered. Every eight hours both bodyweight and fluid intake/output were registered and the cumulative fluid balance and cumulative increase or decrease in bodyweight was measured. If necessary, intervening administration of furosemide was also recorded. Possible calculation errors were checked afterwards. In addition, increased body temperature (>37.5° C) or fever (>38.0° C), vomiting, and diarrhea were registered.

Analysis

The agreement, or concordance, between fluid balance and bodyweight was determined using the Pearson correlation coefficient for the entire cohort [16]. This designates the magnitude of the relationship between these variables. In addition, the Pearson correlation coefficient of the individual first, second, third and fourth fluid balance and its corresponding bodyweight was determined in order to be able to trace specific trends in a possible discordance.

To analyze whether the discordance between fluid balance and bodyweight increases with the increase in bodyweight a Bland-Altman analysis was performed [17]. In this analysis the mean scores of difference in bodyweight minus the mean scores of difference in fluid intake/output are plotted against the mean scores of difference in weight alone. In the Bland-Altman analysis the difference in bodyweight has been used as a reference value, since this is considered to be the most reliable parameter if data are clustered near the zero line, no differences in concordance occur in case of an increase in weight.

The clinical consequence, in terms of safety, of using only one parameter (bodyweight) for registration of the fluid balance instead of both bodyweight and fluid intake/output was analyzed in a 2 x 2 table, depicting (dis)agreement between bodyweight and fluid balance. This way it can be determined how often interventions with diuretics had to be applied. In case they had to be applied, whether this was based on fluid intake/output or bodyweight or both. It gives insight in how many cases with a fluid imbalance one would potentially have missed if only bodyweight had been registered. Finally frequencies of occurring have been calculated for the following factors: vomiting, diarrhea, fever, calculation errors and performed interventions. All data were analyzed with the statistical package S.P.S.S., version 9.0.

Results

Of 43 patients, 279 person days were observed. The mean age of these patients (58.1% men) was 45 years (range 18-73). In 91% (39/43) no co-morbidity was found. The patients underwent a total of 84 first and follow-up courses of treatment, in which a total of 591 combined observations of both fluid balance and bodyweight (cases) were collected. The number of combined cases with more than 11 consecutive fluid balances

(courses > 4 days) was 70% (416/591). Short courses of treatment (1 or 2 days) with fewer than 7 consecutive observations were performed in 24% (143/591). Treatment with cisplatin was most frequently administered, namely in 78% (460/591) (Table 1).

No cases of clinically manifest congestive heart failure were observed. In one case Furosemide was administered based on physical findings, the occurrence of oedematous ankles, but it is unclear whether this incidence actually involved congestive heart failure.

In general, there was a higher increase in bodyweight than in fluid balance; with a mean difference of 728 mg. The Pearson correlation between fluid balance and bodyweight of *all* 591 fluid balances and weight measurements

Table 1. Baseline characteristics

	Numbers	**Percentages (range)**
Patients	43	
Male	25	58.1%
Female	18	41.9%
Mean age	45	(18-73)
Number of fluid balance / weight registrations	591	
Number of courses (range per patient)	84	(1-6)
Mean number of fluid balance / weight registrations per course or treatment	7	(2-18)
Specialism		
Oncology	16	
Haematology	11	
Pulmonary oncology	6	
Gynaecology	10	
Co-Morbidity		
None	39	
Congestive heart failure	2	
Hypothyroidism	1	
Tumour lysis	1	
Duration of course of treatment		
Short 1-2 days Fluid balance < 7	143	24.2%
Middle 3-4 days Fluid balance 7-10	32	5.4%
Long >4 days Fluid balance > 11	416	70.4%
Type of course of treatment		
Fluid balance/Weight course of treatment with cisplatin	460	77,8%
Fluid balance/Weight course of treatment with cyclo-/ ifosfamide	131	22,2%

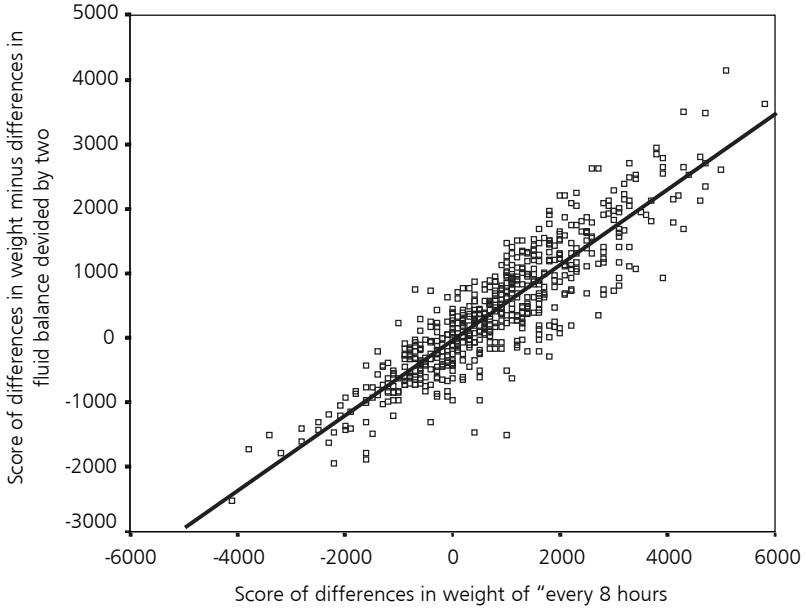

Figure 1. Bland-Altman plot showing that when the discordance between fluid balance and body weight increases, the difference in weight measurements increases as well.

was r = 0.28. At the start, the Pearson correlation between all *first* fluid balances and bodyweight measurements was r = 0.57 (84/591). At the *second* measurement, r was 0.57(83/591), at the *third* r was 0.40 (58/591) and at the *fourth* r was 0.46 (42/591).
The Bland-Altman plot (Figure 1) shows that the discordance between fluid balance and bodyweight also increases as the difference in weight measurements increases. This means that if a patient had gained only a little weight, his fluid balance was more or less in agreement with his weight, whereas if his bodyweight had strongly increased, the discrepancy between fluid balance and bodyweight had become much larger.

Next, we investigated the clinical consequence of the concordance between fluid balance and bodyweight. Of all included cases, 81% (479/591) showed a balance < 2 liters and < 2 kilo, which means that no furosemide was

Table 2. Number of cases above and below the cut-off level of 2 litre and/or 2 kilo

		Δ Weight > 2 kilo		
Δ Fluid balance > 2 litre		Yes	No	Total
	Yes	9 (1.5%)	4 (0.6%)	13 (2.2%)
	No	99 (17%)	479 (81%)	578 (98%)
	Total	108 (18%)	483 (82%)	591

necessary. In 1.5% (9/591) both fluid balance and bodyweight had increased (> 2 liters and > 2 kg, respectively); the administration of furosemide was indicated based on both parameters. In 17% (99/591) the weight increased > 2 kg, but the fluid balance remained < 2 liters, and an intervention with furosemide was indicated based on weight increase alone. The percentage of cases with a fluid balance increase > 2 liters and a bodyweight increase < 2 kg was 0.6% (4/591). In these 4 different cases (P.I.N.), furosemide would not have been administered if the fluid balance had not been measured (table 2). Upon further analysis of these 4 cases, involving different patients, the registered bodyweight of one patient appeared to be dramatically different from the previous and subsequent measurement and must have been a registration error. The other 3 cases involved differences between fluid balance and bodyweight of 230, 350 and 430 ml/gr, in which the fluid balance remained just > 2 liters and bodyweight barely < 2 kg. All 4 cases where different (P.I.N.) and concerned the first or second fluid balance/ bodyweight registration. The mean age of these patients differed not from the complete group (40 years against 45 years) (Table 3).
Of the interacting factors, fever, vomiting and calculation errors, all occurred relatively infrequently and therefore required no further analysis (Table 4).

Table 3. Four cases: D Weight < 2 kilo, D Fluid-balance > 2 litres

No	**Case**	**P.I.N.**	**Age**	**D Weight**	**D Fluid-balance**	**Difference**
1	190	11	51	-700	2200	2900
2	207	12	21	1800	2150	350
3	305	18	35	2000	2430	430
4	311	19	53	1800	2030	230

Table 4. Occurrence of possible interacting variables

	Numbers	**Percentage**	**(range)**
Increased body temperature			
Registrations > 37.5(patients)	8	1.4%	7-43
Registrations > 38.0(patients)	5	0.8%	4-43
Vomiting			
Moderate (< 200 cc)(patients)	24	4.1%	13-43
Severe (> 200 cc)(patients)	27	4.6%	7-43
Calculation errors	30	5.1%	

Discussion

Considering the fact that there is no gold standard for fluid overload, bodyweight and fluid balance seems logical and practical parameters for monitoring possible fluid overload in hyperhydration. In this study we investigated the concordance between bodyweight and fluid balance as parameters of (possible) fluid overload in treatment courses with cytostatics. We also determined the clinical consequences if only the easiest applicable parameter was selected. As a result the administration of fluid we found that bodyweight appears to change more rapidly than the fluid balance. The correlation between bodyweight and fluid balance is rather weak: the maximum correlation is 0.57 at the first measurement and decreases to 0.28 when all measurements are calculated together. The Bland-Altman analysis confirms that the concordance particularly decreases as the bodyweight increases. A possible cause of this discordance is the cumulative incidence of error that has been taken into account in the calculations. Through standardization and training the bodyweight and fluid measurements were assured to be as reliable as possible. It is not expected that more training would have provided even more precise measurements.

With regard to safety of measuring bodyweight only we found that 4 cases in this study (0.6%) would potentially not have received furosemide if the fluid intake/output had not been registered. Except one case, which was a registration error, these 3 cases the differences between fluid balance and bodyweight were so small that they are considered as “borderline”. It should be realized that the cut-off points are arbitrarily and that by slightly increasing the cut-off value to 2.5 kilo/liter these cases would not have been registered at all. The interesting question is whether the current cut-off value for the intervention, i.e. administration of furosemide, is too low and could be raised. Hence, there is no evidence on the basis of which the cut-off point of 2 kg. and 2 liter has been set.

Patients in our study were relatively young and had little co-morbidity. So it is not surprising finding that no case of clinically manifest congestive heart failure was observed. The sample showed a mix of short and long courses of treatment, executed in accordance with the current protocols and with the usual cytostatics, in particular the nephrotoxic cisplatin. However the patients were not selected and therefore can be seen as representative for the oncology patient population in our academic hospital. Of course our results may not be directly extrapolated to other situations involving patients with congestive heart failure, for instance in cardiac, nephrologic patients

and especially older patients. But also in these cases, one could question the effectiveness of using similar parameters to monitor fluid overload. There is one exception for using bodyweight to control fluid intake/output. That is when patients are immobile to be weighted. What still is very important is and should remain is the clinical evaluation and physical findings for signs of fluid overload from the nurses and physicians.

The underlying rationale to opt for bodyweight only as parameter for checking the fluid balance is that measuring fluid intake/output is complex and labor-intensive and it is unsure whether it is a reliable measuring instrument. Inaccurate registration and calculation errors, such as double notation or omission of fluid intake or urine production, may cause a lot of variation in the measurement of the fluid balance. Due to the large number of calculations, calculation errors may easily occur. It seems plausible to assume that fewer errors can occur in bodyweight measurement and that weight is a more reliable indicator to detect potential fluid overload and congestive heart failure than the fluid balance. With respect to time and costs no data were found in the literature on the amount of time used for registering and processing fluid intake/output. However it is clear that omission of the fluid balance registration in chemotherapy protocols will save a lot of time for those doing the registration. A positive side-effect is that the risk of managing cytostatic urine for the nurses will be much lower. It has to be said that this is only the case when one has standardized the weighing procedure properly. We found the results based on 591 observations a sufficient basis for a policy change, and so we implemented this in a new guideline and protocol.

Conclusion

This study has provided a good argument for only measuring bodyweight as a parameter for possible flush overload upon the administration of hyperhydration in a course of treatment with cytostatics. No longer registering the fluid intake/output during courses of treatment with cytostatics hardly has clinical consequences and does not affect the safety of patients. Congestive heart failure rarely occurs and clinical parameters other than bodyweight, such as oedematous ankles and shortness of breath, may also lead to adequate interventions. The weighing method, with the right standardization of procedures, can and should be performed since at appears to be reliable, save, simple and timesaving.

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Chapter 3

Factors influencing long-term adherence to two previously implemented hospital guidelines

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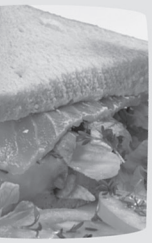

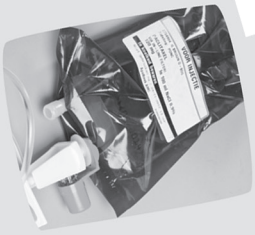

Abstract

Introduction: After successful implementation, adherence to hospital guidelines should be sustained. Long-term adherence to two hospital guidelines was audited. The overall aim was to explore factors accounting for their long-term adherence or non-adherence.

Methods: A fluid balance guideline (FBG) and body temperature guideline (BTG) were developed and implemented in our hospital in 2000. Long-term adherence was determined retrospectively based on data from patient files. Focus groups were launched to explore nurses' perceptions of barriers and facilitators regarding long-term adherence. The predominant themes from the nurses' focus groups were posed to clinicians in questionnaires.

Results: Nurses involved in the FBG (overall adherence 100%) stated that adherence has immediate advantages in terms of safety and a gain in time. Nurses and oncologists acted unanimously which was thought to enhance adherence. On the other hand, opinions differed on the BTG within the nursing teams and medical staff (overall adherence 50%). Although the guideline discourages routine postoperative body temperature measurements, temperature should be measured according to the guideline in a considerable number of cases due to changes in patient characteristics since the year 2000. Therefore, adherence was judged to be rather complex.

Conclusions: To secure adherence to hospital guidelines after their successful implementation, guidelines should preferably be comprehensive in terms of being applicable to the majority of the patients in that particular setting and to the most common clinical situations. All health care professionals involved should be aware of its immediate benefits for themselves or to their patients.

Introduction

Clinical guidelines seek to enhance uniform and appropriate patient care through the translation of scientific evidence on effectiveness or efficiency into clinical recommendations [1]. In hospital practice, guidelines can help to establish evidence-based patient care throughout multiple disciplines. However, the mere existence of a hospital guideline does not guarantee its actual application and sustained use in daily clinical practice [2].

The probability of using a new hospital guideline was found to be higher when the topic was clinically relevant and when the guideline was evidence-based and methodologically sound [3,4]. Adherence was also found to be more likely when guidelines were user-friendly and contained precise definitions of recommended performance [3,5,6]. Subsequently, hospital specific characteristics like capacity, mission, professionalism and patient population influence guideline adherence as well [7,8].

Besides improving guideline characteristics and optimizing the hospital setting characteristics, as far as this is possible, implementation strategies aim to secure guideline adherence. Until now, no dissemination and implementation strategy has been identified that is effective in all circumstances [2,9-11].The effects of audit and feedback of guideline adherence are small to moderate and such strategies are probably most effective when initial adherence is low [12,13]. Educational outreach visits have small to modest improvements on professional practice [14]. Local opinion leaders are capable of improving evidence-based practice, but the feasibility of its widespread use remains uncertain[15]. Multifaceted implementation interventions have been most effective and are therefore recommended nowadays [6,17], although the relative efficacy of each component within the multifaceted approach remains unclear.

After completion of the active implementation phase, hospital guidelines should ideally maintain their successful adherence rate in order to sustain the deliverance of uniform and best care. Likewise, changes in professional performance should not wear out in time, despite turnover in personnel and alterations in the hospital setting. Little is known about how to ensure *long-term* adherence to guidelines in a hospital setting. Some studies found that adherence could be maintained over several years [18,19], but external or internal factors influencing these results were not measured.

In this study the long-term adherence to two hospital guidelines, which were developed and implemented within our hospital in the year 2000, was

audited. The second and overall aim was to explore factors accounting for their long-term adherence or non-adherence.

Methods

Setting

This study was performed in a 1,000 beds university teaching hospital in the Netherlands. All nursing and medical head managers of the seven wards (176 beds) that had implemented one of the guidelines in 2000, gave permission to perform the current study at their wards.

Guidelines

The included guidelines were developed within our hospital (Table 1). Since evidence on both subjects was lacking, clinical trials were performed which served as basis for the guidelines [20,21]. Both clinicians and nurses were involved in the original studies as well as in the guideline development processes.

The first guideline addressed oncology patients receiving intravenous hyperhydration. The nurses' routine of calculating fluid balances thrice daily, and the oncologists' routine of assessing these fluid balances to detect fluid overload was abandoned in the guideline ("fluid balance" guideline: FBG).

Table 1. Hospital guidelines successfully implemented in 2000

	Fluid balance guideline	**Body temperature guideline**
patients	oncology patients receiving intravenous hyperhydration to reduce adverse effects of nephrotoxic chemotherapy	postoperative patients
evidence	In a prospective cohort study was found that fluid balances are unreliable to detect fluid overload[20]	In a diagnostic accuracy study was found that routine body temperature measurements have low sensitivity and low positive predictive value in detecting postoperative infections[21]
practical recommendation	The nurses' routine of calculating fluid balances thrice daily, and the oncologists' routine of assessing these fluid balances, is abandoned. It is now safe for oncologists to trust on regularly assessed patient body weight to detect fluid overload	The routine of nurses measuring body temperature twice a day, and the surgeons' routine of assessing these measures, is abolished. Surgeons should order diagnostic tests when clinical signs and symptoms of a postoperative infection arise

The second guideline concerned postoperative patients. The routine of nurses measuring body temperature twice a day, and the surgeons' routine of assessing these measures, to detect postoperative infections early was abolished ("body temperature" guideline: BTG).
Both guidelines were actively disseminated in 2000, using a validated model for implementing changes [22]. Persuasion was needed during the active implementation phase of the BTG, as opposed to the FBG which was incorporated immediately. But after the active implementation phase of the BTG, a satisfying initial adherence rate of 91% was measured [23].

Assessment of long-term adherence rates

Fluid balance guideline (FBG)

To assess long-term adherence, all oncology patients receiving on or more courses of hyperhydration treatment between January and May 2007 were included. Fluid balances and medical orders for fluid balances were searched for in all patient charts on the wards involved: Oncology/Hematology, Gynecology, and Pulmonary Diseases. Whenever a medical order or an actual fluid balance was identified, relevant documents were searched for valid reasons to monitor fluid balance, i.e. the impossibility to weigh a patient or the necessity to register fluid intake and output for other reasons than monitoring fluid overload.
Long-term adherence was defined as the number of appropriately monitored and omitted fluid balances relative to the total number of fluid balances that would have been monitored, i.e. thrice daily during each course of hyperhydration, according to the pre-guideline routine.

Body temperature guideline (BTG)

Long-term adherence was retrospectively determined on four surgical wards. Medical and nursing records were studied of every fifth admitted patient who had undergone elective surgery between January and March 2007, until discharge or 14 days postoperatively. It was checked how many times body temperature was actually measured or omitted, and if a valid reason to measure body temperature was present: (1) during blood transfusion; (2) when a patient was operated for an infection; (3) when a patient developed a postoperative infection.
Long-term adherence was defined as the number of appropriately measured and omitted body temperatures relative to the total number of temperature measurements that would have been obtained in these patients according to the pre-guideline routine, i.e. two routine measurements per day.

An independent investigator checked this process by repeating a random sample of ten patients per guideline. No discrepancies were found. In case of uncertainty, an independent clinician was consulted to reach consensus.

Exploration of factors influencing nurses' long-term adherence

While long-term adherence was audited, focus groups were launched to explore nurses' perceptions of barriers and facilitators regarding long-term adherence to their guideline (either FBG or BTG [24,25]. It was aimed to perform two focus groups for each ward at the transition between day shift and evening shift. All nurses present were invited to participate by their staff nurse. Firstly, the moderator outlined the aim of the focus group. It was emphasized that participants did not have to agree with each other, their answers could neither be wrong nor right, and all data would be processed anonymously. An introductory question was asked about the participants' awareness of the guideline.

The key question was addressed by means of two exercises. Nurses were first asked to individually write down as many reasons they could think of to adhere to or ignore the guideline on separate notepapers, in order to attain individual and unbiased perceptions. Second, nurses plenary discussed all individual notes and grouped similar notes together. In this process, the moderator summarized and concretized the barriers and facilitators mentioned, in order to maintain a focused discussion. Attendees were also encouraged to bring up new issues, since group dynamics can multiply and broaden perceptions [26].

In the meantime, the observer made additional notes on the barriers and facilitators discussed [26]. Afterwards, the moderator and observer evaluated each focus group to complete the nurses' individual notes with perceptions mentioned or observed during group discussion.

Based on all notes, three investigators independently open-coded the data gathered in the focus groups into keywords. Subsequently, the applicability of each keyword was discussed collectively and they were combined or rephrased if necessary. Moreover, related keywords were grouped into thematic categories.

The thematic categories defined were then assigned to a theoretical framework, comprising five levels of barriers to and incentives for change[27]. The investigators independently assigned each thematic category to one of its levels: the innovation itself, individual professionals, social context,

organizational context or economic and political context. Disagreements in classification were reconciled by discussion.

Exploration of factors influencing clinicians' long-term adherence

In daily clinical practice, it turned out to be impossible to bring all clinicians together in focus groups. Therefore we proposed the frequently emerging themes from the nurses' focus groups in seven multiple choice questions during a regular meeting and by e-mail (Appendix 1 and 2).

Results

Long-term adherence rates

FBG

Hyperhydration during chemotherapy was given 178 times to 68 patients (Table 2). In all, long-term adherence was 100%. According to the pre-guideline routine, 534 fluid balances would have been calculated. In 526 cases no medical orders for fluid balances and no actual fluid balances were found in the patient charts (guideline compliant omission of fluid balance monitoring 100%). Eight fluid balances were calculated because of the inability to weigh a patient or for monitoring a high-output stoma (guideline compliant monitoring of fluid balance 100%).

Table 2. Long-term adherence to the fluid balance and body temperature guidelines

	Fluid balance guideline	**Body temperature guideline**
Pre-guideline routine	534 fluid balances monitored	1226 body temperature measurements
To omit according to guideline	526	547
To monitor according to guideline	8	679
Guideline compliant omission	100% (526/526)	39% (214/547)
Guideline compliant monitoring	100% (8/8)	59% (403/679)
Overall long-term adherence	100% (534/534)	50% (617/1226)

BTG

On the surgery wards a sample of 102 patients who had undergone elective surgery was randomly selected (Table 2). Overall long-term adherence was 50%. As to the pre-guideline routine, 1,226 postoperative body temperature measurements would have been taken. Nowadays, in 547 out of the 1,226

occasions body temperature should not have been measured according to the guideline, which was adhered to 214 times (guideline compliant omission of body temperature 39%). In the other 679 cases body temperature should have been measured according to the guideline, mostly because a preoperative or postoperative infection was present. This was adhered to 403 times (guideline compliant measurement of body temperature 59%).

Factors influencing nurses' long-term adherence

FBG

Five focus group meetings, lasting 40 minutes on average, were attended by 15 nurses (range 2 to 5 nurses per focus group, including 2 staff nurses, 11 registered nurses and 2 student nurses). After evaluation of the fifth focus group, no new factors accounting for long-term (non-)adherence were mentioned. Therefore, no new focus groups were organized [28].

Table 3. Fluid balance and body temperature guidelines: factors accounting for guideline (non-)adherence, mentioned by nurses.

Level	Fluid balance guideline adherence	Fluid balance guideline non-adherence
Innovation itself	It is less labor-intensive to only weigh patients	None mentioned
	I gain in time because I do not have to compose fluid balances anymore	
	It was hard to compose a fluid balance accurately	
	Our own safety improves due to less contact with cytostatic urine	
	The guideline is evidence-based: it was proven that weighing patients is accurate and composing fluid balances is not.	
Individual professional	None mentioned	None mentioned
Social context	We already suspected that it was unnecessary to both weigh patients and compose daily fluid balances	None mentioned
	We remind each other and oncologists to follow the guideline	
	Oncologists support the guideline as well	
	The investigator of the original study engaged us in the study and in implementation, leading to a guideline that was tailored to daily clinical practice	

Table 3. *(Continued)*

Level	Fluid balance guideline adherence	Fluid balance guideline non-adherence
Organizational context	We follow strict protocols during chemotherapy. Including the guideline in these protocols ensures adherence	None mentioned
Economic/political context	The government indirectly stimulated adherence by paying extra attention to a safe work environment in health care	None mentioned
Level	Body temperature guideline adherence	Body temperature guideline non-adherence
Innovation itself	The guideline stimulates the development of my clinical eye	Too many exceptional patients do not meet the guideline's criteria to omit routine body temperature measurements
	A study showed that routine postoperative body temperature measurements are meaningless	
Individual professional	I am confident with my clinical eye considering the detection of signs and symptoms of a postoperative infection	Body temperature measurements reflect how the patient is doing, clinical findings can be misleading
		I want to take a body temperature measurement of each patient once a day, just to feel safe
Social context	Everybody on our ward supports the guideline, including the surgeons	Routine body temperature measurements is a persistent routine, nurses correct each other when a measurement was omitted
		Surgeons expect the body temperature to be measured twice a day
		Patients expect me to measure their body temperature regularly. It is neither harmful, nor time-consuming.
Organizational context	It is hard to find thermometers on the ward	None mentioned
Economic/political context	None mentioned	Taking routine body temperature measurements is still instructed at nursing school

Nurses mainly mentioned factors contributing to the adherence to the FBG. They stated that the innovation, in which the routine of monitoring fluid balances had been abolished, saved them a lot of time and trouble

(Table 3). They had always suspected that it was unnecessary to both weigh patients and compose daily fluid balances (individual level). Nurses reminded each other and oncologists about applying the guideline, leading to a favorable social context of the guideline. On an organizational level, nurses indicated that they are required to follow strict protocols during courses of chemotherapy. Because the guideline had been incorporated in the existing chemotherapy protocol, they perceived adherence to the FBG to be non-problematic. No factors accounting for guideline non-adherence emerged in the meetings.

BTG

Seven focus group meetings were attended by 47 nurses (range 5 to 8 nurses per focus group, including 4 senior nurses, 38 registered nurses and 5 student nurses) and lasted 60 minutes on average. After 7 focus groups, a saturation point was reached as no new issues came up. Therefore, no new focus groups were organized [28].

Nurses of the surgery wards mainly mentioned factors accounting for non-adherence to the BTG (all factors grouped together in thematic categories in Table 3). Nurses particularly claimed that the innovation within the guideline had made daily clinical practice complex, because there were too many patients on their wards who did not meet the guideline criteria to omit regular body temperature measurements. Other nurses stated that application of the guideline prevented patients from unnecessary diagnostic research due to false-positive body temperature measurements. Regarding individual factors, nurses still believed body temperature to be an objective as well as a more reliable measure than their clinical judgment to demonstrate or exclude a postoperative infection, despite evidence stating the opposite. Within the social context, many nurses appeared to remind each other to stick to the old routine of measuring body temperature twice a day. They were also encouraged by orders of surgeons and expectations of patients to measure body temperature.

Factors influencing clinicians' long-term adherence

FBG

The multiple choice questions based on the nurses' focus groups were answered by 25 out of 44 oncologists (57%). Although the majority of the oncologists was unaware of the FBG or its exact content (17 out of 25; 68%, Appendix 1), they did follow its practical recommendations stating to rely only on the patients' weight to detect fluid overload (18 out of 25; 72%).

BTG

Thirty out of 51 surgeons responded to the multiple choice questions (59%). About half of the surgeons were aware of the BTG (14 out 30; 47%, Appendix 2). However, they appeared to have misinterpreted its content. While all routine body temperature measurements should be abolished, 20 of the 30 surgeons (67%) claimed they still checked body temperature to diagnose a postoperative infection when clinical signs or symptoms of a possible postoperative infection were observed. The same number of surgeons (67%) did not always trust nurses in their clinical judgment to notice significant signs and symptoms of a postoperative infection. This led them to assign nurses to measure body temperature routinely in order to "objectify" the presence or absence of any postoperative infection.

Discussion

Seven years after successful implementation of two hospital guidelines we found 100% adherence to the FBG versus only 50% for the BTG. Factors accounting for this (non-)adherence particularly regarded the presence of direct advantages to applying the guideline, the number of patients that fit the guideline's criteria and the interaction between clinicians and nurses involved.

Long-term adherence was attributed to immediate advantages to the nurses involved of applying the guideline. This confirms the finding of a previous study in primary and acute care trusts in the United Kingdom, where long-term adherence was achieved when practitioners and managers saw immediate advantages to adoption to pieces of guidance [29]. Clinicians stated that patient-oriented advantages of guideline adherence, such as decreased mortality and morbidity due to cardiac events, were major stimulators for long-term adherence to ischemic heart disease guidelines [30]. Eventually, the perceived benefits of adhering to a guideline must outweigh its barriers, as was found with the implementation of guidelines of hand hygiene in health care[31].

Adherence to the BTG was found to be troublesome in the long run. Our adherence measurement revealed that, although the guideline discourages routine postoperative body temperature measurements, in current clinical practice body temperature should nevertheless be measured according to the guideline in a considerable number of cases. This might be explained by changes in patient characteristics over the years. When preoperative and postoperative infections are more prevalent, the number of body

temperature measurements that should be taken increases, particularly because these patients will stay longer on the surgical ward.
Some patient groups, like pancreatic cancer patients, are admitted to our surgical wards in considerably large numbers nowadays. However, they were not represented in the diagnostic study on which the guideline was based at that time[21]. It was uncertain for surgeons and nurses involved whether these severely ill patients fitted the guideline criteria for omitting routine body temperature measurements. This drawback of individual patients not meeting guideline criteria has been described more often. It may even have harmful effects. For example, patients' lipid profile on admission for ischemic stroke was the least likely to be at guideline recommended levels for patients at the greatest risk of cardiovascular events [32]. Moreover, female patients with acute coronary syndromes and extensive co morbidities were less likely to be treated with recommended acute therapies and recommended discharge therapies [33].
Adherence to the BTG was also hampered because of misinterpretation: surgeons still tended to check body temperature when clinical signs or symptoms of a possible postoperative infection were observed, and nurses still believed body temperature to be an objective as well as a reliable measure to demonstrate or exclude a postoperative infection. A lack of self-efficacy or disbelief in the evidence base of the guideline could underpin these findings [34,35], but these possible barriers were neither confirmed in the focus groups for nurses nor in the questionnaires for clinicians.
Social interaction between the healthcare professionals involved appeared to influence long-term adherence in both a positive and a negative way. With respect to the FBG, nurses and oncologists acted unanimously which was thought to enhance adherence. In several previous studies peer support, teamwork and leadership support have shown to be important to the implementation of other guidelines [15,36,37]. In the opposite direction opinions differed on the BTG within the nursing teams and medical staff, as well as between these disciplines, which was thought to hinder long-term adherence.
Some potential limitations of this study should be discussed. We focused on only two guidelines within a single hospital setting, which inevitably limits the external validity of our findings. Secondly, we limited our study to individual opinions of nurses and clinicians. This means that we could not find a causal relation between guideline characteristics or system characteristics and long-term guideline adherence. However, by adding a qualitative approach to a quantitative measurement, we have gathered some

signs that may be worth further study regarding their potential to influence long-term guideline adherence in the hospital setting [38,39].
In conclusion, to secure long-term hospital guideline adherence, guidelines are preferably comprehensive in being applicable to the majority of the patients aimed at, and being applicable to the most common clinical situations. All health care professionals involved should be aware of its immediate benefits to themselves or to their patients. Adherence to guidelines should be monitored repeatedly. If adherence rates appear to diminish over time, we suggest that barriers to guideline adherence should be explored both among the individual healthcare professionals involved as well as regarding the characteristics of the hospital setting. In a post-initial miniature implementation strategy we suggest interventions should be tailored to the newly revealed barriers and direct advantages of applying the guideline should be emphasized to the health care professionals involved. Adherence to hospital guidelines after the active and successful initial implementation phase cannot be taken for granted.

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Appendix 1. Oncologists' guideline adherence: questions derived from the nurses' focus groups

Fluid balance guideline adherence: questions for oncologists	%	n
1. To detect fluid overload in patients with intravenous hyperhydration, I want to know:		
a. fluid balance every 8 hours	12	3
b. body weight every 8 hours	72	18
c. fluid balance and body weight every 8 hours	16	4
d. otherwise	0	0
2. When I ask for a fluid balance, this is because:		
a. I do it out of routine	24	6
b. my colleagues expect me to do so	8	2
c. the nurses hand me the fluid balance	12	3
d. I never ask for a fluid balance	44	11
3. Are you aware of the guideline regarding the omission of fluid balances to detect fluid overload?		
a. Yes, and I adhere to the guideline	28	7
b. Yes, but I do not adhere to the guideline	0	0
c. Yes, but I am not aware of the exact content of the guideline	24	6
d. No, I am not aware of this guideline at all	44	11
4. Do your patients fit this guideline?		
a. Yes, most of them do	80	20
b. No, it is impossible to weigh most patients	4	1
c. No, I often want to have a fluid balance monitored for other reasons	4	1
5. Do you feel that the evidence base of this guideline is sufficient to apply the guideline?		
a. Yes, sufficient to apply the guideline	33	8
b. More research is needed before I am willing to apply the guideline	0	0
c. No, the evidence base is insufficient	0	0
d. Not applicable, I am not aware of the evidence or the guideline	64	16
6. Are you confident in detecting fluid overload without knowing fluid balance?		
a. Yes, weighing patients is sufficient to detect fluid overload	80	20
b. No, balances are unreliable	0	0
c. No, I do not trust the nurses	0	0
d. No, I want a fluid balance to be monitored to be sure that I will not miss out on fluid overload	16	4

Appendix 2. Surgeons' guideline adherence: questions derived from the nurses' focus groups

Body temperature guideline adherence: questions for surgeons	%	n
1. To detect a postoperative infection in a non-infected patient, I want to know body temperature:		
a. on a daily basis	23	7
b. when signs or symptoms of an infection occur	67	20
c. only in seriously ill patients	3	1
d. never	3	1
2. When I ask to measure body temperature in a non-infected patient, this is because:		
a. I do it out of routine	40	12
b. my colleagues expect me to do so	10	3
c. the nurses tell me the body temperature	20	6
d. I never ask for a body temperature	30	9
3. Are you aware of the guideline in which routine body temperature measurements are omitted?		
a. Yes, and I adhere to the guideline	23	7
b. Yes, but I do not adhere to the guideline	23	7
c. Yes, but I am not aware of the exact content of the guideline	33	10
d. No, I am not aware of this guideline at all	20	6
4. Do your patients fit this guideline?		
a. Yes, most of them do	77	23
b. No, a considerable number of patients have a preoperative infection	0	0
c. No, a considerable number of patients develop a postoperative infection	17	5
5. Do you feel that the evidence base of this guideline is sufficient to apply the guideline?		
a. Yes, sufficient to apply the guideline	37	11
b. More research is needed before I am willing to apply the guideline	17	5
c. No, the evidence base is insufficient	7	2
d. Not applicable, I am not aware of the evidence or the guideline	37	11
6. Are you confident in detecting a postoperative infection without knowing body temperature?		
a. Yes, routine temperature measurements are not needed to detect a postoperative infection	50	15
b. No, when I suspect a postoperative infection, I want the body temperature to be measured	47	14
c. No, I always want to know body temperature so that I will not miss a postoperative infection	3	1
7. Do you trust nurses to notice significant signs and symptoms of a postoperative infection?		
a. Yes	33	10
b. No	67	20

Chapter 4

Is there still an indication for nursing patients with prolonged neutropenia in protective isolation?

An evidence based nursing and medical study of four years experience with nursing patients with neutropenia without isolation

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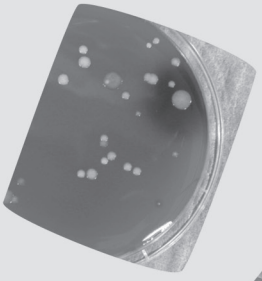

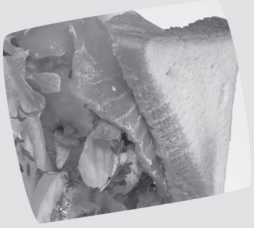

Abstract

Introduction: Patients with severe neutropenia due to high-dose chemotherapy and/or total-body irradiation are at risk for serious infections and are frequently nursed in strict protective isolation. This is a costly procedure and means a psychological burden to the patient. The significance has been in debate for a long time. The introduction of very potent systemic antibiotics, antibiotic prophylactics, haematopoietic growth factors and peripheral stem cell transplantation might have decreased the need for it. We performed a systematic review on the literature and a medical/ nursing guideline study.
In the literature we searched especially for prospective randomised studies. Only 6, mostly older, prospective randomised studies contradict each other on the usefulness of protective isolation.

Method: In a campaign of our centre aimed at promoting evidence based medicine we conducted a combined medical and nursing guideline study consisting of three parts: 1. Inventory of (inter) national guidelines; 2. Analysis of potential sources of infection sources; 3. Follow up study with new guidelines.

Results: 1. The practices in different centres in Europe appeared to vary widely. 2. Micro-organisms spread easily, especially if hands are not adequately dried. Isolation does not prevent this. Based on these findings we decided to stop protective isolation. This change of policy was combined with a campaign for optimal hygiene and introduction of hand alcohol. 3. We monitored the incidence of febrile neutropenia, infections and use of systemic antibiotics and antifungals in a 3-year period without protective isolation and compared this with the findings in the preceding three years with isolation. No significant differences in infections and mortality were found.

Conclusion: We conclude after the follow up study that abandoning protective isolation combined with increased hygienic measures in nursing of patients with severe neutropenia does not increase the risk of infections, improves the quality of care and patient satisfaction and reduces costs.

Introduction

Patients with prolonged neutropenia are highly susceptible to infections. These are mainly patients with haemato-oncologic malignancies treated with high dose chemotherapy and patients undergoing stem cell transplantation. When these treatments were introduced in the sixties patients were nursed in strict isolation. This was done in plastic tents, so-called life islands, or in laminar airflow rooms using air filtration and overpressure to keep out germs. This was combined with special measures regarding hygiene, food preparation and cleaning. During the phase of the neutropenia the patient was confined to his room, usually a time period of about 3 weeks. In that time these seemed intelligent and understandable measures. Yet, from the beginning the benefit of these measures has been questioned [1]. Already in 1984 Armstrong published a paper in the American Journal of Medicine entitled: "Protective environments are discomforting and expensive and do not offer meaningful protection" [2].

For many years' protective isolation stayed (and still is) standard practice though with remarkable differences and variety of infection prevention between centres as an national survey in the United States showed [3]. It is remarkable that there is so little adequate research on this subject. Nurses should do this research because they are more than doctors confronted with the consequences.

Nursing in strict protective isolation is a considerable burden for the patients, sick as they are and uncertain over the outcome. Direct contact with their relatives is impaired and limited. Strict isolation may lead to important psychological problems and frustration, especially fear for abandonment, depression and disorientation [4-8]. This psychosocial burden may also reach beyond the isolation room after return to the home situation. Patients often experience this change as a vacuum. Furthermore protective isolation is expensive and makes nursing these patients much more labour intensive.

If there has been an indication for protective isolation, has the introduction of antibiotic prophylaxis, the more potent systemic antibiotics, the haematopoietic growth factors and the peripheral stem cell transplantation with its shorter duration of neutropenia changed the need for it?

An important article appeared in the Lancet in 1992 describing 50 patients undergoing allogeneic bone-marrow transplantation [9]. Thirty had strictly isolated care and 20 were partly treated on outpatients' basis. The infection rate and mortality were similar.

This encouraged us to perform a combined medical and nursing study about the value of protective isolation and determine whether the hospital guidelines for isolated care of patients with neutropenia could be reduced. The guidelines study on the value of protective isolation was part of a special programme of the Amsterdam University Hospital (AMC) to promote and implement more evidence based guidelines.
Our study consisted out 3 parts: (1) an (inter)national inventory on practices elsewhere (2) an assessment of potential infection sources and (3) an follow up study with comparing the incidence of infections during an observation period and after implementing new guidelines.

Systematic literature review

We performed a medline/cinahl literature search of the English/American, German, French and Dutch literature as from 1966. We selected prospective randomised trials on protective isolation. Keywords: Protective isolation, protective environment, patient isolators, neutropenia, bone marrow transplantation and peripheral blood-stem-cell transplantation.

With our literature search we identified 160 publications on protective isolation in neutropenic patients, mostly dating from the seventies. Most are descriptive or compare different prophylactic measures, including isolation, at the same time. We found 6 prospective randomised studies. Most studies were done before the introduction of prophylactic antibiotics. Outcomes are contradictory: some showing less infection in isolated patients [10-11], where others find no differences [12-15]. Only one of the studies shows a lower mortality in the patients treated in protective isolation[10]. In a non randomised study significantly less Aspergillus infections were found in bone marrow transplantation patients nursed in laminar air flow rooms with HEPA (high particulate-efficiency particulate air filtration) [16]. In two other studies this difference was not found [17-18]. Another study found a lower transplant related mortality in patients treated in isolation combined with HEPA filtration compared with isolation and no air filtration) [19]. Russell et al. [9] reported no difference in infections and mortality in patients undergoing allogeneic bone marrow transplantation without isolation, compared what is reported in the literature for patients transplanted with strict isolation. They later expanded these findings in a larger group of patients [20]. The same findings were reported for patients undergoing autologous transplantants [21]. In the past decades there has been a remarkable switch in bacterial pathogens causing infection in neutropenic patients. In the seventies these

were predominantly Gram-negative bacteria as E.Coli and Pseudomonas [22]. Because colonisation with these potential pathogens usually precedes infection strict isolation might be of benefit.
A potential benefit of isolation is protection against Aspergillus infections [23]. These occur predominantly in patients with prolonged neutropenia treated with broad spectrum antibiotics and are airborne. Also here the literature data are conflicting. Several studies indicate that special air filtration is obligatory to offer meaningful protection. The risk of Aspergillus infection is especially increased in case of construction work in the vicinity of these susceptible patients [24]. Best would be not to treat these patients during construction works, or as second best give them prophylaxis with for instance low dose intravenous amphotericine B.
In conclusion: There are only a few older prospective randomised studies and they contradict each other. There are a lot of opinions of respected authorities or expert committees but they are based on clinical experience or descriptive studies. We couldn't find in the literature enough evidence on the usefulness of protective isolation.

Patients and methods

1. Inventory of international hospital guidelines

This was done using questionnaire sent to Dutch (13 hospitals) and European (141 hospitals in 23 countries) transplantation centres. Questions were asked about the form of isolation, start and end of it, hand-washing procedures, the use of aprons, mouth masks, dietary precautions, visiting rules and cleaning procedures.

2. Potential sources of infection

In collaboration with the department of medical microbiology, cultures were grown and air samples were taken. We took samples from the hands (nurses, doctors and other personnel) and matters like toothbrush, taps, bed and surroundings (alarm bells, infusion pumps, bed handles and doorknobs). Collection followed the daily nursing practice in the ward with special attention to the hands of the care providers, the 'route' of the hands. Air samples were taken 3 times (3 x 8 hours per 24 hours) on 8 different places near and inside the isolation room; this procedure was repeated later on in the study period. Moreover, samples of air were taken with an air sampler at different times and from different sites. Hygienic aspects were also

comprehensively examined (wash basin, lavatory). Our main interest was the spread of micro-organisms, particularly between the ward and the isolation rooms. Assisted by the AMC technicians, we measured the air-conditioning system several times, especially in the isolation rooms. A similar procedure was followed for the cleaning of the ward.

3. Follow up study after implementation of new guidelines

Pre isolation/ Old situation

On our 28 bed medical ward both hematological and oncological patients were nursed. Most patients received more than one course chemotherapy for remission induction or consolidation. In the AMC, both autologous and allogeneic bone-marrow transplantations, as well as peripheral blood-stem-cell transplantations are performed. Patients undergoing stem cell transplants have different diagnoses: acute and chronic myelogenous leukaemia, acute lymphoblastic leukaemia, multiple myeloma and lymphomas.
At the start of our study patients undergoing intensive chemotherapy or stemcel transplantation were nursed in overpressure single rooms with filtered air. The rooms have a corridor with low air pressure with two doors, only one of which was allowed to be opened at a time. This prevents unsterile air from the hospital corridors to enter the patient room. Before entering the patient room hands were carefully washed and all personnel had to put on an apron, for visitors an apron was also obligatory. Sterile gloves were worn only during specific nursing activities such as care of central venous catheters. Patients had germ-poor diet and received antibiotic prophylaxis with oral ciprofloxacin and amphotericine. Special attention was given to the cleaning of the room and the materials used in the room.

Post isolation/ New guidelines

Mainly based on our literature study we decided to stop protective isolation from January first 1995. Patients were still nursed in single rooms but free to come and go as they please like the other patients. The use of aprons was discontinued. Other measures were: use of an own lavatory; avoidance of groups of people in small areas, e.g. elevators; arrangement of precise appointments for examinations so that there would be no waiting times. Only when there was construction work on or near the ward there was temporarily protective isolation with a prophylactic intravenous amphotericine B. There were no specific limitations other than the hospital regulations as far as visits to the patient rooms are concerned. Only in case that the visitors were ill and there could be a risk of infection. The same applies to children (children's

disease). Finally, flowers and plants are not allowed because of the risk of contaminating micro-organisms. All visitors who have a direct contact with the patients or their vicinity have to wash their hands and use hand alcohol. Leaflets with information about the special care regimen were made available for the patients and for their visitors. The instruction for a correct use of hand alcohol, obligatory for medical and nursing actions, was linked to a campaign for proper hand washing. For this purpose, we gave information and prepared a special poster, which hangs at the entrance of the patient room (fig. 1). In this way, attention is drawn to the special situation of the neutropenic patient. Finally, dots on the floor mark the entrance of the room to indicate that the zone requires special attention.

Figure 1. Poster displaying need for handwashing and use of hand alcohol.

Data collection

During our study we collected data on the pre- and post isolation period: baseline characteristics, duration of neutropenia, days with fever (>38.0 degrees Celsius), documented infections, systemic amphotericine B use and

mortality due to infection. This was done during an inventarisation period (1992-1995) and after implementing new guidelines (1995-1999). Two groups of patients groups were studied: patients with acute myelogenous leukaemia (81 patients, 219 treatment episodes) and patients undergoing bone marrow- or peripheral blood-stem-cell transplants (97 patients, 97 episodes).

Results

1. Inventory of international hospital guidelines

One honderd and one of the 141 European centres in 23 countries responded (fig. 2). There were remarkable differences in the use of masks, gloves, aprons and the use of hand alcohol. Factors which triggered, as the starting and stopping of the isolation, are presented in table 1 and 2.

Figure 2. Number of responses depicted by country responding to survey of hospital guide lines.

2. Potential sources of infection

Cultures showed low concentrations of gram-negative bacteria in the isolation room. Hands of caregivers frequently contained micro-organisms, especially when they were not dried properly. These spread readily through

Table 1. Start isolation

Start Chemotherapy	59
Leucocytes < 0.5	20
No isolation	1
Other reasons	19
· Day 0	4
· Day –1	2
· After TBI	2
· Different auto/allo	3
· After chemotherapy	1
· Leuco's < 1.0	3
· Leuco's < 1.0 or day 0	1
· Granulo's < 0.3	2
· Granulo's < 1.0	1
No response	2

Table 2. Stop isolation

Leucocytes > 1.0	43
Leucocytes > 0.8	6
No isolation	1
Granulocytes > 0.5	22
Discharge	5
Other reasons	23
· Difference auto/allo/pbsct	4
· 30-50 days	3
· granulo's > 0.2	1
· granulo's > 0.3	4
· granulo's > 0.3 more days	1
· granulo's > 0.5	3
· granulo's > 0.5/ free of infection	1
· leuco's > 0.5	2
· leuco's > 1.0 and after 23 days	1
· leuco's > 1.0 for 3 days	1
· leuco's > 2.0-3.0	1
· needs for room for isolation	1
No response	1

the room of the patient by contact of the contaminated hands with the bed of the patient and infusions systems. Use of hand alcohol significantly diminished the colonisation of the hands with micro-organisms. Many samples were very illustrative for the caretakers. They were photographed and are now used for training on the job. Air sampling showed minor differences in cultured colonies in time and site. There were no difference between isolation rooms and ward.

3. Follow up after implementation of new guidelines

We compared the pre- and post isolation period over two 3-year time periods with respect to different infection parameters: 1992-1995 with strict isolation and 1995-1999 without isolation but emphasis on optimal hygiene. Results are summarised in table 3. Baseline characteristics of the AML patients and the transplantation group in both time periods are comparable. The duration of admission and of neutropenia was also comparable.

We found no differences between the patients nursed in protective isolation and those not with respect to median number of days with fever, days until first systemic antibiotic therapy and the duration. Neither was there a difference in the use of intravenous amphotericine B. The most frequently isolated pathogen were coagulase negative Staphylococci, associated with

Table 3. Patient Data: Pre Isolation (1992-1994) versus Post isolation (1995-1998)

	AML		TRANSPLANT	
	1992-1994 Pre isolation	**1995-1998 Post isolation**	**1992-1994 Pre isolation**	**1995-1998 Post isolation**
Baseline Characteristics				
No. of patients	44	37	34	63
Number of episodes	134	85	1	1
Episodes per patient (range)	1-5	1-6	-	-
Male / Female	22 / 22	22 / 15	25 / 9	35 / 28
Age in years, median (range)	51.4 (19-80)	52.2 (32-70)	33.4 (15-57)	43.2 (17- 65)
Days duration of hospital stay, median (range)	29 (15-60)	33 (20-73)	30 (16-112)	31 (18-102)
Neutropenia				
Days granulocytes < $0.1*10^9$ /l., median (range)	19 (7-75)	18 (9-44)	14.5 (6-29)	14 (6- 55)
Days granulocytes < $0.5*10^9$ /l., median (range)	22 (9-75)	22 (12-57)	20 (7-54)	18 (11-107)
Fever and Antibiotics				
Episodes with fever, days, (% of total episodes)	107 (82.1)	66 (78.0)	24 (70.6)	44 (69.8)
Days with fever, median (range)	8 (0-31)	7 (0-45)	6 (0-44)	4 (0-30)
Days until syst. Antibiotics, median (range)	13 (0-35)	13 (0-28)	8 (0-18)	9 (0-20)
Days on syst. Antibiotics, median (range)	12 (0-60)	12 (0-60)	10 (0-32)	10 (0-71)
Episodes without any syst. Antibiotics (% of total episodes)	40 (29.9)	26 (30.6)	11 (32.4)	29 (46.0)
Episodes with iv. Amfo-B (% of total episodes)	15 (11.2)	10 (11.8)	3 (8.8)	4 (6.4)
Infections				
Episodes with documented infection (%)	53 (39.5)	22 (25.8)	8 (23.5)	15 (23.8)
Episodes with central venous catheter infection (%)	40 (30.8)	12 (15.3)	5 (14.7)	12 (19.1)
Episodes with positive bloodculture (%)	13 (9.8)	10 (11.8)	3 (8.8)	3 (4.7)
Episodes with major clinical documented infection (%)	15 (11.2)	17 (20.0)	7 (20.6)	5 (7.9)
Patients died of infection (%)	9 (20.5)	2 (2.4)	3 (8.8)	3 (4.8)

central venous catheter infection. The same held's true for number of documented infections or positive blood cultures. The mortality rate from infection was comparable, though not statistically significantly higher in the patients nursed in protective isolation.

Discussion

In recent years there is much debate about the need of protective isolation in hematological patients during the phase of severe neutropenia. Nurses, who are more than doctors confronted with the consequences, take here the lead. On nursing conferences special sessions are dedicated to this subject. It is remarkable that there is so little adequate medical or nursing research on this subject. Probably in the past everybody took the benefit of protective isolation for granted. From our survey we drew the same conclusion as made in the survey in the United States [3].There are great differences in nursing protocols/ instructions between the centres.

Our literature study revealed contradictory results. One of the advantages of isolation could be psychological, that is it makes everybody aware of the increased risk of infection of the patient. However our study demonstrated that isolation does not keep the pathogens out of the patient room when hands are not properly washed and dried. The use of hand alcohol is then more efficient and a lot easier. Nowadays infections for the greatest part are caused by Gram-positive micro-organisms which belong to the endogenous flora of the patient, such as coagulase negative staphylococci and streptococci [24]. These infections cannot be prevented by strict isolation. For this shift in pathogens there are several reasons: the sharp increased use of central venous catheters, the more intensive chemotherapy leading to mucosal damage and the prophylaxis directed against Gram-negative bacteria.

During our study we grew to the conclusion that protective isolation was not evidence based. The good results in two studies were stemcel transplantation's were performed without protective isolation [9,21] that we could change our policy and stop isolating patients. We combined this with an intensive program on educating all workers with respect to hygiene and introduction of hand alcohol (fig.2). We carefully monitored the prevalence and nature of infections and noticed no differences. We therefore felt confident to continue this new strategy to great satisfaction of both patients and workers in our department.

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Chapter 5

Providing oral care in haematological patients: Nurses' knowledge and skills

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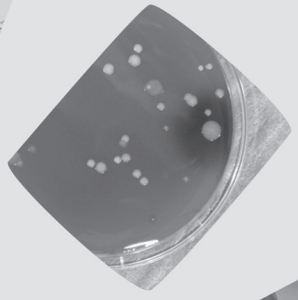

Abstract

Introduction:	In the international literature, the most commonly recommended intervention for managing oral mucositis is good oral care, assuming that nurses have sufficient knowledge and skills to perform oral care correctly. The aim of the present study was to investigate if knowledge and skills about oral care improve when education in oral care is provided to nurses in charge of patients who are at risk of oral mucositis.
Method:	This intervention study consists of a baseline test on the knowledge and skills of nurses of the hematology wards of two different hospitals. Oral care education sessions were given in one hospital and follow-up tests were performed in both hospitals. Nursing records were examined and observations of nurses performing oral care were made at baseline as well as at follow-up.
Results:	The results show significant differences in the scores for knowledge and skills before and after the education, whereas there was no difference in scores at the two points in time for the comparison hospital, where no education had taken place. The records test showed no differences at baseline or follow-up for the two groups. Observations showed that nurses who followed the education session implemented the oral care protocol considerably better than those who did not attended.
Conclusion:	Education in oral care has a positive influence on the knowledge and skills of nurses who care for patient at risk of oral mucositis, but not on the quality of oral care documentation.

Introduction

Patients who receive chemotherapy to treat malignant disease, often experience oral mucositis as the most debilitating side effect [1, 2] resulting in a poorer quality of life can be affected by pain, infection, altered nutrition and impaired oral function [3, 4]. Oral mucositis is one of the most common causes of treatment delay and dosage reductions in cancer therapy [5]. Prevention and treatment are as important to oral mucositis as they are to fatigue, nausea and vomiting and many other side effects affecting patients with cancer.

Nurses play a central role in preventing and managing oral mucositis and reducing its debilitating effects on patients. In fact they have 3 main tasks in managing oral mucositis: (1) assessing and monitoring changes in the oral cavity; (2) providing appropriate oral care; and (3) offering patient education [6]. Nurses give oral care of patients with cancer a high priority [7], but very little is known on day-to-day practice [8].

In the international literature, regular oral care is most commonly mentioned for managing oral mucositis [9-11] though the standards for oral care are not consistently implemented and advice on the frequency of oral care frequency varies from "once every shift" to 'only if patient requests it'.

Furthermore, obstacles to providing oral care have been little investigated. McGuire outlined barriers to implementing oral care standards and proposed strategies to overcome them [12]. In a study by Wallace attitudes and subjective norms predicted 39% of the behaviour of nurses in providing oral care [13].

Simple lack of knowledge about oral care is a major barrier to providing optimal oral care [12.]A first and necessary step in the process of change is to identify the educational needs that exist in order to be able to offer adequate education and support, both theoretically and practically. However, knowledge deficits are not the only barriers. To manage oral care effectively, nurses require more and continuing education [7, 8].

An important part of daily oral care is to assess the oral cavity of each patient at risk for oral mucositis. To this end, nurses should be trained in the use of standardised tools for screening and assessment [14] in order to be proficient in using such instruments [15]. Besides this, training increases the inter-observer reliability of the oral assessment and improves the evaluation of mucositis [16].

The aim of the present study was to investigate whether knowledge and skills regarding oral care improve when education is provided to nurses caring for patients who are at risk for oral mucositis.

Methods

Study design

Baseline tests on the knowledge and skills of nurses in hematology wards of two different hospitals were conducted. Oral care education sessions were given in one hospital and follow-up tests were performed in each hospital (Figure 1).

The baseline and follow-up consisted of performance observations as well as the nursing record tests. A knowledge test was also employed to investigate nurses' familiarity with the key principles of oral care. Oral care education sessions were tailored to the baseline scores. The follow-up tests were performed one month after the last education session in the intervention hospital.

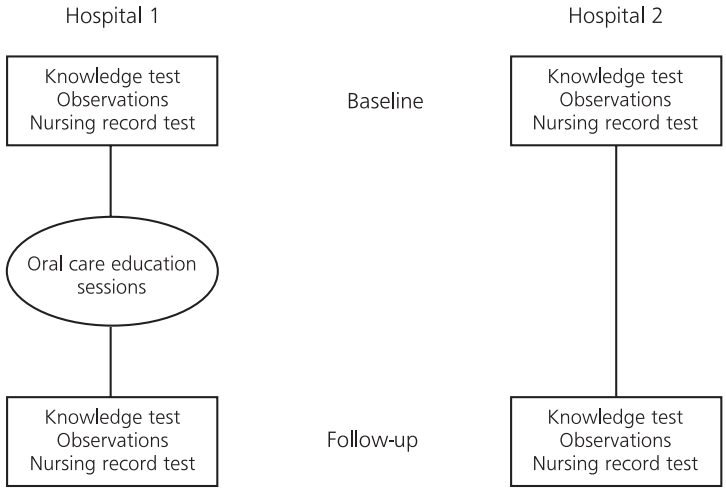

Figure 1. study plan

Setting and sample

The study population consisted of nursing staff of the hematology wards of two university hospitals in the Netherlands. The intervention group was made up of qualified nurses experienced in nursing on the hematology ward of the Radboud University Nijmegen Medical Centre (RUNMC). The ward

has 28 patient beds and admits 100 patients a year for autologous and allogeneic HSCT. The Daily Mucositis Score (DMS) [17] was used to assess oral mucositis on a daily basis as it is easy to use and is valid and reliable. Briefly, this requires the nurse to score erythema, oedema, dysphagia, lesions and pain assigning a score of 0 to 3 on a specially designed chart containing each day of the week.

Nursing staff developed an oral mucositis care plan when the first signs of oral mucositis appeared which consisted of brushing the teeth four times daily using a soft toothbrush and using oral rinses with normal saline (0.9% NaCl) or water.

The control group consisted of experienced nurses from the hematology/ oncology ward of the Academic Medical Centre of Amsterdam (AMC). The ward has 18 hematological beds and admits 60 patients a year for autologous and allogeneic HSCT. Patients admitted to this ward received an oral care regime similar to that included in the RUNMC care plan. Oral inspection was done every day for patients at risk for oral mucositis without employing a specific assessment instrument. Signs of oral mucositis were recorded, though not in a standardised manner and a checklist was used to monitor daily oral care.

The protocols of both wards were based on published guidelines including those of the MASCC [11, 18].

The intention was to examine 60% of the nurses per ward at both baseline and follow-up. All nurses were informed that participation was voluntary, and their anonymity was guaranteed.

Instruments and procedures

Demographic data were collected on gender, age, years of nursing experience and basic nursing degree.

Knowledge test

The knowledge test was a 32-item questionnaire including open-ended and multiple-choice questions and 8 photographs of the mouth illustrating different stages of oral mucositis. A team of experts including a hematologist (NB) nurse specialist (CP) dental hygienists (AO, MO) and an oncology nurse (AM) developed the test from existing protocols, the international literature and their own specialized knowledge. Topics included:

- Anatomy and pathology of the oral cavity (10 open questions, max. score 123 points).

- Oral hygiene (10 open questions, 3 multiple-choice questions, max. score 166 points).
- Oral mucositis (4 questions, max. score 45 points).
- Patient education (5 open questions, max. score 76 points).
- Assessment of oral mucositis in 8 photographs, (max. score 40 points).

The overall maximum score was 450 points. On average, 30-45 minutes were needed to complete the test. In the intervention hospital, only the nurses who had received these sessions were asked to participate in the follow-up test.

Observation of skills

The observations were designed to evaluate nurses' oral care skills. A list consisting of 44 observations points (OP) was developed to audit these activities and each was answered with "yes" (done) or "no" (not done). The OP was grouped into 5 subsections;

- Checking patient's oral status of the previous days (3 OP)
- Assessment of the patient's oral cavity according to the protocol (12 OP)
- Assisting with or performing, oral hygiene for the patient (23 OP)
- Patient directed advice for oral care (3 OP)
- Documentation of findings in the nursing record (3 OP)

The maximum score was 44 points. The list was a mix of the standardised protocols of both hospitals, though some questions were not relevant for both settings (e.g. locally standardised preventive or treatment prescriptions). The observations at both baseline and follow-up were done during the day by examining the mouths of patients known to have oral complaints. Two dental hygienists observed the nurses while they assessed the oral cavity and delivered oral care.

Nursing record test

Correct and adequate reporting of findings and interventions is essential to nursing care. The nursing record test consisted of 6 questions derived from the hospital protocols:

- The status of the oral cavity is recorded daily
- Results of oral assessment are reported
- The patient's oral pain is recorded
- In case of signs of oral mucositis, the oral care protocol is started
- Advice concerning oral care is provided to the patient and documented
- Interventions are started and documented

Ten nursing records from each ward were reviewed in retrospect, both at baseline and follow-up. Each question was assigned a maximum of 4 points and the completeness of the records was given up to 24 points

Oral care education sessions

The oral care education sessions were offered to the nursing staff of the RUNMC only. The results of the baseline knowledge tests directed the content of these sessions.
The training was given by two dental hygienists who provided theoretical education on the anatomy of the oral cavity, relevant pathology, oral hygiene, oral mucositis and options for prevention and treatment. Oral assessment training was archived with the help of slides. A second component of the training consisted of nurses cleaning each other's teeth, which helped them rehearse their skills and experience the process from the patient's perspective. The education session took 1½ hours. Four identical sessions were offered to enable as many nurses as possible to attend.

Statistical analyses

The tests on the nursing record, nurses' knowledge and the skills performance observations resulted in summary scores and were analysed using the Statistical Package for the Social Science (SPSS version 14.0) using simple descriptive statistics. A total score for both tests was used to give a final analysis of nurses' knowledge, skills and performance in documentation.
The effect of the intervention (education sessions), compared to no intervention was analyzed using two-way independent 2^2 ANOVA. A significant (alpha=0.05) interaction of the main effects for time point (baseline versus follow-up) and group (intervention versus control) was to indicate a positive effect of the education sessions.

Results

Knowledge test

Thirty-one and 29 nurses participated in the knowledge test at base line and at follow-up respectively. Two nurses of the control group started the knowledge test but did not finish it. Their tests results were not analysed. Nurses were predominantly females, with a mean age of 34.3 years (range

Table 1. Nurses' age and experience for both nursing teams at both time points

	Intervention group baseline	Intervention follow-up	Control group baseline	Control group follow-up	Total
N	20	20	11	9	60
Mean age (years)	36.4	34.9	36.6	31.9	34.9
Mean experience (years)	7.6	5.9	5.7	5.6	6.2

24-54) and a mean number of 6.4 years (range 1-15) of experience in care of oncology patients (Table 1).

At baseline, only 30% of the nurses knew all the characteristics of mild mucositis, whereas 60% of the nurses were able to describe severe mucositis. Most of the nurses knew the most important risk factors for development of oral mucositis. On the other hand, only half of the nurses gave correct answers to the questions on anatomy and pathology. Knowledge about oral hygiene varied, with more than 50% of the nurses being unable to offer advice to a patient with dental prostheses and oral mucositis. Three out of eight photographs showing various stages of oral mucositis were assessed correctly by 75% of the nurses. The test was a revelation to some nurses as it showed how little they knew about aspects of oral mucositis.

Table 2 shows the means and standard deviations on the knowledge test for the two groups and both points in time. There was a significant interaction effect (illustrated in figure 2) between time (baseline versus follow-up) and group (control versus intervention): $p = 0.008$. The difference in the increase in mean knowledge was 56.9, 95%CI: [15.7; 98.0], indicating a relevant positive effect of education on knowledge (Figure 2).

Table 2. Knowledge test mean score and standard deviation per group and time point

	Intervention group baseline	Intervention group follow-up	Control group baseline	Control group follow-up
N	20	20	11	9
Mean	212.3	276.2	200.3	207.3
Std. deviation	36.9	35.5	43.2	34.9

The difference in mean increase is 56.9, 95%CI: [15.7; 98.0], p = 0.008

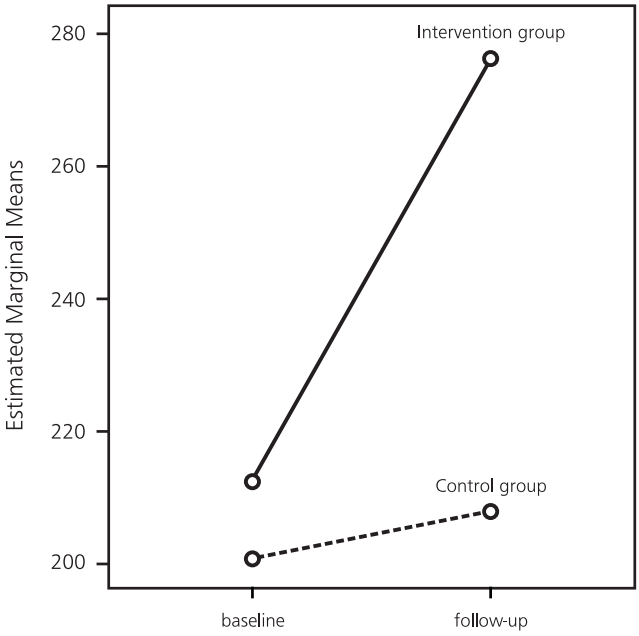

Figure 2. Estimated marginal means of total score knowledge test.

Table 3. Observations mean scores per item and overall mean score and standard deviation per group

	Intervention baseline N=10 Mean	**Intervention follow-up N=10 Mean**	**Control baseline N=10 Mean**	**Control follow-up N=10 Mean**
Checking patient's oral status of previous days before oral assessment.	4.5	5.6	5.0	2.7
Assessment of patient's oral cavity according to the protocol.	15.8	21.9	15.2	15.3
Assisting with- or performing oral hygiene for the patient.	32.4	39.5	29.8	34.2
Patient directed advice for oral care	5.2	5.8	4.4	5.1
Documentation of findings in the nursing record.	2.7	2.7	2.6	2.3
Overall Mean	60.6	75.5	57.0	59.6
St. deviation	9.0	5.6	7.9	8.8

The difference in mean increase is 12.3, 95%CI: [2.1; 22.5], p = 0.019

Observation of skills performance

The results of the observation test are shown in Table 3 (to facilitate the interpretation of the results, the maximal score per section is presented next to the actual scores).

At baseline, almost half of nurses assessed the patient's oral cavity without knowing the previous oral status. Many mistakes (50%) were made with oral inspection. The equipment required was not always used, and the floor of the mouth was overlooked in two-thirds of cases. However, 65% of the nurses gave at least some advice about oral care to the patients.

Nurses who attended the oral care sessions implemented the oral care protocol significantly better than those who did not attend (p = 0.019). The difference in mean increase in total score was estimated at 12.3, 95%CI: [2.1; 22.5].

Table 4. Record tests mean scores per item

	Intervention group baseline N= 10	**Intervention group follow-up N=10**	**Control group baseline N=10**	**Control group follow-up N=10**
A daily notation concerning the status of the oral cavity is written	1.2	0.9	1.3	1.9
Results oral assessments are reported.	1.2	2.7	2.4	1.9
Patient's oral pain is recorded.	0.8	0.8	1.0	0.8
If there are signs of oral mucositis, the oral mucositis protocol is started.	2.6	2.3	1.7	1.3
Advice concerning oral care is given to the patient and is recorded.	1.1	2.4	1.7	1.6
Interventions are started and recorded.	1.4	1.1	1.0	1.2
Overall Mean	8.3	10.2	9.1	8.7
St. Deviation	4.3	4.0	4.5	3.3

The difference in mean increase is 2.3, 95%CI: [- 2.9; 7.5], p = 0.376.

Nursing record test

Only records of patients at risk for oral mucositis were included in the nursing record test. Each record was carefully studied by two dental hygienists with the help of the checklist (Tables 4). There were no significant overall differences between the groups $p = 0.367$. The difference in mean increase in total score was estimated at 2.3, 95%CI: [- 2.9; 7.5].

Discussion

The aim of this study was to investigate whether knowledge and skills in oral care improve when education is offered to the nurses who care for patients at risk for oral mucositis. Nursing skills were assessed by reviewing nursing records and observing nurses while they were providing oral care. Furthermore, knowledge tests at baseline and at follow-up provided a clear impression of the effect of oral education sessions.
To our knowledge, this particular study design has not been used previously though; there are a number of studies in other areas that used educational interventions to change knowledge and skills. For example, Dalton et al. [19] designed an educational program to improve knowledge in order to change pain management practices and patient outcomes. This program was offered to nurses who provided day-to-day care for patients with cancer. A quasi-experimental design was used to measure the effectiveness of the program in changing nurses' knowledge, attitude and behaviour. Data were collected from nurses and patient charts before and after the program. Nurses' knowledge improved, but the change was not statistically significant. In contrast with the study by Dalton and similar studies on the effects of education in nurses, our study added observations on performance, a less common element in this type of study.

Knowledge tests

In our study, we tested the actual knowledge of nurses in the area of oral care. This is in contrast to other studies that investigated nurses' self-reported knowledge or personal views on oral care by means of questionnaires or interviews [7, 8, 20, 21]. Nevertheless, the results are the similar; baseline data revealed that nurses have gaps in their knowledge of oral care, particularly in their knowledge and assessment of the different stages of oral mucositis.

Observation of performance

At baseline, observations of nurses carrying out oral care revealed mistakes in assessing the oral cavity as well as in assisting with- or providing oral hygiene. Moreover, even though oral assessment had become a daily routine, procedures that were wrongly learned, persisted.
Observations by dental hygienists during the daily nursing routine are not common for nurses or their patients, which will alter their behaviour as they know that they are being watched. This could have resulted in more favourable scores for nurses. However, as observations were used at both points in time, the changes from baseline identified in our study are likely to be genuine. Follow-up data showed significant improvement of oral care given by nurses who attended the oral care sessions indicating that quality of oral care will likely be improved by refreshing existing knowledge and providing new knowledge [22].

Nursing records

Nursing records are the main source of information on each patient's oral care as their purpose is to have an easily accessible reference that describes the patient's needs and wishes. Nursing interventions can also be documented and evaluated in these records [23].
At baseline, the results for the record test showed inadequacies in the documentation of oral care. Most of the records were incomplete and sometimes oral assessment was documented but the accompanying intervention was not described. Although special attention was given to this during the education sessions, the follow-up test showed no improvement in the quality of the records. This likely reflects a more general attitude of nurses towards reporting. To improve the quality of nursing records, a more comprehensive training should be provided, together with continuous feedback based on regular evaluations[24]. The development of electronic nursing records might possibly improve accuracy and make them a more useful source for information on patient outcome[25].

Oral care education session

The effects of educational sessions showed the impact of education and training. Training in oral assessment is necessary even for experienced nurses to prevent mistakes when inspecting the oral cavity and to ensure the results are judged correctly[15, 16]. During the education sessions, slides were used of photographs of the mouth showing different stages of oral mucositis. In future studies, videotaped demonstrations[26] and guided practice in assessing

patients' mouth under supervision of an experienced nurse or a dental hygienist could optimise the trainings. The practical part of the education sessions consisted of nurses brushing each other's teeth. This 'simple' task was regarded as unpleasant but after the session many nurses changed their attitude towards the cleaning of teeth.

Limitations

The tools used in this study were specifically designed for this study and were not extensively tested for their validity and reliability beforehand. However, the record test was based on expert validity and only two observers used the observation and the nursing record tool and they fine-tuned their interpretation to provide greater consistency.
The follow-up data were collected one month after the education sessions so we do not know whether the same results would be obtained after 6 months or later.
Our study included two wards of two different hospitals which, though similar in admission policy and patient demographics, will likely differ in other aspects. In addition, paired analysis was not possible because of the anonymity of the participants. The sample of nurses was different pre- and post-test which could have introduced bias into our study.
Generalizability is also limited as our study was conducted in only two hematology wards in the Netherlands. It is therefore not certain whether the results can be generalized to hematology wards in other centres or general oncology wards and outpatient clinics here in the Netherlands or indeed elsewhere. None the less, the literature does suggest that similar problems and challenges exist elsewhere [7, 8, 20, 21, 27, 28].

Conclusion

Knowledge and skills improve when education in oral care is given to nurses. Baseline data showed a lack of knowledge and skills concerning oral care. These data gave direction to the need for and desired content of education sessions. Our education sessions met the need for oral care knowledge among nurses.

Recommendations

Regular oral care education sessions to improve or refresh oral care knowledge, are the most important recommendation from this study. Audits

and feedback are likely to improve oral care skills in practice. Senior nursing staff should consider selecting interested and experienced nurses to become 'resource nurses in oral care'. They can act as advisors, an information source and counsellor on oral care at the ward. These nurses should be responsible for oral care education sessions and they can also supervise and teach oral assessment and care in clinical practice.

Follow up studies are necessary to validate our findings, and to determine the most effective training interval and type of instruction and research is needed to determine the impact of knowledge on patient outcomes.

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Chapter 6

Examining Low Bacterial Dietary Practice: A Survey on Low Bacterial Food

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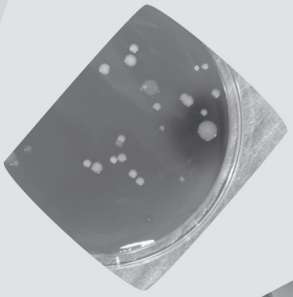

Abstract

Introduction: Patients with hematological malignancies have periods of neutropenia caused by the disease process and subsequent treatments, during which time they are at an increased risk of developing life threatening infections. Historically many measures have been initiated to protect patients during this time. One such measure has been to provide a low bacterial diet to minimise the number of pathogens ingested from food. However, scientific literature lacks any substantial evidence confirming whether this is beneficial in the management of these patients while guidelines are often unclear and give conflicting advice.

Method: A detailed survey was carried out to examine the use of low bacterial diets considering criteria, conditions and specific dietary products.

Results: 108 questionnaires were completed, mainly European. 95 (88%) centres used guidelines to advise practice for inpatients. Although 88 % of the hospitals have guidelines, when these were examined there were enormous differences in both the guidelines themselves and the way in which they are implemented. The restrictions seen are varied and sometimes even contradict each other. 48 (44%) of the respondents imposed restrictions on all products mentioned. Conditions for starting or stopping dietary restrictions were also diverse.

Conclusion: This survey highlights the need to attempt to standardise dietary restrictions in a patient group for whom good nutrition is paramount.

Introduction

Despite modern advances in the clinical management of neutropenic cancer patients, infection remains the major cause of morbidity and mortality associated with neutropenia [1]. The hypothesis that there may be a beneficial effect on the incidence of infection by serving pathogen-free foods has been alluded to since the early eighties [2]. Imposing dietary restrictions for immunocompomised patients continues to be widely used despite the lack of any rigorous research to support it [3]. These restrictions are referred to throughout the literature and different institutions by a variety of titles such as low bacterial diet, low microbial diet, clean diet or neutropenic diet. Furthermore actual food restrictions vary from centre to centre adding to the confusion. For the purpose of this paper we will use the term low bacterial diet to refer to any dietary restrictions used for the purpose stated above.

When the absolute neutrophil count (ANC) is less than $0.5x10^9$/l there is a significant rise in infection risk with the risk increasing in proportion to the length and severity of neutopenia. Gram-negative bacilli are a frequent cause of death associated with infection and generally arise from the patient's own endogenous flora or are acquired during hospitalization [1, 4] .
Neutropenia is a consequence of hematological malignancies and the chemotherapy regimes used to treat them [5]. Treatment modalities such as Stem Cell Transplant (SCT), which can provide long term remission or cure for many patients, often results in periods of profound neutropenia [6]. Patients undergoing allogeneic transplant receive high doses of chemotherapy with or without the addition of radiotherapy and prolonged periods on anti-rejection drugs, therefore immunosupression is generally lengthy and severe. Patients undergoing autologous transplant receive chemotherapy resulting in a shorter duration of severe neutropenia and less overall immunosuppression.

Background

Treatments, including SCT, commonly used for hematology patients often results in damage to the oral and gastrointestinal mucosa. This alteration in the mucosal barrier in combination with the immunosuppressive effects of treatment, subjects the patients to increased bacterial colonisation and risk of infection [7]. The low bacterial diet was designed to reduce pathogens

by excluding foods that may cause systemic bacteraemia or gram-negative sepsis via the host's gastrointestinal tract [8] .
In an attempt to expand and improve the semi-sterile "cooked food diet" usually administered to patients undergoing gastrointestinal decontamination or protective isolation, Pizzo et al [9] evaluated the microbiologic content of 236 commercially available food items. Since then, the low bacterial diet has changed from a sterile diet prepared under laminar-flow hoods to a more liberal diet that avoids high-risk foods and emphasizes safety in food handling practices[10] . Problems of limited availability of single-serve sterile foods, lack of standardization of recipes, and low patient acceptance of autoclaved sterile foods were reported as reasons for the move toward less stringent dietary procedures[11].

Research to support any dietary restrictions during periods of neutropenia is limited. The only studies evaluating low bacterial diet are mainly outdated and have used it in combination with multiple other interventions therefore the independent effect of diet alone remains unknown [2, 12-14]. Moody recently carried out a small pilot study which used a randomised design to look at infection rates between two groups of patients receiving low bacterial diet and standard food safety guidelines, but the numbers were so small that no significant conclusion relating to infection rates could be made [15] .
Several surveys have been published regarding the actual usage of dietary restrictions for patients with neutropenia, however these have utilised relatively small samples, are outdated [11, 16-18], or excluded patients undergoing BMT/SCT [19]. Poe surveyed 92 BMT units across the United States but the specific diets or criteria for implementation were not reported [20].

It seems that no definitive guidance exists to assist the implementation of a standardised approach to low bacterial diet resulting in variation and inconsistencies of practice [21]. This is problematic for health professionals trying to provide advice and reassurance for neutropenic patients but more importantly causes great confusion and distress for the patients themselves. A detailed survey to examine the use of low bacterial diets considering criteria, conditions and specific dietary products and including SCT patients across both paediatric and adult centres will provide important current data on which further studies or guidelines can be based.

Methods

On behalf of the research group of the European Blood and Marrow Transplant (EBMT)Nurses' group, a questionnaire on low bacterial food was sent to 248 EBMT Nurses' group members in 201 centres encompassing 25 European and 12 Non-European countries. The members were first accessed through the EBMT congress in 2004 in Barcelona. Questionnaires were administered to each delegate during educational sessions. Following the congress an analysis of completed questionnaires was undertaken and missing centres were identified using the EBMT data base of members.

Eighteen questions were developed with the aim of providing data on existing guidelines, patient information, reference points for starting and stopping low bacterial diets and dietary restrictions. We were interested in both the range and level of restrictions which were enforced for specific dietary products. The restrictions were divided into three categories to make the questionnaire more users friendly, these were: completely forbidden, product restrictions only and process restrictions only. Product restrictions are mentioned when some of the product is forbidden, such as "*candy bars with nuts"*. Process restrictions are mentioned when the food item can be eaten only in a particular way, for example *"only when cooked"*.
Due to the variety of products available, 18 were chosen according to a brief literature search in which specific products thought to be problematic were identified: for example ice cream [22]; tap water [23]; bottled water [24]; poultry with the risk of salmonella infections [25]; juices [26]; cooked dishes [27]; spices [28]; raw cheeses [29]; raw vegetables [30]. Additionally, individual contacts with some dieticians working with this patient group in the Netherlands was made and advice taken following discussion. The questionnaire was piloted with the Dutch Stem Cell Transplantation Group so that any problems or weaknesses could be identified and addressed.

Results

Two hunderd and forty-eight questionnaires were distributed, with 108 responses (44 %). The results came from 29 countries, 20 European and 9 others (Fig 1). Table 1 shows the demographics of the questionnaire. The majority of the questionnaires were completed by a nurse (74/69%) while other professions were: transplant coordinators (21/19.4%), dieticians

Figure 1.

Table 1. Demographic and Guidelines N = 108 respondents

Number / %				
Profession	Nurse 74/ 68.5	Dietician 8/ 7.4	Transplantcoor. 21/ 19.4	Others 4/ 3.7
Ward	> 18 years 62/ 57.4	< 18 years 23/ 21.3	Both 20/ 18.5	Others 3/ 2.8
Number of SCT annually	≤ 50 51/ 47.2	51-100 37/ 43.3	101-200 14/ 13.0	≥ 200 2/ 1.9
Type of SCT	Allo SCT 92/ 85.2	Auto SCT 102/ 94.4	RIST 78/ 72.2	
Permanent dietician connected to the ward	Yes 76/ 70.4	No 26/ 24.1	Missing 6/ 5.6	
Moment dietician consulted	Admission 33/ 30.6	Start protocol 16/ 14.8	Not specific 38/ 35.2	Others 12/ 11.1
Guidelines concerning low bacterial food during hospitalisation	Yes 95/88.0	No 11/10.2		missing 2/1.9
Guidelines concerning low bacterial food after discharge	Yes 79/73.1	No 11/10.2		18/16.7

(8/7.4%) or others (4/3.7%). Of the respondents 62 (57%) worked on a ward with adult patients (> 18 years). The number of SCT's performed were ≤ 50 for 51 respondents (47%) and between 51 and 100 for 37 (43%). Surprisingly, not every centre reported using guidelines: 95 (88%) did use guidelines during hospitalisation and 79 (73%) used guidelines following discharge. A permanent dietician is connected to the ward in 76 hospitals (70%). Adding further to the diversity of the results one hospital used no low bacterial diet at all and three used a very liberal version of the diet. These all came from North–European countries.

Table 2 indicates which conditions are used for starting and stopping low bacterial diet according to individual guidelines. As expected we found a great deal of diversity in these conditions. The results are divided into answers for autologous and allogeneic SCT patients, this is due to the difference in length and severity of neutropenia of these groups: 37 (34%) centres start the low bacterial diet on admission for autologous transplant patients and 33 (31%) for allogeneic transplant patients. The start of the chemotherapy regime was indicated by 25 (23%) centres for autologous patients and 23 (21%) for allogeneic. The actual blood values were used as an indicator by 27 (25%) centres for autologous patient and 20 (19%) for allogeneic. The blood values mentioned also vary greatly, for example granulocytes < 0.5 x 10^9/l or leucocytes < 1.5/ 1.0/ 0.5 x 10^9/l.

Table 2. Conditions used to start and stop low bacterial diet (LBD) N= 108 respondents

Number / %						
Conditions LBD should be **started** (Autologous SCT)	Admission 37/34.3	Start chemo 25/23.1	Dependant on blood value 27/25.0	Start AB 9/8.3	others 5/4.6	missing 5/4.6
Conditions LBD should be **started** (Allogeneic)	Admission 33/30.6	Start chemo 23/21.3	Dependant on blood value 20/18.5	Start AB 9/8.3	others 5/4.6	missing 18/16.7
Conditions LBD should be **stopped** (Autologous SCT)	Discharge 28/25.9		Dependant on blood value 39/36.1	Stop AB 9/8.3	others 22/20.4	missing 10/9.3
Conditions LBD should be **stopped** (Allogeneic)	Discharge 18/16.7		Dependant on blood value 24/22.2	Stop AB 7/6.5	others 38/35.2	missing 21/19.4

A range of conditions were also identified for stopping the low bacterial diet with blood values being the most common condition mentioned. Particular blood values were indicated by 39 (36%) centres for autologous patients and 24 (22%) for allogeneic. Again a huge variety of values were indicated such as: granulocytes > 0.5 x 10^9/l and 1.0 x 10^9/l, leucocytes > 1.0 x 10^9/l and 1.5 x 10^9/l. A relatively high number of respondents, 22 (20%) for autologous patients and 38 (35%) for allogeneic patients, mentioned other conditions as a reason for stopping, these were mainly time periods for example days, weeks or months following treatment.

Table 3 gives an overview of the diversity of restrictions implemented for 18 specific dietary products. Almost half the respondents (48/44%) imposed

Table 3. Product Restrictions N= 108 respondents. Results presented as n / %

	N /%	Yes				Missing
		Forbidden	Product restriction	Process restriction	Total	
1 Bread	55/ 50.9	-	20/ 18.5	31/ 28.7	51/ 47.2	2/ 1.9
2 Breakfast cereals	52/ 48.1	3/ 2.8	26/ 24.1	22/ 20.4	51/ 47.2	5/ 4.6
3 Meat and poultry	25/ 23.1	3/ 2.8	26/ 24.1	53/ 49.1	82/ 75.9	1/ 0.9
4 Butter or margarine	58/ 53.7	2/ 1.9	40/ 37.0	6/ 5.6	48/ 44.4	2/ 1.9
5 Jam, marmalade or peanut butter	48/ 44.4	-	32/ 29.6	27/ 25.0	59/ 54.6	1/ 0.9
6 Bottled water	56/ 51.9	6/ 5.6	14/ 13.0	28/ 25.6	48/ 44.4	4/ 3.7
7 Tap water	24/ 22.2	41/ 37.9	-	38/ 35.2	79/ 73.1	5/ 4.6
8 Cold drinks such as juices or soft drinks	41/ 38.0	-	10/ 9.3	51/ 47.2	61/ 56.5	6/ 5.6
9 Fresh fruit	6/ 5.6	14/ 12.9	21/ 19.4	61/ 56.5	96/ 88.9	6/ 5.6
10 Raisins, Nuts and other dried fruits	25/ 23.1	46/ 42.6	20/ 18.5	7/ 6.5	73/ 67.6	9/ 8.3
11 Raw vegetables	15/ 13.9	48/ 44.4	16/ 14.8	22/ 20.4	86/ 79.5	7/ 6.5
12 Cheese	7/ 6.5	41/ 38.0	31/ 28.7	23/ 21.3	95/ 88.0	6/ 5.6
13 Spices	32/ 29.6	7/ 6.5	28/ 25.9	35/ 32.4	70/ 64.8	6/ 5.6
14 Wrapped ice-cream	45/ 41.7	21/ 19.4	11/ 10.2	25/ 23.1	57/ 52.8	6/ 5.6
15 Foods brought by visitors	13/ 12.0	32/ 29.6	6/ 5.5	50/ 46.3	88/ 81.5	7/ 6.5
16 Hot meals prepared at home	23/ 21.3	38/ 35.2	-	39/ 36.1	77/ 71.3	8/ 7.4
17 Candy and chocolate	37/ 34.3	7/ 6.5	19/ 17.6	39/ 36.1	65/ 60.2	6/ 5.6
18 Alcoholic drinks	30/ 27.8	51/ 47.2	13/ 12.0	-	64/ 59.3	14/ 13.0

restrictions on all 18 products. Bread and bottled water were the least restricted where over 50% of centres did not restrict them at all. Fresh fruit, (96/ 89%), and cheese (95/ 88%) are the products with the most stringent restrictions. Meat and poultry and fresh fruit has the highest number of process restrictions, 53 (49%) and 61 (56.5) respectively. Food brought into hospital by visitors was found to be frequently restricted (88/81%), and especially so for process restrictions (50/46%). Paradoxically, some respondents report no restrictions for some products where other centres forbid them completely: Raisins, nuts and other dried fruit were reported as having no restrictions in 25/ 23% centres but were forbidden in 46/ 43%. Tap water was reported as having no restrictions in 24/22% centres but forbidden in 41/38%.

Discussion

Although 88 % of the hospitals have guidelines, when these were examined there were enormous differences in both the guidelines themselves and the way in which they are implemented. This is in keeping with finding from previous surveys of low bacterial diet practices [16, 17, 19]. Unexpectedly 10% of centres appear not to use any guidelines during patients stay on the ward. One can only assume that the reason for this is the lack of evidence available to support the efficacy of low bacterial diet in combination perhaps with the growing recognition of the importance of good nutrition on patient outcomes.

The conditions indicated for when to start or stop the low bacterial diet were diverse, predominantly when the patients were admitted or discharged but also depending on a variety of blood values. It would seem that not only do centres use different indicators for starting and stopping dietary restrictions but even when indicators are based on the same thing, such as blood values, there is no consensus on what these values should actually be. It is clear from the diversity of when restrictions start and stop that policymakers are unsure of what to implement because there are no evidence based guidelines.

Furthermore, it is evident that results were not only varied but worryingly often contradict each other, for example products such as tap water or bottled water are forbidden in some centres but allowed in others. This theme also continues with process restrictions where heating food with microwaves is forbidden in some institutions and authorized in others. An

early survey carried out in SCT centres in the UK found that only one out of 20 centres mentioned the use of microwaves at all when questioned [17]. Another survey indicated that the use of microwaves was contraindicated by all centres surveyed [19]. The practice of using microwaves to heat/cook food does seem to have increased; although the opposing views of forbidden against recommended regarding the safety of this practice again highlights the lack of evidence on which to base practice.

An important observation we made from this survey is the possibility that cultural and geographical differences may have an impact on local practice. Although it is not clear from the results there is a definite trend for stricter guidelines when moving from North to South over the European map. For instance the most liberal guidelines are from the Northern countries like Norway, Sweden and Finland. Reasons for this are likely to be diverse. For example the temperature of the environment may play a role. A higher temperature, like in the Southern European countries, is known to be harmful for the preparation of food thus this could impact on differences seen in the guidelines. It's obvious to have in this situation more strict guidelines. Cultural and geographical differences are an area which has not been previously studied in relation to low bacterial diet but one which certainly warrants further investigation.

Limitations

The self selection that results from a survey is a limitation; consequently it is fair to conclude that these results are not necessarily representative of practice elsewhere. The response rate of 43.5% is low although typical of the sample group of health care professionals. However, the results are spread over the majority of countries in Europe and therefore still give a good view of the diversity in which many hospitals deal with the issue of the low bacterial diet.

Conclusion

It is clear from the literature that the evidence base supporting the use of the low bacterial diet is unsubstantiated and in fact the existence of the dietary restrictions which are currently imposed in many institutions where neutropenic patients are cared for seems to be based on a "better safe than sorry" philosophy. This view is highlighted in the results of the survey. Dietary restrictions are generally imposed throughout most of the admission period,

although there is great diversity in the criteria used for starting and stopping restrictions and stopping times seem even more varied. The restrictions which are imposed are varied and sometimes even contradict each other. It is currently unknown as to the amount or types of infection prevented by using low bacterial diet but interestingly some centres do not appear to adhere to strict dietary restrictions for their neutropenic patients without any obvious reports of increase in infection rates.

Implications for practice

More detailed information taken from centres which utilise a more liberal approach to dietary restrictions could form a useful case study series from which further research could possibly develop.

Until further evidence is available, clinicians should assist in identifying clinical practices that require additional research. Ultimately, interventions of neutropenic diet with little or no demonstrated efficacy should be examined systematically or abandoned [31]. It seems that little progress has been made in attempting to standardize practice in relation to low bacterial diet and there is no doubt that nutrition should remain high on the agenda for research. The pilot study carried out by Moody et al. demonstrated that a randomised design can be feasible and while numbers were too small to reach any significant conclusions of efficacy using a particular diet, it certainly leads the way for larger randomised studies [32]. Although these studies remain statistically complicated due to the influence of many parameters linked to hospital infection such as: treatment modalities, diagnosis and antibiotics use. The future would be eventually to develop consensus based or evidence based international guidelines in order to make some progress in this important but neglected area.

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Chapter 7

Low bacterial diet versus normal diet to prevent infection in neutropenic cancer patients treated with chemotherapy: Review information

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Abstract

Background: Neutropenia is a potentially serious side effect of chemotherapy and a major risk factor for infections, which can be life-threatening. It has been hypothesised that a low bacterial diet (LBD) can prevent the occurrence of infections and (infection-related) mortality in cancer patients receiving chemotherapy causing episodes of neutropenia, but much remains unclear.

Objectives: The primary objective was to determine the efficacy of an LBD versus a control diet in preventing the occurrence of infection and to decrease (infection-related) mortality in adult and paediatric cancer patients receiving chemotherapy causing episodes of neutropenia. Secondary objectives were to assess the time to first febrile episode, the need for empirical antibiotic therapy, diet acceptability and quality of life.

Selection criteria: Randomised controlled trials (RCTs) comparing the use of an LBD with a control diet with regard to infection rate, (infection-related) mortality, time to first febrile episode, need for empirical antibiotic therapy, diet acceptability, and quality of life in adult and paediatric cancer patients receiving chemotherapy causing episodes of neutropenia.

Collection and analysis: Two review authors independently performed the study selection, 'Risk of bias' assessment and data extraction. Analyses were performed according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.

Main results: We identified three RCTs assessing different intervention and control diets in 192 patients (97 randomised to intervention diet; 95 to control diet) with different types of malignancies. Co-interventions (e.g. protective environment, antimicrobial prophylaxis, central venous catheter care, oral care, hygiene practices and colony-stimulating factors) and outcome definitions also differed between studies. In all included studies it was standard policy to give empirical antibiotics (and sometimes also antimycotics) to (some of) the patients diagnosed with an infection. Two studies included adults and one study included children. In all studies only a scant description of treatment regimens was provided. All studies had methodological limitations. Pooling of results of included studies was not possible. In two individual studies no statistically significant difference

in infection rate between the intervention and control diet was identified; another study showed no significant difference in the number of chemotherapy cycles with an infection between the treatment groups. None of the studies mentioned infection-related mortality, but in one study no significant difference in overall survival between the treatment groups was observed. Time from onset of neutropenia to fever, the duration of empirical antibiotics and antimycotics, diet acceptability (i.e. following the diet easily and following the diet throughout all chemotherapy cycles) and quality of life were all evaluated by only one study; for all outcomes no statistically significant differences between the treatment arms was observed.

Authors' conclusions: At the moment there is no evidence from individual RCTs in children and adults with different malignancies that underscores the use of an LBD for the prevention of infection and related outcomes. All studies differed with regard to co-interventions, outcome definitions, and intervention and control diets. Since pooling of results was not possible and all studies had serious methodological limitations, no definitive conclusions can be made. It should be noted that 'no evidence of effect', as identified in this review, is not the same as 'evidence of no effect'. Based on the currently available evidence, we are not able to give recommendations for clinical practice. More high-quality research is needed.

Background

Neutropenia, defined as an absolute neutrophil count (ANC) of < 0.5 x 10^9/L, is a potentially serious side effect of chemotherapy and high-dose irradiation (MacVittie 1997) and a major risk factor for infection and sepsis. Neutrophils, constituting 55% to 70% of the circulating white blood cells, have the ability to identify, ingest and destroy the majority of foreign invaders (Candell 1991). When the ANC falls to < 1.0 x 10^9/L there is an increased susceptibility to infection. The frequency and severity of infections is inversely proportional to the neutrophil count and directly proportional to the duration of neutropenia (Hughes 2002). Patients with both solid tumours and hematological malignancies treated with high-dose chemotherapy have a significantly increased risk of developing life-threatening infections.
The infection-related mortality in patients with severe neutropenia is approximately 4% to 6% in adult patients and 0.4% to 1.0% in paediatric patients (Hughes 2002; Pizzo 1999; Roguin 1996). At least 50% of the neutropenic patients who become febrile have an established or occult infection and at least 20% of patients with a neutrophil count of < 0.1 x 10^9/L have bacteraemia (Hughes 2002).
Approximately 80% of the organisms causing infections in neutropenic patients arise from endogenous microbial flora colonising the skin and respiratory, genitourinary and gastrointestinal tracts (Barber 2001). Currently, coagulase-negative staphylococci are the most common blood isolates in most centres; Enterobacteriaceae (i.e. *Enterobacter* species, *Escherichia coli* and *Klebsiella* species) and non-fermenting gram-negative rods (i.e. *Pseudomonas aeruginosa* and *Stenotrophomonas* species) are isolated less often (Freifeld 2011). Invasive fungal infections are also an important cause of morbidity and mortality. Predisposing factors for fungal infections include the use of broad-spectrum antibiotics, corticosteroids, parenteral nutrition, indwelling intravenous catheters and graft-versus-host disease after an allogeneic stem cell transplantation. The most commonly isolated fungal pathogens are *Aspergillus* and *Candida* species (Barber 2001).
Significant advances in supportive care for neutropenic patients have been made since the mid-1990s. Nowadays the supportive care management for neutropenia is directed by risk assessment in adults (Klastersky 2000; Talcott 1992), and evidence-based guidelines for the management of neutropenia and the prevention of opportunistic infections developed by the Centers for Disease Control and Prevention (CDC, US) in both adults and children (Dykewicz 2001; Hughes 2002). These recommendations to prevent

healthcare-associated infections concern the use of antimicrobial prophylaxis, colony-stimulating factors, protective environment, oral care, central venous catheter (CVC) care, hand washing, personal hygiene practices, dietary restrictions and outpatient treatment (Dykewicz 2001). However, despite these achievements, infection continues to be a major cause of morbidity and mortality in the neutropenic patient.

With regards to dietary restrictions it has been hypothesised that a diet for neutropenic patients should reduce pathogens in the gastrointestinal tract by excluding specific foods that may act as a vector for bacteria. The first diet was developed in the 1960s with the intention of providing a completely germ-free diet (Reimer 1966). Since then foods have been sterilised by autoclaving, prolonged baking, gamma irradiation or canning (Aker 1983). Since germ-free diets were considered unpalatable by patients, the US National Institutes of Health, Department of Dietary and Environmental Sanitation, designed the 'cooked-food' diet. Although not germ-free, this diet was aimed at eliminating foods with high bacterial counts (Preisler 1970). In a randomised trial, the National Cancer Institute demonstrated that within a decontaminated environment, a germ-free diet gave little advantage over a cooked-food diet with reference to bacterial stool cultures (Preisler 1970). Although the cooked-food diet was more acceptable to patients than the germ-free diet, patients who adhered to this diet for longer than four to six weeks often became frustrated with the food selection (Moody 2002). Occasionally this diet affected their acceptance of other medical therapies as well, which led clinicians to investigate liberalisation of the diet (Pizzo 1982). Pizzo et al cultured 236 commercially available foods and identified < 500 colony-forming units/g in 66% of these foods. They proposed that these foods were acceptable for neutropenic patients. This liberalised diet became known as the low bacterial diet (LBD) (Pizzo 1982).

The role of diet in the risk of infection in patients with neutropenia is still controversial (French 2001). Dietary restrictions vary in the literature and among institutions. Recommendations range from no dietary restrictions to extensive restrictions. Two surveys (French 2001; Smith 2000) indicated that several differences existed in LBDs used by hospitals in the US. Furthermore, there was much variation regarding the initiation and discontinuation point of the LBD. Few clinical studies have been undertaken to assess the efficacy of the LBD in reducing infection rates in neutropenic patients and currently there is no substantial evidence to prove the benefit of the LBD (Larson 2004). As it may pose an unnecessary burden for patients who already have problems with maintaining an adequate oral intake due to complications of high-dose chemotherapy (e.g. mucositis), it would be beneficial to expand

our knowledge regarding the efficacy of LBD. To our knowledge this is the first systematic review in this area.

Objectives

The primary objective was to determine the efficacy of an LBD versus a control diet in preventing the occurrence of infection and to decrease (infection-related) mortality in cancer patients receiving chemotherapy causing episodes of neutropenia. Secondary objectives were to assess the time to first febrile episode, the need for empirical antibiotic therapy, diet acceptability and quality of life.

Methods

Criteria for considering studies for this review

Types of studies
Randomised controlled trials (RCTs) comparing the use of an LBD versus a control diet.

Types of participants
Cancer patients who received chemotherapy causing episodes of neutropenia. Both adults and children aged one year and above were eligible for inclusion. Children less than one year of age were excluded due to the large differences in metabolism and feeding patterns.

Types of interventions
An LBD versus a control diet. LBD was defined as any diet intended to reduce the ingestion of bacterial and fungal contaminants by the exclusion of foods such as uncooked fruits and vegetables, cold cuts, undercooked eggs and meat, unsterilised water, unpasteurised milk products and soft cheeses. The control diet could be any other diet.

Types of outcome measures

Primary outcomes
- Infection rate (as defined by the authors of the original studies)
- (Infection-related) mortality (as defined by the authors of the original studies)

Secondary outcomes

- Time to first febrile episode (as defined by the authors of the original studies)
- Need for empirical antibiotic therapy (as defined by the authors of the original studies)
- Diet acceptability (as defined by the authors of the original studies)
- Quality of life (as defined by the authors of the original studies)

Search methods for identification of studies

See: Cochrane Childhood Cancer Group (CCG) and Cochrane Gynaecological Cancer Group (GCG) methods used in reviews (Module CCG 2010; Module GCG 2010).

Electronic searches

The following electronic databases have been searched: the Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, issue 3 2011; including earlier searches in 2008 and 2010), the Database of Abstracts of Reviews of Effects (DARE) (*The Cochrane Library*, issue 3 2011; including earlier searches in 2008 and 2010), PubMed (from 1946 to 20 October 2011; including earlier searches in 2008 and 2010), EMBASE (from 1980 to 20 October 2011; including earlier searches in 2008 and 2010) and CINAHL (from 1981 to 20 October 2011; including earlier searches in 2008 and 2010). The search strategies for the different electronic databases (using a combination of controlled vocabulary and text word terms) are stated in the appendices (Appendix 1, Appendix 2, Appendix 3, Appendix 4).

Searching other resources

Information about trials not registered in *The Cochrane Library*, PubMed, EMBASE or CINAHL, either published or unpublished, was located by searching the reference lists of relevant articles and review articles. The following conference proceedings were searched electronically: American Society of Hematology (ASH; from 2000 to 2011), European Bone Marrow Transplantation (EBMT; from 2000 to 2010), Oncology Nurses Society (ONS; from 2000 to 2011), International Society for Paediatric Oncology (SIOP; from 2000 to 2010), Multinational Association of Supportive Care in Cancer (MASCC; from 2000 to 2010), American Society of Clinical Oncology (ASCO; from 2000 to 2011), Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC; from 2000 to 2011), European Society for Clinical Nutrition and Metabolism (ESPEN; from 2000 to 2011), American Society for Parenteral and Enteral Nutrition (ASPEN; from 2000 to 2011) and European Hematology Association (EHA; from 2000 to 2011) (see Appendix

5 for search terms). We have searched for ongoing trials in the register of the National Institute of Health and the ISRCTN Register (via controlled-trials.com; see Appendix 5 for search terms; both were screened in June 2010, October 2011 and May 2012). Researchers working in this area were contacted to enable identification of ongoing trials. Language restrictions were not imposed.

Data collection and analysis

Selection of studies

After employing the search strategy described previously, identification of studies meeting the eligibility criteria were performed by two review authors independently. We obtained any study in full that seemed to meet the inclusion criteria on grounds of the title or abstract, or both, for closer inspection. Reasons for exclusion of any study considered for the review were clearly stated. Disagreement between the review authors was resolved by consensus and no third party arbiter was needed.

Data extraction and management

Data extraction was performed independently by two review authors using standardised forms. Data on study design, characteristics of participants (e.g. age, sex, disease, treatment, antimicrobial prophylaxis, colony-stimulating factors, protective environment, oral care, CVC care, hand washing and hygiene practices), interventions (description of diet in intervention and control group), outcome measures (as described previously) and length of follow-up were extracted. Disagreement between the review authors was resolved by consensus and no third party arbiter was needed.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias in included studies (i.e. selection bias, performance bias, detection bias (for each outcome separately, with the exception of overall mortality, since for that outcome blinding was not relevant), attrition bias (for each outcome separately), reporting bias and other bias). We used the 'Risk of bias' items as described in the module of the CCG (Module CCG 2010), which are based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Reporting bias was assessed by comparing the methods and results sections of the manuscript; protocols were not obtained. Disagreement between the review authors was resolved by consensus and no third party arbiter was needed. The risk of bias in included studies was taken into account in the interpretation of the review's results.

Measures of treatment effect

Dichotomous variables were analysed using risk ratios (RR). All results were presented with the corresponding 95% confidence interval (CI).

Dealing with missing data

When relevant data were missing with regards to study selection, we contacted the principal investigator of the study. Only Van 't Veer 1987 was able to provide additional information. We extracted data by the allocated intervention, irrespective of compliance with the allocated intervention, in order to allow an intention-to-treat analysis. If this was not possible, this was stated and an 'as treated' analysis was performed.

Assessment of heterogeneity

Since pooling of results was not possible, the assessment of heterogeneity (both by visual inspection of the forest plot and by a formal statistical test for heterogeneity. i.e. the I^2 statistic (Higgins 2003; Higgins 2011)) was not applicable.

Assessment of reporting biases

In addition to the evaluation of reporting bias as described in the 'Assessment of risk of bias in included studies' section, we planned to assess reporting bias by constructing a funnel plot when there were a sufficient number of included studies (i.e. at least 10 studies included in a meta-analysis), because otherwise the power of the tests would be too low to distinguish chance from real asymmetry (Higgins 2011)). But since pooling of results was not possible, this was not applicable.

Data synthesis

We entered data into the Review Manager software as provided by The Cochrane Collaboration (RevMan 2011); analyses were performed according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A fixed-effect model was used throughout the review. We performed pooling of results only if study groups were comparable, including the definitions of LBD and the control diet. Studies for which pooling of results was not possible were summarised descriptively.

Sensitivity analysis

Since pooling of results was not possible, sensitivity analyses for 'Risk of bias' items (i.e. exclude studies with a high risk of bias and studies for which the risk of bias is unclear and compare the results of studies with a low risk of bias with the results of all available studies) were not applicable.

Results

Description of studies

Results of the search

Running the searches in the electronic databases of CENTRAL, DARE, PubMed, EMBASE and CINAHL yielded a total of 619 references (n = 373 in 2008, n = 75 in 2010 and n = 171 in 2011). Following initial screening of the titles or abstracts, or both, we excluded 612 references that clearly did not meet all criteria for considering studies for this review. The seven remaining references were assessed in full, of which three fulfilled all the criteria for considering studies for this review and were thus eligible for inclusion (Gardner 2008; Moody 2006; Van Tiel 2007). The other four references were excluded for reasons described in the Characteristics of excluded studies table (DeMille 2006; Fopp 1975; Wilson 2002; Ziegler 1992).

Scanning the reference lists of included articles and reviews did not identify any additional eligible studies. By scanning the ongoing trials databases we identified two ongoing trials (see the Characteristics of ongoing studies table). Researchers working in this area were not aware of any ongoing trials. By scanning the conference proceedings we identified one possible eligible study that has not been published in full yet and is thus awaiting further classification (Van 't Veer 1987; for more information see the Characteristics of studies awaiting classification table), while one study was added to the Characteristics of excluded studies table (Veber 2010).

In summary, the total number of included studies was three. We also identified one study that has not been published in full yet and is awaiting further classification and two ongoing trials. See Figure 1 for a flow diagram of the selection of studies for this systematic review.

Included studies

Characteristics of the included studies are summarised below. For more detailed information see the Characteristics of included studies table.

We identified three RCTs (Gardner 2008; Moody 2006; Van Tiel 2007) assessing different intervention and control diets (see Characteristics of included studies table for more detailed information). The total number of patients included in these three RCTs was 192: 97 were randomised to the intervention groups and 95 to the control groups. Two studies included adults (Gardner 2008; Van Tiel 2007), while one study included children (Moody 2006); patients had different types of hematological malignancies or

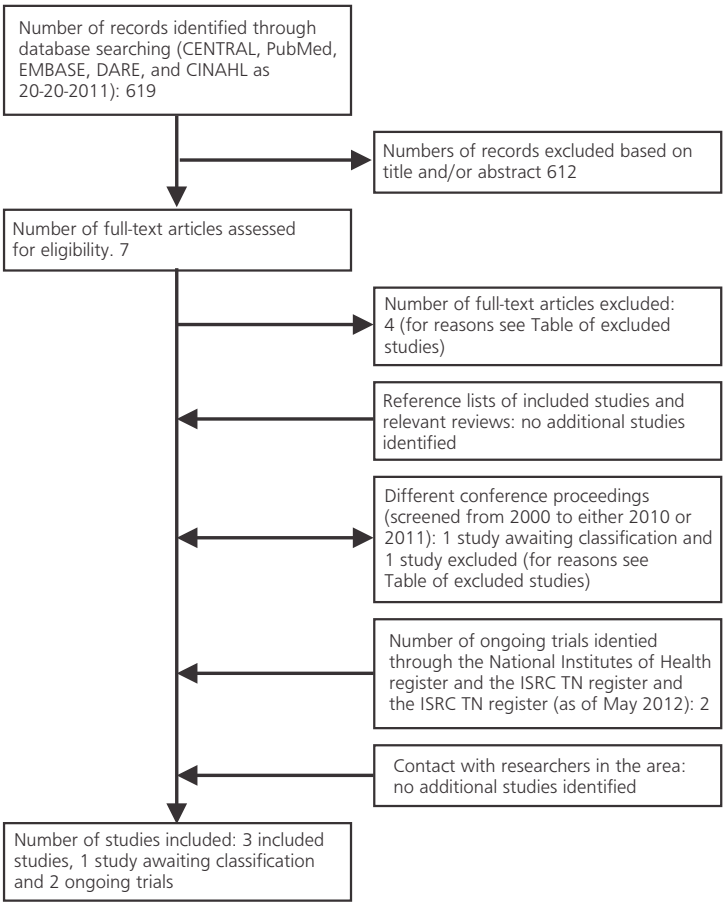

Figure 1. Flow diagram of selection of studies

solid tumours (in all studies only a scant description of treatment regimens was provided).

Supportive care measures differed between studies. In one study patients were treated in high-efficiency particulate air-filtered rooms (Gardner 2008); in the other studies the use of a protective environment was unclear (Moody 2006; Van Tiel 2007). Patients in two studies received antimicrobial prophylaxis, but the type of agents differed between and within studies (Gardner 2008; Van Tiel 2007); in the other study this was unclear (Moody 2006). Granulocyte colony-stimulating factors were used in part of the patients in two studies (Gardner 2008; Moody 2006); in the other study this was unclear (Van Tiel 2007). In two studies all patients had central lines (Gardner 2008; Moody 2006); in the other study this was unclear (Van Tiel 2007). CVC care was not mentioned in any of the studies. Oral care was not

mentioned in any of the studies. Hygiene practices (including hand washing) were not mentioned in two studies (Gardner 2008; Van Tiel 2007), whereas in the other study all patients received hygiene instructions (Moody 2006).

Risk of bias in included studies

See the 'Risk of bias' table of the Characteristics of included studies table and Figure 2 for the exact scores per study and the support for the judgements made.

Allocation (selection bias)

For the evaluation of selection bias we have assessed the random sequence generation and the allocation concealment. Both these items, and thus the risk of selection bias, were unclear in one study (Gardner 2008). In the other two studies (Moody 2006; Van Tiel 2007) there was a low risk of selection bias.

	Van Tiel 2007	Moody 2006	Gardner 2008
Random sequence generation (selection bias)	⊕	⊕	?
Allocation concealment (selection bias)	⊕	⊕	?
Blinding of patients (performance bias)	?	⊕	-
Blinding of health care providers (performance bias)	?	?+	-
Blinding of outcome assessors (detection bias): infections	?	-	?
Blinding of outcome assessors (detection bias): time to first febrile episode		?	
Blinding of outcome assessors (detection bias): duration of empirical antibiotics or antimycotics	?		
Blinding of outcome assessors (detection bias): diet acceptability		?	
Blinding of outcome assessors (detection bias): quality of life		?	
Incomplete outcome data (attribution bias): infections	?	⊕	⊕
Incomplete outcome data (attribution bias): overall survival			⊕
Incomplete outcome data (attribution bias): time to first febrile episode		⊕	
Incomplete outcome data (attribution bias): duration of empirical antibiotics or antimycotics	?		
Incomplete outcome data (attribution bias): diet acceptability		?	
Incomplete outcome data (attribution bias): quality of life		?	
Selective reporting (reporting bias)	⊕	⊕	⊕
Other bias	?	-	?

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

Blinding (performance bias and detection bias)

For the evaluation of performance bias we have assessed the blinding of participants and healthcare providers. In two studies the risk of performance bias was unclear: in Van Tiel 2007 blinding of both participants and healthcare providers was unclear, whereas in Moody 2006 participants were blinded, but for healthcare providers blinding was unclear. In the other study the risk of performance bias was high (Gardner 2008).

For the evaluation of detection bias we have assessed the blinding of outcome assessors for all outcomes separately, with the exception of mortality, since for that outcome blinding was not relevant. Three studies evaluated the infection rate: in two studies the risk of detection bias was unclear (Gardner 2008; Van Tiel 2007), whereas in one study the risk of detection bias was high (Moody 2006). Time to first febrile episode (Moody 2006), need for empirical antibiotic therapy (Van Tiel 2007), diet acceptability (Moody 2006) and quality of life (Moody 2006) were evaluated in only one study; for all these outcomes the risk of detection bias was unclear.

Incomplete outcome data (attrition bias)

For evaluating attrition bias we have assessed incomplete outcome data for all outcomes separately. Three studies evaluated the infection rate: in two studies the risk of attrition bias was low (Gardner 2008; Moody 2006), whereas in the other study this risk was unclear (Van Tiel 2007). The following outcomes were evaluated in only one study: overall survival (Gardner 2008; low risk of attrition bias), time to first febrile episode (Moody 2006; low risk of attrition bias), need for empirical antibiotic therapy (Van Tiel 2007; unclear risk of attrition bias), diet acceptability (Moody 2006; unclear risk of attrition bias) and quality of life (Moody 2006; unclear risk of attrition bias).

Selective reporting (reporting bias)

For evaluating reporting bias we have assessed selective reporting. In all included studies the risk was low.

Other potential sources of bias

For evaluating other potential sources of bias we have assessed differences between the treatment groups for the following items: received anticancer treatment more likely to cause neutropenia, co-interventions (i.e. protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices and colony-stimulating factors) and other (as reported in original study).

In two studies the risk of other potential sources of bias was unclear (Gardner 2008; Van Tiel 2007), whereas in the other study the presence of this type of bias could not be ruled out (Moody 2006). For a more detailed description of all different items see the risk of bias section of the Characteristics of included studies table.

Effects of interventions

Not all articles allowed data extraction for all end points (see the Characteristics of included studies table for a more detailed description of the extractable end points of each article). All RR, 95% CI and P values mentioned below were calculated in RevMan 2011, unless stated otherwise. Unfortunately, due to differences in co-interventions (i.e. protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices, colony-stimulating factors), used outcome definitions and intervention and control diets, it was not possible to pool the results of the included studies. Also, Van Tiel 2007 did not present the necessary data to perform adequate analyses (for further information see below).

Infection rate

All included studies used different definitions of infection rate.
Gardner 2008 assessed the rate of infections (i.e. major infections, minor infections and fever of unknown origin; see Characteristics of included studies table for the exact definition). No statistically significant difference between the treatment groups was identified: 68 out of 78 patients (87%) in the cooked diet group and 57 out of 75 patients (76%) in the raw diet group developed an infection (RR 1.15; 95% CI 0.98 to 1.34; P = 0.08; see Figure 3). Among the 68 infections in the cooked diet group there were 23 major infections (34%), five minor infections (7%) and 40 fevers of unknown origin (59%). In the raw diet group there were 26 major infections (46%), four (7%) minor infections and 27 (47%) fevers of unknown origin. Among the 23 major infections in the cooked diet group there were 12 microbiologically documented infections (52%), whereas among the 26 major infections in the raw diet group there were 22 (85%); this was not reported for minor

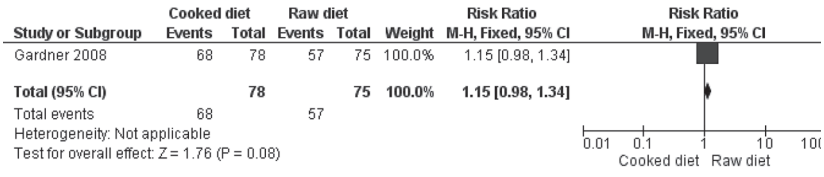

Figure 3. Forest plot of comparison: 1 Cooked diet versus raw diet, outcome: 1.1 Infections (i.e. major infection, minor infection and fever of unknown origin).

infections. Although not explicitly stated, we assumed that in all patients tests to determine the pathogenic organisms were performed. Among the 23 major infections in the cooked diet group there were 12 cases of pneumonia (52%), seven cases of bacteraemia or fungaemia (31%), and four cases of pneumonia and bacteraemia or fungaemia combined (17%), whereas among the 26 major infections in the raw diet group there were four cases of pneumonia (16%), 17 cases of bacteraemia or fungaemia (65%), and five cases of pneumonia and bacteraemia or fungaemia combined (19%); this was not reported for minor infections.

Moody 2006 assessed the rate of neutropenic infections (see Characteristics of included studies table for the exact definition). No statistically significant difference between the treatment groups was identified: four out of nine children (44%) in the US Food and Drug Administration (FDA)-approved food safety guidelines and neutropenic diet guidelines group and four out of 10 children (40%) in the FDA-approved food safety guidelines-only group developed a neutropenic infection (RR 1.11; 95% CI 0.39 to 3.19; P = 0.84; see Figure 4). None of the four neutropenic infections (0%) in the FDA-approved food safety guidelines and neutropenic diet guidelines group were documented (see Characteristics of included studies table for the exact definition), whereas two out of the four neutropenic infections (50%) in the FDA-approved safety guidelines-only group were documented (i.e. one pseudomonas sepsis and one respiratory virus pneumonia).

Van Tiel 2007 did not report the infection rate as number of patients with an infection (defined as a temperature ≥ 38.5°C or < 36°C with a single measurement for which empiric antibiotics were administered), but as number of chemotherapy cycles with infection present. As a result, we could not adequately analyse the infection rate in this study, but we do provide descriptive results: in the LBD group there were 14 chemotherapy cycles with infection (of which seven were microbiologically confirmed (50%)) among 20 chemotherapy cycles given (70%), whereas in the normal hospital-diet group there were 17 chemotherapy cycles with infection (of which seven were microbiologically confirmed (41%)) among 21 chemotherapy cycles given (81%). No significant difference was observed (P = 0.48 as reported in the original article). Please note that this outcome was assessed in all available chemotherapy cycles, but that it was unclear if all patients were evaluated within these cycles; we can therefore not be certain that an intention-to-treat analysis has been performed.

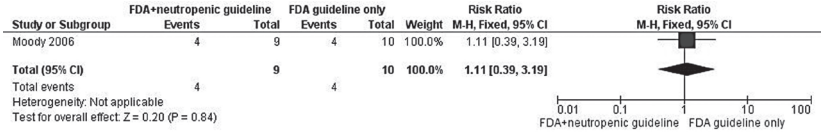

Figure 4. Forest plot of comparison: 2 FDA food safety guideline and neutropenic diet guideline versus FDA food safety guideline only, outcome: 2.1 Neutropenic infection.

(Infection-related) mortality

Infection-related mortality was not mentioned in any of the included studies. Gardner 2008 stated that overall survival (no definition provided) in both treatment groups was as expected in newly diagnosed acute myeloid leukaemia and high-risk myelodysplastic syndrome; no significant difference was observed (P = 0.36 as reported in the original article).

Time to first febrile episode

Time to fever was evaluated in one study. Moody 2006 identified no significant difference in time to fever (defined as time from onset of neutropenia to fever) between both treatment groups (no further information and no significance level provided).

Need for empirical antibiotic therapy

In all included studies it was standard policy to give empirical antibiotics (and sometimes also antimycotics) to (part of) the patients diagnosed with an infection (for more information see the Characteristics of included studies table). Only one study provided explicit data on the use of empirical antibiotics and antimycotics (Van Tiel 2007). In the LBD group the median number of days per chemotherapy cycle with empirical antibiotics and antimycotics was 11 days (range 0 to 22 days) and 0 days (range 0 to 9 days), respectively, whereas in the normal hospital-diet group it was 14.5 days (range 0 to 28 days) and 0 days (0 to 20 days), respectively. No significant difference between treatment groups was detected for duration of empirical antibiotics (P = 0.09 as reported in the original article) or duration of empirical antimycotics (P = 0.96 as reported in the original article). Please note that it was unclear if this outcome was assessed in all patients; we can therefore not be certain that intention-to-treat analyses have been performed.

Diet acceptability

Diet acceptability was evaluated in one study (Moody 2006). In the FDA-approved food safety guidelines and neutropenic diet guidelines group all nine children (100%) reported that they were easily able to follow the guidelines, while seven out of nine children (78%) felt they could follow

them through all chemotherapy cycles. All children (100%) reported some difficulty with the food restrictions, especially avoidance of fast foods and raw fruits. In the FDA-approved guidelines only group nine out of 10 children (90%) reported that they were easily able to follow the guidelines and that they could follow them through all chemotherapy cycles. No significant differences between treatment groups were identified for following the diet easily (RR 1.10; 95% CI 0.84 to 1.45; P = 0.50) and for following the diet throughout all chemotherapy cycles (RR 0.86; 95% CI 0.58 to 1.30; P=0.48) (see Figure 5). Please note that it was not stated if all patients were evaluated for this outcome, although it is likely that they were (it was stated that no patients discontinued the study). An intention-to-treat analysis has been performed.

Quality of life

Quality of life was evaluated in one study. Moody 2006 assessed it using the Peds QL Pediatric Quality of Life Inventory Core Module and Cancer Module by self-reports or parent-proxy reports, or both (Varni 2002) and identified no statistically significant changes in score from baseline to follow-up for either arm by child self-report or parent-proxy report (for both the Core and Cancer Modules; no further information provided). Please note that it was not stated if all patients were evaluated for this outcome, although it is likely that they were (it was stated that no patients discontinued the study). However, we are not certain that an intention-to-treat analysis has been performed.

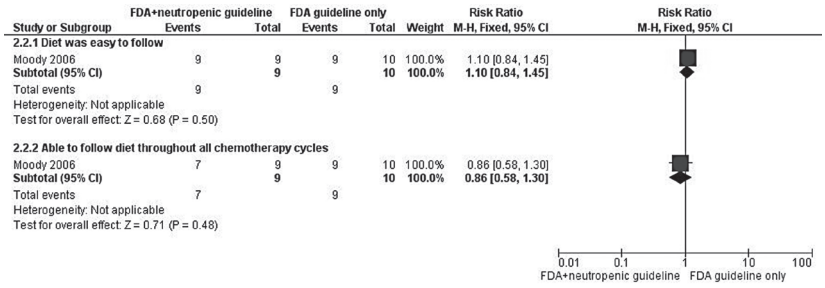

Figure 5. Forest plot of comparison: 2 FDA food safety guideline and neutropenic diet guideline versus FDA food safety guideline only, outcome: 2.2 Diet acceptability.

Discussion

Neutropenia is a potentially serious side effect of chemotherapy and a major risk factor for infections, which can be life-threatening. It has been argued that an LBD can prevent the occurrence of infections and (infection-related) mortality in cancer patients receiving chemotherapy causing episodes of neutropenia, but much remains unclear. To our knowledge this is the first systematic review evaluating this important topic in both adults and children. To ascertain the efficacy of a dietary intervention adequately the best study design, provided that the design and execution are correct, is an RCT in which the only difference between the intervention and control group is the used diet.

We identified three RCTs including a total of 192 patients with different types of hematological malignancies and solid tumours evaluating different intervention and control diets. In all studies only a scant description of treatment regimens was provided. In all included studies it was standard policy to give empirical antibiotics (and sometimes also antimycotics) to (part of) the patients diagnosed with an infection. The first study (Gardner 2008) included adults and defined infection as major infections, minor infections and fever of unknown origin. Patients were randomised to a diet that contained only cooked fruits and vegetables versus a diet that permitted fresh (i.e. raw) fruits and vegetables. Patients were treated in high-efficiency particulate air-filtered rooms and they received antimicrobial prophylaxis. Granulocyte colony-stimulating factors were used in some of the patients. All patients had central lines, but CVC care was not mentioned. Oral care and hygiene practices were not mentioned. The second study (Moody 2006) included children and evaluated neutropenic infections. Patients were randomised between both FDA-approved food safety guidelines and neutropenic diet guidelines versus FDA-approved food safety guidelines only. Granulocyte colony-stimulating factors were used in some of the patients. All patients received hygiene instructions. All patients had central lines, but CVC care was not mentioned. The use of a protective environment, antimicrobial prophylaxis and oral care was not mentioned. The third study (Van Tiel 2007) included adults and defined infection as a temperature ≥ 38.5°C or < 36°C with a single measurement for which empiric antibiotics were administered. Patients were randomised between an LBD and a normal hospital-diet. The use of a protective environment, granulocyte colony-stimulating factors, oral care and hygiene practices were not mentioned, but patients did receive

antimicrobial prophylaxis. It was unclear if patients had central lines; CVC care was not mentioned.
Due to differences in co-interventions (e.g. protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices and colony-stimulating factors), used outcome definitions and intervention and control diets, it was not possible to pool the results of the included studies. This should be kept in mind when interpreting the results of the individual studies. Also, one study did not present the necessary data (i.e. the number of patients with an infection) to perform adequate analyses (Van Tiel 2007).
In two individual studies no statistically significant difference in infection rate between patients receiving the intervention and control diet was identified (Gardner 2008; Moody 2006); the study that did not present the necessary data to perform adequate analyses did not show a significant difference in the number of chemotherapy cycles with an infection between the treatment groups (Van Tiel 2007). Infection-related mortality was not mentioned in any of the included studies, but in one study (Gardner 2008) no significant difference in overall survival (no definition provided) between treatment groups was observed. One study (Moody 2006) evaluated time to fever (defined as time from onset of neutropenia to fever) and identified no significant difference between treatment groups. One study provided data on the use of empirical antibiotics and antimycotics apart from infection rate (Van Tiel 2007). Again, no significant difference in duration of empirical antibiotics and antimycotics between the treatment groups was identified.
One study evaluated diet acceptability (Moody 2006) and no significant differences between treatment groups were identified for following the diet easily and for following the diet throughout all chemotherapy cycles.
Finally, one study evaluated quality of life (Moody 2006) and identified no statistically significant changes in score from baseline to follow-up for either treatment arm by child self-report or parent proxy report.
In this review we tried to perform intention-to-treat analyses, since they provide the most realistic and unbiased answer to the question of clinical effectiveness (Lachin 2000). However, for the assessment of infection rate and the use of empirical antibiotics by Van Tiel 2007 and quality of life by Moody 2006 it was unclear if these outcomes were assessed in all patients, so we cannot be certain that an intention-to-treat analysis has been performed.
'No evidence of effect', as identified in this review, is not the same as 'evidence of no effect'. The reason that no significant difference between treatment groups was identified could be the fact that the number of patients included in these studies was too small to detect a difference (i.e.

low power). Also, it is possible that baseline imbalances between treatment groups (as included in the other potential sources of bias assessment) played a role.
The risk of bias in the included studies varied. Often bias could not be ruled out due to lack of reporting. However, at the moment this is the best available evidence from RCTs comparing an LBD with a control diet.
We are awaiting the results of two ongoing studies (NCT00726934; NCT00947648).

Authors' conclusions

Implications for practice

At the moment there is no evidence from individual RCTs in children and adults with different malignancies that underscores the use of an LBD for the prevention of infection and related outcomes. All studies differed with regard to co-interventions, used outcome definitions, and used intervention and control diets. Since pooling of results was not possible and all studies had serious methodological limitations, no definitive conclusions can be made. It should be noted that 'no evidence of effect', as identified in this review, is not the same as 'evidence of no effect'. Based on the currently available evidence, we are not able to give recommendations for clinical practice.

Implications for research

Before definitive conclusions can be made about the efficacy of different LBDs, more high-quality research is needed. Future trials should preferably be RCTs. They should be performed in homogeneous study populations (e.g. with regards to received anticancer treatment). Also, valid outcome definitions should be used, according to existing guidelines (such as Freifeld 2011). Possible risk factors and preventive measures for neutropenia and infection should be taken into account. The number of included patients should be sufficient to obtain the power needed for the results to be reliable.

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Contributions of authors

Elvira van Dalen performed the data extraction and 'Risk of bias' assessment of the included studies. She analysed the data and interpreted the results. She wrote and revised the review.

Arno Mank designed the study and wrote the protocol. He identified the studies meeting the inclusion criteria. He contributed to the review manuscript and critically reviewed it.

Edith Leclercq developed the updated search strategy for the CENTRAL, DARE and CINAHL databases and she ran the searches in the different databases for the 2010 and 2011 updates. She identified the studies meeting the inclusion criteria. She contributed to the review manuscript and critically reviewed it.

Renée Mulder performed the data extraction and 'Risk of bias' assessment of the included studies. She contributed to the interpretation of the results. She critically reviewed the manuscript.

Michelle Davies designed the study and wrote the protocol. She identified the studies meeting the inclusion criteria. She provided general advice and critically reviewed the review manuscript.

Marie José Kersten provided general advice and critically reviewed the review manuscript.

Marianne van de Wetering designed the study and wrote the protocol. She contributed to the interpretation of the results and provided general advice. She critically reviewed the review manuscript.

All authors approved the final version.

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Characteristics of included studies

Gardner 2008	
Methods	Randomisation performed by the Leukaemia Department Data Management Office using patients' early risk of mortality score as a stratification factor
Participants	153 patients (median age in cooked-diet group 64 years (range 17 to 88 years), median age in raw-diet group 63 years (range 47 to 84 years); sex not reported) with untreated acute myeloid leukaemia (75 in cooked-diet group and 69 in raw-diet group) or high-risk myelodysplastic syndrome (i.e. 10%-19% blasts in marrow or blood) (3 in cooked diet group and 6 in raw diet group). Patients were treated with remission induction chemotherapy on an ongoing leukaemia department protocol
Interventions	Diet that contained only cooked fruits and vegetables (n = 78) versus diet that permitted fresh (i.e. raw) fruits and vegetables (n = 75) Patients in the raw diet group were instructed to eat a fresh fruit or vegetable each day All patients were treated in high-efficiency particulate air-filtered rooms All patients received antimicrobial prophylaxis with levofloxacin, valacyclovir and, depending on protocol, itraconazole, voriconazole (n = 14 in cooked diet group and n = 8 in raw diet group) or a lipid preparation of amphotericin B; no further information provided All patients had central lines; CVC care not reported Oral care not reported Hygiene practices (including hand washing) not reported Granulocyte colony-stimulating factor was used only when there was a delay (i.e. 6 weeks) in neutrophil recovery or after a major infection developed. Its use was equally infrequent in the cooked- and raw-diet groups; no further information provided If fever of unknown origin or pneumonia occurred, patients received intravenous ceftazidime or equivalent; if fever did not resolve, antifungal coverage was broadened; no further information provided
Outcomes	Infections including: • major infections (defined as pneumonia, bacteraemia, fungaemia or pneumonia accompanied by bacteraemia or fungaemia); • minor infections (no definition provided); • fever of unknown origin (no definition provided) A diagnosis of pneumonia required a compatible chest x-ray or computed tomography scan. Bronchoalveolar lavage to isolate a causative organism was performed if no resolution had occurred after 3 to 5 days A diagnosis of bacteraemia as a result of frequent contaminants required 2 positive blood cultures No definition for a diagnosis of fungaemia was provided Overall mortality (no definition provided)
Notes	Median number of days on study: 24 days (range 10 to 47 days) in cooked diet group and 24 days (range 6 to 42 days) in the raw diet group. Patients remained on study until they were discharged from the high-efficiency particulate air-filtered room to the outpatient setting, usually after return of the neutrophil count to more than 500/μL or after 6 weeks in patients in whom neutrophil recovery was delayed All patients remained on the correct diet while on study, although some did not eat a fresh fruit or vegetable each day as suggested There were 206 eligible patients for this study, but 53 refused randomisation; they all choose the cooked fruits and vegetables diet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that patients were randomly assigned to the different treatment groups by the Leukaemia Department Data Management Office using patients early risk of mortality score as a stratification factor, but no further information on the methods of randomisation was provided
Allocation concealment (selection bias)	Unclear risk	It was stated that patients were randomly assigned to the different treatment groups by the Leukaemia Department Data Management Office using patients early risk of mortality score as a stratification factor, but no further information on the methods of randomisation was provided
Blinding of patients (performance bias)	High risk	Compliance with the assigned diet was facilitated by placing notices of this diet on patients' charts and by use of diaries in which patients recorded what they ate each day. As a result patients were not blinded
Blinding of health care providers (performance bias)	High risk	Compliance with the assigned diet was facilitated by placing notices of this diet on patients' charts and by use of diaries in which patients recorded what they ate each day. As a result healthcare providers were not blinded
Blinding of outcome assessors (detection bias): infections	Unclear risk	No information on blinding of outcome assessors was provided
Blinding of outcome assessors (detection bias): time to first febrile episode	Unclear risk	
Blinding of outcome assessors (detection bias): duration of empirical antibiotics or antimycotics	Unclear risk	
Blinding of outcome assessor (detection bias): diet acceptability	Unclear risk	
Blinding of outcome assessor (detection bias): quality of life	Unclear risk	
Incomplete outcome data (attrition bias): infections	Low risk	In all patients the outcome infections was assessed
Incomplete outcome data (attrition bias): overall survival	Low risk	In all patients the outcome overall survival was assessed
Incomplete outcome data (attrition bias): time to first febrile episode	Unclear risk	
Incomplete outcome data (attrition bias): duration of empirical antibiotics and antimycotics	Unclear risk	

Risk of bias table *(Continued)*

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias): diet acceptability	Unclear risk	
Incomplete outcome data (attrition bias): quality of life	Unclear risk	
Selective reporting (reporting bias)	Low risk	There was no protocol mentioned in the manuscript (and we did not search for it), but all expected outcomes are reported
Other bias	Unclear risk	Differences between the treatment groups in baseline characteristics related to outcome: 1) received anticancer treatment more likely to cause neutropenia: unclear (no large difference in types of malignancies, but stage of disease and exact treatment including doses not reported) 2) co-interventions (protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices, colony-stimulating factors): no large differences for protective environment, antimicrobial prophylaxis and colony-stimulating factor use; not reported for the other items (maybe not used at all) 3) other (as reported in original study): not reported

Moody 2006	
Methods	Random numbering was used to assign patients to the treatment groups; patients were randomised in blocks of 10, stratified by disease (i.e. leukaemia, brain tumour or sarcoma)
Participants	19 children (aged 18 years or less, median age in the neutropenic diet group 4.4 years, median age in the FDA food safety group 4.1 years; 8 boys and 11 girls) with a medulloblastoma (2 in each group), acute lymphocytic leukaemia (5 in each group), osteosarcoma (2 in each group) or Ewing's sarcoma (1 patient in the FDA food safety group). Patients were on active treatment with myelosuppressive chemotherapy. Exclusion criteria included comorbid immunosuppressive disease, myeloablative chemotherapy in preparation for bone marrow transplant, documented fever or infection at time of enrolment, patients who could not tolerate oral feeding and concurrent radiation to the central nervous system or gastrointestinal tract
Interventions	Both FDA-approved food safety guidelines (Food Safety 2005) and neutropenic diet guidelines (i.e. not eating raw fruits (except for fruits that could be peeled by hand, such as oranges and bananas), raw vegetables, aged cheeses, cold meat cuts, fast food and take-out food; cook all produce to well done, eggs must be hard-boiled) (n = 9) versus FDA-approved food safety guidelines only (n = 10) Patients were instructed to start following their diet on the first day of the chemotherapy cycle and to continue it until completion of the study period Protective environment not reported Antimicrobial prophylaxis not reported All patients had central lines (either a Broviac/Hickman or a Port-a-Cath); CVC care not reported Oral care not reported Hygiene practices (including hand washing) were included in the FDA food safety guidelines, so all patients received them Use of colony-stimulating factors: 4 patients in the neutropenic diet group and 5 patients in the FDA food safety group received post chemotherapy filgrastim If fever was detected, the patient was admitted to the hospital and started on broad-spectrum antibiotics as per the standard of care; no further information provided
Outcomes	Infections including: • neutropenic infections operationalised to include febrile neutropenia defined as either an oral temperature of ≥ 38°C as measured by parent or documented by clinic/hospital staff and an ANC < 500 x 109/L or admission to hospital and treatment with broad-spectrum antibiotics for presumed infection and an ANC < 500 x 109/L; • documented infections such as positive blood, urine, stool or sputum cultures or positive radiographic evidence of infection including abscess, pneumonia or typhlitis Time to first fever (defined as time from onset of neutropenia to fever) Acceptability of diet (assessed by interviewing the patients and their parents qualitatively with 7 questions) Quality of life (assessed using the Peds QL Pediatric Quality of Life Inventory Core Module and Cancer Module by self-reports or parent-proxy reports, or both; Varni 2002)
Notes	Length of follow-up: not reported (median number of chemotherapy cycles in the neutropenic diet group 5 and in the FDA food safety group 4; no significant difference). Patients were followed until neutrophil recovery (defined as an ANC > 500 x 109/L on 2 consecutive complete blood counts) All patients received their assigned diet and the planned chemotherapy. Diet adherence rate was 94.1% in the intervention group and 99.99% in the control group There were 21 eligible patients for this study, but 2 were not included: 1 refused to participate because of depression and 1 suffered from a new-onset psychosis and was therefore not approached At baseline there were statistically significant differences between treatment groups in history of febrile neutropenia (all patients in the neutropenic diet group versus 5 out of 10 patients in the FDA food safety group) and in quality of life (core module lower in the neutropenic diet group; no significant differences in the cancer module; the authors state that this is most likely secondary to the small sample size)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbering was used to assign patients to the treatment groups
Allocation concealment (selection bias)	Low risk	It was stated that the patients' diet allocation was concealed from the investigator until after the patient consented to participate in the study
Blinding of patients (performance bias)	Low risk	It was stated that patients and their parents were blinded to the intervention
Blinding of health care providers (performance bias)	Unclear risk	It was stated that the medical team was blinded to the intervention (so a low risk of performance bias), but that the primary investigator was not. It was not clear if the primary investigator was involved in patient care, so we cannot know for certain that the risk of performance bias was indeed low
Blinding of outcome assessors (detection bias): infections	High risk	The primary investigator assessed all infections and was not blinded
Blinding of outcome assessors (detection bias): time to first febrile episode	Unclear risk	No information on blinding of outcome assessors was provided
Blinding of outcome assessors (detection bias): duration of empirical antibiotics or antimycotics	Unclear risk	
Blinding of outcome assessor (detection bias): diet acceptability	Unclear risk	No information on blinding of outcome assessors was provided
Blinding of outcome assessor (detection bias): quality of life	Unclear risk	No information on blinding of outcome assessors was provided
Incomplete outcome data (attrition bias): infections	Low risk	All patients were evaluated for this outcome
Incomplete outcome data (attrition bias): overall survival	Unclear risk	
Incomplete outcome data (attrition bias): time to first febrile episode	Low risk	All patients were evaluated for this outcome
Incomplete outcome data (attrition bias): duration of empirical antibiotics and antimycotics	Unclear risk	
Incomplete outcome data (attrition bias): diet acceptability	Unclear risk	It was not stated if all patients were evaluated for this outcome, although it is most likely that they were (it was stated that no patients discontinued the study)

Risk of bias table *(Continued)*

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias): quality of life	Unclear risk	It was not stated if all patients were evaluated for this outcome, although it is most likely that they were (it was stated that no patients discontinued the study)
Selective reporting (reporting bias)	Low risk	There was no protocol mentioned in the manuscript (and we did not search for it), but all expected outcomes are reported
Other bias	High risk	Differences between the treatment groups in baseline characteristics related to outcome: 1) received anticancer treatment more likely to cause neutropenia: unclear (no large difference in types of malignancies, but stage of disease and exact treatment including doses not reported) 2) co-interventions (protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices, colony-stimulating factors): no large differences in hygiene practices and colony-stimulating factors use; not reported for the other items (maybe not used at all) 3) other (as reported in original study): a statistically significant difference in quality of life (lower in neutropenic diet group) and history of febrile neutropenia (higher in neutropenic diet group)

Van Tiel 2007	
Methods	Randomisation performed by using a pre-determined randomisation schedule produced by a computerised randomisation program
Participants	20 cytopenic patients (mean age in the LBD group 51.8 years (range 40 to 69 years), mean age in the normal hospital-diet group 53.3 years (range 30 to 68 years); 5 women and 15 men) with acute lymphoblastic leukaemia (4 in the LBD group and 1 in the normal hospital-diet group: see notes) or acute myelogenous leukaemia (6 in the LBD group and 9 in the normal hospital-diet group: see notes). Patients were treated with remission induction chemotherapy; no further information provided (see notes)
Interventions	LBD (i.e. omits raw vegetables, salads, soft cheeses, raw meat products, most fresh fruits, tap water and spices added after cooking; bread, cheese and ham are individually packed and yogurt deserts, soda drinks and soups are served in single serving containers) (n = 10) versus normal hospital-diet (no further information provided) (n = 10) Patients started their assigned treatment as soon as possible after inclusion Protective environment: not reported All patients received antimicrobial prophylaxis including ciprofloxacin (500 mg every 12 hours, orally) and fluconazole (50 mg every 24 hours, orally). It was adjusted or switched to alternative drugs according to the results of the surveillance cultures; no further information provided. It was started before initiation of chemotherapy and discontinued when leukocyte counts had recovered to ≥ 1000/mm3 It was unclear if patients had central lines; CVC care: not reported Oral care, hygiene practices (including hand washing) and use of colony-stimulating factors: not reported
Outcomes	Infection (defined as a temperature ≥ 38.5°C or < 36°C with a single measurement for which empiric antibiotics were administered) Duration of empirical antibiotics or antimycotics (no definition provided)
Notes	Length of follow-up: not reported (total number of chemotherapy cycles in the LBD group was 20 and in the normal hospital-diet group 20; total number of days within chemotherapy cycles was 406 in the LBD group and 509 in the normal hospital-diet group, it was not stated if this was a significant difference; median number of days per chemotherapy cycle in the LBD group was 18 (range 4 to 34 days per chemotherapy cycle) and in the normal hospital-diet group 24 (range 1 to 39 days per chemotherapy cycle), this was not a significant difference) All patients received their assigned diet Number of eligible patients that were not randomised: not reported It was not stated if the difference in diagnoses (i.e. acute lymphoblastic leukaemia or acute myelogenous leukaemia) between the treatment groups were significant. Also, the exact treatment patients with each diagnosis received was not reported, thus making it impossible to know if patients in 1 of the treatment groups received treatment more likely to cause neutropenia

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by using a pre-determined randomisation schedule produced by a computerised randomisation program
Allocation concealment (selection bias)	Low risk	Randomisation performed by using a pre-determined randomisation schedule produced by a computerised randomisation program
Blinding of patients (performance bias)	Unclear risk	No information on blinding of patients was provided
Blinding of health care providers (performance bias)	Unclear risk	No information on blinding of healthcare providers was provided
Blinding of outcome assessors (detection bias): infections	Unclear risk	No information on blinding of outcome assessors was provided
Blinding of outcome assessors (detection bias): time to first febrile episode	Unclear risk	
Blinding of outcome assessors (detection bias): duration of empirical antibiotics or antimycotics	Unclear risk	No information on blinding of outcome assessors was provided
Blinding of outcome assessor (detection bias): diet acceptability	Unclear risk	
Blinding of outcome assessor (detection bias): quality of life	Unclear risk	
Incomplete outcome data (attrition bias): infections	Unclear risk	This outcome was assessed in all available chemotherapy cycles, but unclear if all patients were evaluated within these cycles
Incomplete outcome data (attrition bias): overall survival	Unclear risk	
Incomplete outcome data (attrition bias): time to first febrile episode	Unclear risk	
Incomplete outcome data (attrition bias): duration of empirical antibiotics and antimycotics	Unclear risk	Unclear if this outcome was assessed in all patients
Incomplete outcome data (attrition bias): diet acceptability	Unclear risk	
Incomplete outcome data (attrition bias): quality of life	Unclear risk	
Selective reporting (reporting bias)	Low risk	There was no protocol mentioned in the manuscript (and we did not search for it), but all expected outcomes are reported

Risk of bias table *(Continued)*

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	Differences between the treatment groups in baseline characteristics related to outcome: 1) received anticancer treatment more likely to cause neutropenia: unclear (there was a difference in types of malignancies, but it was not reported if this was statistically significant; stage of disease and exact treatment including doses not reported) 2) co-interventions (protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices, colony-stimulating factors): no large differences in antimicrobial prophylaxis use; not reported for the other items (maybe not used at all) 3) other (as reported in original study): not reported

Footnotes ANC: absolute neutrophil count; CVC: central venous catheter; FDA: Food and Drug Administration; LBD: low bacterial diet; n: number.

Characteristics of excluded studies

DeMille 2006	
Reason for exclusion	No RCT; no control group
Fopp 1975	
Reason for exclusion	No randomisation of LBD versus a control diet
Veber 2010	
Reason for exclusion	No RCT; infection not evaluated
Wilson 2002	
Reason for exclusion	No RCT; review
Ziegler 1992	
Reason for exclusion	No evaluation of an LBD versus control treatment

Footnotes LBD: low bacterial diet; RCT: randomised controlled trial.

Characteristics of studies awaiting classification

Van 't Veer 1987	
Methods	RCT, but method of randomisation not clear
Participants	42 granulocytopenic children (age (see notes) and sex not reported) with aplastic anaemia, acute lymphocytic leukaemia, acute non-lymphocytic leukaemia or granulocytopenia of unknown origin. Anticancer treatment not reported
Interventions	Cooked-food diet versus standard hospital-food (numbers per group not reported). All patients received partial protective isolation and selective gastrointestinal decontamination

Van 't Veer 1987 *(Continued)*	
Outcomes	42 children had 55 episodes (29 episodes in cooked-food group and 26 episodes in standard hospital-food group) of at least 10 days with granulocyte counts below 500/µL Cooked-food diet (637 study days): • 3 septicaemias, 2 major infections, 2 minor infections and 5 episodes of fever of unknown origin; no deaths from infections; • number of infections per 1000 days at risk (i.e. granulocytes < 500/µL): 11.0 days; • number of febrile episodes per 1000 days at risk (i.e. granulocytes below 500/µL): 7.8 days Standard hospital-food diet (925 study days): • 9 septicaemias, 5 minor infections and 13 episodes of fever of unknown origin; no deaths from infections; • number of infections per 1000 days at risk (i.e. granulocytes below 500/µL): 15.1 days; • number of febrile episodes per 1000 days at risk (i.e. granulocytes below 500/µL): 14.1 days; • number of infections per 1000 days at risk and number of febrile episodes per 1000 days at risk: no significant differences between the treatment groups; • for all other outcomes no level of significance for the difference was mentioned No definitions of the mentioned outcomes were provided
Notes	This study has not been published in full text (checked December 2011); the information provided here is based on a conference abstract of the 1997 edition of the Annual Meeting of the American Society of Hematology and additional information provided by the authors (i.e. from the abstract it was not clear that the participants were children, however, the authors were only able to confirm that participants were indeed children, the exact age range was not provided by them). From the currently available data it is unclear if this study fulfils all inclusion criteria for this review

Footnotes RCT: randomised controlled trial.

Characteristics of ongoing studies

NCT00726934	
Study name	The effectiveness of the neutropenic diet in paediatric oncology patients
Methods	Method of randomisation not clear
Participants	Patients (aged 1 to 30 years) with different paediatric malignancies receiving a cycle of chemotherapy that predictably renders neutropenia at least 70% of the time or has a risk of febrile neutropenia of at least 20%
Interventions	Low bacterial/neutropenic diet (e.g. excluding raw food and vegetables) versus FDA-approved food safety guidelines
Outcomes	Neutropenic infection, documented infection and quality of life
Starting date	sep-07
Contact information	Principal investigator Karen Moody
Notes	No full-text publication available as per 17 May 2012

NCT00947648	
Study name	Are neutropenic diets beneficial to improve outcome?
Methods	Method of randomisation not clear
Participants	Patients (aged 18 years or older) with acute myelogenous leukaemia, acute lymphocytic leukaemia or myelodysplastic syndrome who will be receiving myelosuppressive chemotherapy
Interventions	Raw diet (i.e. cooked food and in addition raw fruits and vegetables) versus cooked diet (i.e. the standard neutropenic diet with only cooked food)
Outcomes	Infection rate, incidence of fever requiring intravenous antibiotics and death rate
Starting date	July 2009
Contact information	Principal investigator Alison Gardner
Notes	No full-text publication available as per 17 May 2012

Footnotes FDA: Food and Drug Administration.

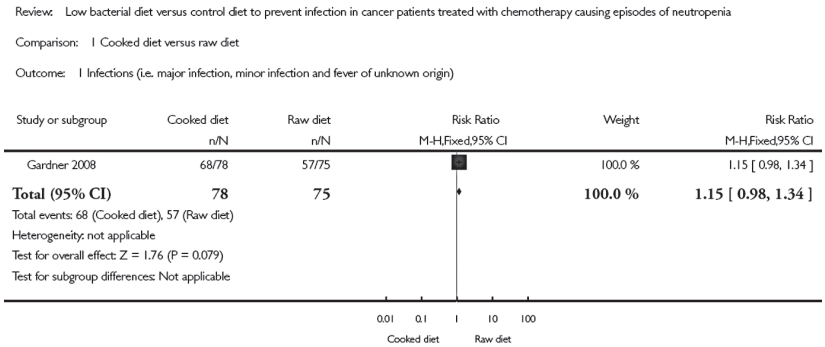
Data and analyses

Comparison 1. Cooked diet versus raw diet

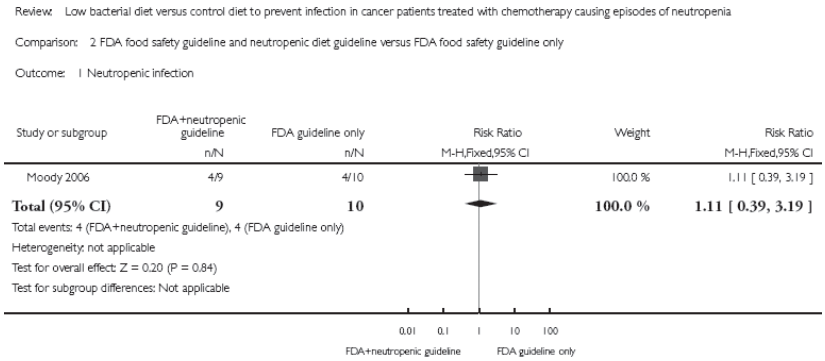
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect size
1.1 Infections (i.e. major infection, minor infection and fever of unknown origin)	1	153	Risk Ratio(M-H, Fixed, 95% CI)	1.15[0.98, 1.34]

Comparison 2. FDA food safety guideline and neutropenic diet guideline versus FDA food safety guideline only

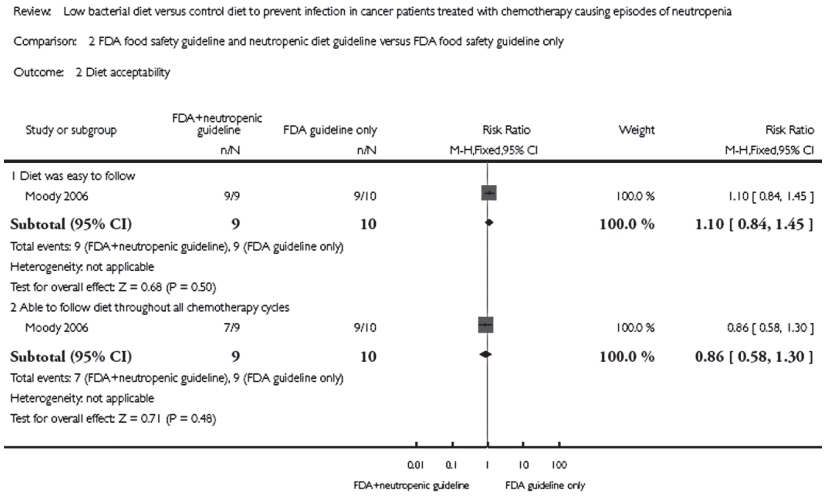
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect size
2.1 Neutropenic infection	1	19	Risk Ratio(M-H, Fixed, 95% CI)	1.11[0.39, 3.19]
2.2 Diet acceptability	1		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
2.2.1 Diet was easy to follow	1	19	Risk Ratio(M-H, Fixed, 95% CI)	1.10[0.84, 1.45]
2.2.2 Able to follow diet throughout all chemotherapy cycles	1	19	Risk Ratio(M-H, Fixed, 95% CI)	0.86[0.58, 1.30]



Analysis 1.1. Comparison 1 Cooked diet versus raw diet, Outcome 1 Infections (i.e. major infection, minor infection and fever of unknown origin)



Analysis 2.1. Comparison 2 FDA food safety guideline and neutropenic diet guideline versus FDA food safety guideline only, Outcome 1 Neutropenic infection



Analysis 2.2. Comparison 2 FDA food safety guideline and neutropenic diet guideline versus FDA food safety guideline only, Outcome 2 Diet acceptability

chapter 7

Appendices

1 PubMed search strategy

bone marrow transplantation[mesh] OR bone marrow transplantation[tw] OR cytopen*[tw] OR stem cell transplantation[mesh] OR stem cell transplantation[tw] OR agranulocytosis[mesh] OR agranulocytosis[tw] OR bacterial translocation[mesh] OR bacterial translocation[tw] OR immunocompromised host[mesh] OR immunocompromised host[tw]

OR neutropeni*[tiab] OR leukopeni*[tiab] OR leucopeni*[tiab] OR granulocytopeni*[tiab] OR immunocompromized[tiab] OR immunocompromised[tiab] AND ((sterile[tiab] OR clean[tiab] OR low bacteria*[tiab] OR low microb*[tiab] OR minimal bacteria*[tiab] OR minimal microb*[tiab] OR germ poor[tiab] OR cooked[tiab] OR reduced bacteria*[tiab]) AND (diet[mesh] OR diet[tw] OR feeding[tiab] OR dietar*[tiab] OR food*[tiab] OR nutrition[tiab]) OR dietary restriction*[tiab]) [tw = text word; tiab = title or abstract; mesh = medical subject heading; * = zero or more characters]

2 EMBASE (Ovid) search strategy

1 agranulocytosis.mp. or exp AGRANULOCYTOSIS/
2 stem cell transplantation.mp. or exp stem cell transplantation/
3 bone marrow transplantation.mp. or exp bone marrow transplantation/
4 bacterial translocation.mp. or exp Bacterial Translocation/
5 exp Immune Deficiency/
6 (neutropeni$ or leukopeni$ or cytopeni$ or granulocytopeni$ or leucopeni$ or immunocompromized or immunocompromised).tw.
7 or/1-6
8 (sterile or clean or low bacteria$ or low microbia$ or minimal bacteria$ or minimal microbia$ or germ poor or neutropenic or cooked or reduced bacteria$).tw.
9 exp Diet/
10 (diet$ or water or feeding or food$ or nutrition).tw.
11 8 and (9 or 10)
12 dietary restriction$.tw.
13 11 or 12
14 7 and 13

[tw = text word; / = Emtree term; $ = zero or more characters; mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

3 CENTRAL and DARE (The Cochrane Library) search strategy

1 MeSH descriptor Agranulocytosis explode all trees in MeSH products
2 MeSH descriptor Bacterial Translocation explode all trees in MeSH products
3 MeSH descriptor Immunocompromised Host explode all trees in MeSH products

4 (agranulocytosis or bacterial translocation or immunocompromised or cytopeni* or immunocompromized or neutropeni* or leukopeni* or leucopeni* or granulocytopeni*)
5 (1 OR 2 OR 3 OR 4)
6 MeSH descriptor Diet explode all trees in MeSH products
7 (low near bacteria* or low near microbia* or minimal near bacteria* or minimal near microbia* or germ near poor or neutropenic or cooked or reduced near bacteria* or sterile or clean)
8 (diet* or feeding or food* or water or nutrition)
9 (6 OR 8)
10 (dietary restriction*)
11 ((7 AND 9) OR 10)
12 (5 AND 11)
13 (dietary near restriction*)
16 (12)
17 MeSH descriptor Bone Marrow Transplantation explode all trees
18 MeSH descriptor Stem Cell Transplantation explode all trees
19 (bone marrow transplantation):ti,ab,kw or (stem cell transplantation):ti,ab,kw
20 (5 OR 17 OR 18 OR 19)
21 (7 AND 8)
22 (21 OR 13)
23 (20 AND 22)

Adjusted search strategy used in June 2010 and October 2011:

1 MeSH descriptor Agranulocytosis explode all trees
2 MeSH descriptor Bacterial Translocation explode all trees
3 MeSH descriptor Immunocompromised Host explode all trees
4 (agranulocytosis or bacterial translocation or immunocompromised or cytopeni* or immunocompromized or neutropeni* or leukopeni* or leucopeni* or granulocytopeni*)
5 (1 OR 2 OR 3 OR 4)
6 MeSH descriptor Diet explode all trees
7 (low near bacteria* or low near microbia* or minimal near bacteria* or minimal near microbia* or germ near poor or neutropenic or cooked or reduced near bacteria* or sterile or clean)
8 (diet* or feeding or food* or water or nutrition)
9 (dietary restriction*)
10 (dietary near restriction*)
11 (6 OR 7 OR 8 OR 9 OR 10)

12 MeSH descriptor Bone Marrow Transplantation explode all trees
13 MeSH descriptor Stem Cell Transplantation explode all trees
14 (bone marrow transplantation) or (stem cell transplantation):ti,ab,kw
15 (5 OR 12 OR 13 OR 14)
16 (11 AND 15)
[ti,ab,kw = title or abstract or keywords; * = zero or more characters]

4 CINAHL search strategy

S1 AB sterile or clean or low bacteria$ or low microbia$ or minimal bacteria$ or minimal microbia$ or germ poor or neutropenic or cooked or reduced bacteria$
S2 TI sterile or clean or low bacteria$ or low microbia$ or minimal bacteria$ or minimal microbia$ or germ poor or neutropenic or cooked or reduced bacteria$
S3 S2 or S1
S4 MH diet+
S5 AB diet$ or water or feeding or food$ or nutrition
S6 TI diet$ or water or feeding or food$ or nutrition
S7 S6 or S5
S8 S7 or S4
S9 S8 and S3
S10 MH agranulocytosis+ or bacterial translocation+ or bone marrow transplantation+ or immunocompromised host+
S11 AB neutropeni$ or leukopeni$ or granulocytopeni$ or leucopeni$ or immunocompromized or immunocompromised or agranulocytosis or bone marrow transplantation or stem cell transplantation or bacterial translocation or cytopen$
S12 TI neutropeni$ or leukopeni$ or granulocytopeni$ or leucopeni$ or immunocompromized or immunocompromised or agranulocytosis or bone marrow transplantation or stem cell transplantation or bacterial translocation or cytopen$
S13 S12 or S11 or S10
S14 AB dietary restriction$
S15 TI dietary restriction$
S16 S15 or S9
S17 (S15 or S9) and (S16 and S13)
Adjusted search strategy used in June 2010 and October 2011:
S1 AB sterile or clean or low bacteria$ or low microbia$ or minimal bacteria$ or minimal microbia$ or germ poor or neutropenic or cooked or reduced bacteria$

S2 TI sterile or clean or low bacteria$ or low microbia$ or minimal bacteria$ or minimal microbia$ or germ poor or neutropenic or cooked or reduced bacteria$
S3 S2 or S1
S4 MH diet+
S5 AB diet$ or water or feeding or food$ or nutrition
S6 TI diet$ or water or feeding or food$ or nutrition
S7 S6 or S5
S8 S7 or S4
S9 S8 and S3
S10 MH agranulocytosis+ or bacterial translocation+ or bone marrow transplantation+ or immunocompromised host+
S11 AB neutropeni$ or leukopeni$ or granulocytopeni$ or leucopeni$ or immunocompromized or immunocompromised or agranulocytosis or bone marrow transplantation or stem cell transplantation or bacterial translocation or cytopen$
S12 TI neutropeni$ or leukopeni$ or granulocytopeni$ or leucopeni$ or immunocompromized or immunocompromised or agranulocytosis or bone marrow transplantation or stem cell transplantation or bacterial translocation or cytopen$
S13 S12 or S11 or S10
S14 AB dietary restriction$
S15 TI dietary restriction$
S16 S14 or S15
S17 S16 or S9
S18 S17 and S13

[AB = abstract; TI = title; MH = exact subject heading; $ = zero or more characters; + = explosion]

5 Ongoing trial registers and conference proceedings search strategies

We have searched the register of the National Institutes of Health and the ISRCTN register (via www.controlled-trials.com) with the following key words: low bacterial AND diet; neutropenic AND diet; low bacterial AND cancer.

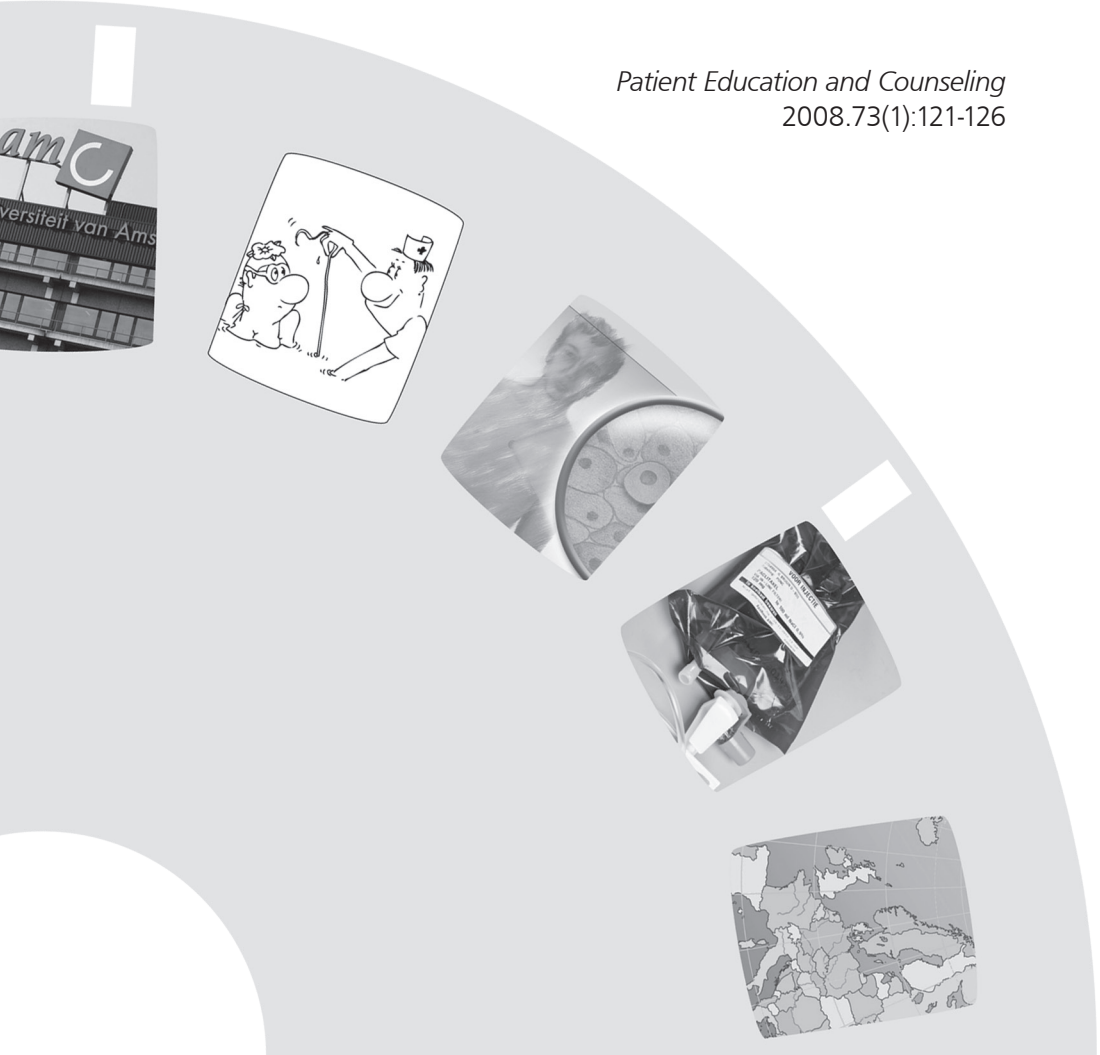
The conference proceedings (ASH, ASCO, ASPEN, EBMT, EHA, ESPEN, ICAAC, MASCC, ONS and SIOP) were searched electronically using the following search terms: “neutropenic diet”, “low bacterial”, “hospital diet”, “normal diet”, and LBD.

Chapter 8

An interactive CD-ROM to inform patients about Stem Cell Transplantation

Arno Mank and Sjaak Molenaar

Patient Education and Counseling
2008.73(1):121-126



Abstract

Introduction: Cancer patients receiving chemotherapy or a Stem Cell Transplantation (SCT) are in need of information about their disease, treatment options and side effects. Patient education usually has to be given within limited time. Under these circumstances, patients may find it difficult to completely understand and to retain the information given.

Methods: As a supplement to standard information methods we developed an interactive CD-Rom with information on SCT. This CD-Rom provides both medical information and more subjective patients' experiences. Part one provides information regarding the treatment course from diagnosis through to post-discharge care. The second part consists of interviews with former patients and describes their experiences.
As the system is interactive, it can be utilized according to the patient's individual preferences. The CD-Rom comprises audio, video, animations, pictures, and text. Printing of certain sections is optional. The technical format of the CD-Rom makes it relatively simple to utilise the information and to make it suitable for other institutions or even other treatments. In this preliminary study the acceptability of the interactive CD-Rom by patients undergoing a SCT is described.

Results: Patients' overall evaluations of the interactive CD-Rom were highly positive. For example, 90.2% (N=51) found it interesting, clear, useful and valued getting information by means of a CD-Rom. Most patients would recommend the interactive CD-Rom to other patients in the same situation.

Conclusion: The content of the CD-Rom on SCT as well as the computer-based, interactive method are well accepted by patients. Practice implications: Computer-based education may enhance patient education and thus the quality of patient care. We must now establish the program's effectiveness. Moreover, plans have been developed to disseminate the information on SCT over the Internet. Future development of comparable programs and their evaluation should be encouraged to promote the well-being of cancer patients.

Introduction

Patient education is an important aspect of good-quality care. Most patients prefer to receive detailed, tailored information, especially in the case of life-threatening diseases like cancer [1-3]. For example, 87% of the patients in an English study wanted to have all possible information about diagnosis, treatment, treatment outcomes, side effects and quality of life [4]. Education is especially important in cancer care since patients and their families are faced with many difficult decisions that have a large impact on their health and quality of life [5]. Many patients turned to the Internet for information [6]. Cancer patients may engage in interactions with fellow patients to exchange information and emotional support.

Adequate communication

Patients have a legal right to be informed about their disease [7]. However, information giving and participation in decision making is not without problems. In a study with cancer patients, 54 percent said they were not informed adequately [8].

Several factors have been identified that hinder the exchange of information. For example, after a diagnosis of cancer, emotions may inhibit information processing. Adequate communication implies that health care providers are sensitive to patients' emotional state, and that they adapt the provision of information toward patients' emotional and cognitive functioning. Low health literacy may also complicate information giving [9, 10]. In addition, insufficient skills of the health care provider may complicate information giving. Physicians may over or under estimate patients' information needs. Moreover, their language may complicate the patients' ability to understand information. Lack of time, low quality of information materials, and lack of privacy may also give problems. Finally, patients are often seen by many health care providers. Rarely has a systematic coordination of the provision of information been taken care off. As a result gaps, contradictions and duplications in the process may occur.

Interactive CD-Rom as a solution to information needs

Several interventions have been developed to improve information giving to patients. Since the 90's Internet and CD-Rom technology are used to provide patient education [2].

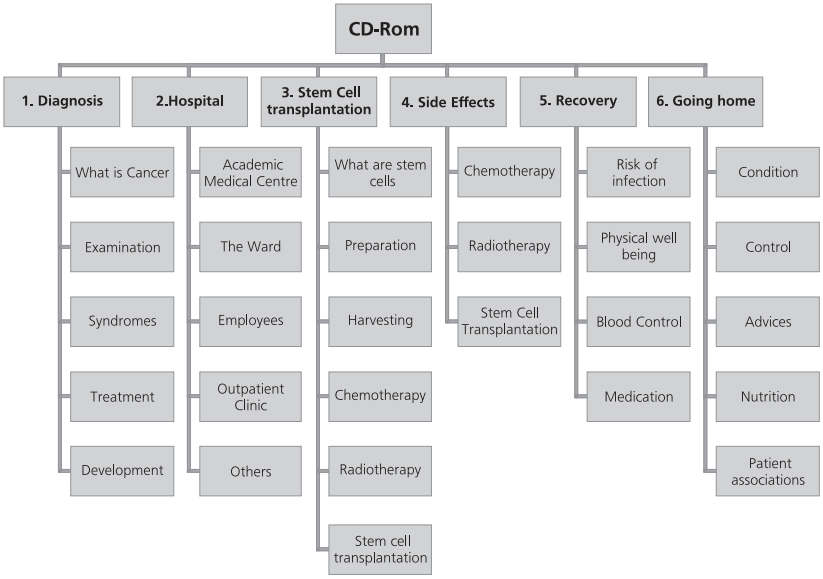


Figure 1. Module 1: from diagnosis through post-discharge care

Two systematic reviews concluded that computer-based patient education is effective in improving knowledge, health attitudes, shared decision-making, health services utilization, costs, and clinical outcomes [11, 12].
Interactive CD-ROMs may enhance education, learning, and the quality of patient care [13]. For example, a CD-Rom regarding childhood leukaemia has been developed for children and parents. It was found to be useful, engaging and empowering [14]. Moreover, cancer-related computer-based patient education was found to provide a greater depth of content, and better able to satisfy a broad range of educational needs, compared to other media [15]. Several other studies have found that computer programmes are accepted across educational and socioeconomic levels [16] and ages [17].
Our own institute developed and evaluated an interactive CD-Rom with information for breast cancer patients on treatment options. Patients who were given the CD-Rom were more satisfied with patient care, and their quality of life improved [18]. In a subsequent project, an interactive CD-Rom was developed for patients receiving chemotherapy and, subsequently, a Stem Cell Transplantation (SCT). This CD-Rom is used by health care providers like the physician, the SCT coordinator and nurses as a supplement to information which is given in consultations. In the current paper, patients' acceptance of this interactive CD-Rom is being addressed.

Development of the interactive CD-Rom

First we installed a team of professionals with varying competencies in the areas of oncology, psychology, patient education and Information and Communication Technology (ICT). Secondly, the informational content was derived from treatment protocols and procedures in our institute. Third a demonstration version was constructed for pilot testing.
The resulting CD-Rom presents combinations of photographs, animations, videos, and text with underlying verbal explanations from a hematologist and fellow patients. All textual components can be printed.
The informational content of the CD-Rom has been split into two sections. The first section is divided into six modules. This section of the CD-Rom addresses more-or-less 'objective' information regarding the diagnosis, treatments, side-effects etc. (figure 1). The second section addresses the subjective experiences of patients who underwent an SCT. The age, sex, and diagnosis of those patients chosen to be interviewed and videotaped varied to provide a broad picture of experiences. Most of the interviewed patients were members of the patient association for cancer patients, with the remaining participants being made up of former patients from our hospital. The interviews were conducted by a medical psychologist using a structured questionnaire. Patients may use both sections interchangeably depending on their desire (figure 2).

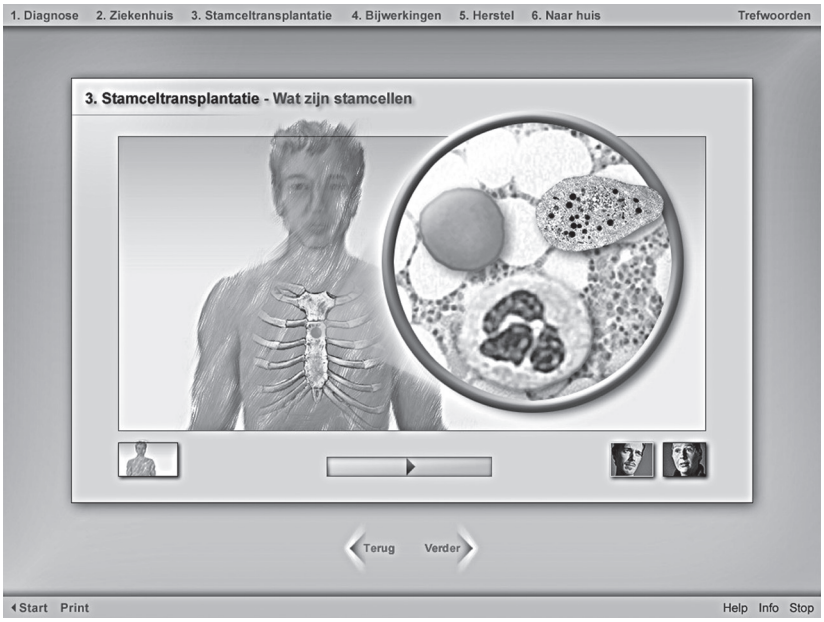


Figure 2. Print screen from the program

Method

To assess the interactive CD-Rom's acceptability we used a one group post-test only design. All consecutive patients eligible for a SCT between June 2006 - 2007 were asked to participate, with the exception of patients not familiar with Dutch. Patients were invited to participate by the SCT-coordinator. A questionnaire was developed for the current study. Questions were related to patients' socio-demographic background: e.g. age, sex, marital status, education. Patients were asked with whom the CD-Rom was used.
The second part of the questionnaire was related to the content of the interactive CD-Rom itself. The items were: A: Overall rating of the whole program? B: Is it interesting? C: Was it clear? D: Was it useful in my situation? E: Was it encouraging or discouraging? F: Was it comforting or distressing? G: Is it useful to get this information by CD-Rom? H: How is the interactive method assessed? I: Would the CD-Rom be recommend to other patients? J: What's the value of video fragments featuring fellow patients? K: How is the quantity of the information evaluated?
Each question could be answered using a five-point scale ranging, for example from 1: very interesting to 5: not interesting at all. From the items A. until J. the ratings 1 and 2 indicate a positive response to the information and 4 and 5 a negative response to the information, In the item K. (quantity of information) the response the middle response is the most positive (1 and 2 indicate too much information, 4 and 5 indicate too little information and 3 is the correct quantity)
Patients were also asked to rate each module of the program from 1 to 10 were 1 was the lowest and 10 the highest possible rating. Furthermore, patients could give comments on the quality and the content of the interactive CD-Rom: what they had missed, or appreciated, could be expressed in written comments in the questionnaire.

Procedure

Prior to the study five patients were asked to fill in the questionnaire for validity and reliability testing. As a result small changes were made in the questionnaire.
During the study period, eligible patients first had a standard consultation with the hematologist, and subsequently with the SCT-coordinator. At the end of the consultation with the SCT-coordinator, patients received the CD-Rom which they took home together with instructions how to use the CD-Rom. In

addition, all patients receiving the CD-Rom received the questionnaire. They were asked to return the questionnaire within three weeks in a pre-stamped envelope. When they did not respond within the given timeframe patients received a reminder. All the patients consented to participate.

Results

There were 66 consecutive patients eligible for a SCT between June 2006 – 2007. Four patients were excluded because they didn't understand Dutch. Thus, the CD-Rom was offered to 62 patients. Eleven patients (18%) failed to complete the questionnaire; where upon the response group consisted of 51 patients (82%). Reasons for not returning the survey were diverse. Seven patients (11%) were emotionally unable and/or too sick to view the CD-Rom, two patients (3%) could not be reached at home, and two patients (3%) had died.

Table 1. Demographic N = 51

Characteristic	**n**	**%**
Sex		
Male	27	53
Female	24	47
Mean Age in years (Range)	50.6	25-73
Marital status (%)		
Living alone	11	22
Married/ /Lives with partner	32	63
Divorced/Widow, Widower	6	12
Highest level of education		
Primary education	4	8
Secondary education	9	18
Vocational training	19	37
Higher Vocational education	15	29
University education	4	8
With whom is the CD-Rom watched?		
Alone	15	30
Partner	25	49
Friends	4	8
Others	7	14

Background

Of the 51 respondents 27 (53%) were male and 24 (47%) were female (table 1). Patients' mean age was 51 years (range 25-73). Slightly more than half of the patients (32; 63%) were married or lived together with a partner. Nineteen patients (37%) had a vocational training. As table 1 indicates, the majority of patients (36; 70%) viewed the interactive CD-Rom with a partner or a friend (Table 1).

Acceptability

Table 2 shows patients' ratings of the information provided with the interactive CD-Rom. Patients perceived that the program was interesting (27; 53%) or even very interesting (23; 45%). The clarity of the information gives comparable results: very clear (17; 33% and clear (28; 55%). 37 (72%) of the patients finds the information useful. Two patients (4%) found the interactive CD-Rom discouraging, however a considerable number of other patients (19; 37%) found it encouraging. Eleven patients (22%) found the information distressing; while 13 patients (25%) said that it was comforting. The amount of information given was exactly right for 41 patients (80%). Patients said that the computer-based education was 'pleasant' (31; 61%) or very pleasant (16; 31%). The interactive format of the device was also rated good (32; 63%) or excellent (13; 25%). One comment was: "nice *graphics and videos, gives more in-depth information".*

Most patients (41; 80%) would recommend the CD-Rom "indeed" or "probably" to other patients in the same situation. One patient made the comment *"Wish I had it when I was diagnosed".* Almost half of the patients

Table 2. Patients' ratings information provided with the CD-Rom N = 51

number (%)	**1**	**2**
A. Overall rating?	Excellent 20 (40)	Good 26 (51)
B. Interesting?	Very Interesting 23 (45)	Interesting 27(53)
C. Clear?	Very Clear 17 (33)	Clear 28 (55)
D. Useful?	Very Useful 09 (18)	Useful 37(72)
E. Hope?	Very Encouraging 1 (2)	Encouraging 19 (37)
F. Emotional impact?	Very Comforting -	Comforting 13 (25)
G. Computer-based method?	Very Pleasant 16 (31)	Pleasant 31 (61)
H. Interactive character?	Excellent 13 (25)	Good 32 (63)
I. Recommended to other patients?	Yes 23 (45)	Probably Yes 18 (35)
J. Videos fellow patients?	Very Important 4 (8)	Important 19 (37)
K. Quantity of information?	Much too much -	Too much 08 (16)

(23; 45%) rated the videos from fellow patients as 'important' or 'very important'. A considerable number of patients (21; 41%) said that these videos were of 'average importance' and seven patients (14%) found it 'less important or 'not important at all'.
The overall rating for the information provided with CD-Rom was 'excellent' for 20 patients (40%) and 'good' for 26 patients ((51%). The following quote illustrates the highly positive evaluations given to the overall program overall:

> "*It (the CD-Rom) is well executed and flows well and covers a lot of information clearly. It is user-friendly which is important. I enjoyed watching it, and when I watched it, it was a revelation to me. I think this information offers support to future patients".*

Table 3 presents ratings for each module. All mean scores were above seven (range 5-10). The module on the procedure and practice of the SCT scored highest with a mean score of 8.3 (range 6-10).
Perceived missing topics were sexuality and palliative care. Moreover, patients indicated that they had expected more information about harvesting of the transplant and donor issues.

Discussion

This study demonstrates the acceptability of an interactive CD-Rom for SCT patients. The overall rating of the CD-Rom was excellent (90%); moreover, most patients gave high scores for the clarity of the CD-Rom and they found it interesting and useful. A large majority of the patients would recommend

3	**4**	**5**
Average 04 (8)	Moderate 1 (2)	Insufficient -
Average 1 (2)	Uninteresting -	Not Interesting -
Average 6 (12)	Not Clear -	Not Clear at all -
Average 5 (10)	Not Useful	Not Useful at all -
Average 29 (57)	Discouraging 2 (4)	Very Discouraging -
Average 27 (53)	Distressing 11 (22)	Very Distressing
Average 4 (8)	Unpleasant -	Very Unpleasant -
Average 6 (12)	Moderate -	Insufficient -
Possible 10 (20)	Probably Not -	No -
Average 21 (41)	Less Important 06 (12)	Not Important 1 (2)
Exactly right 41 (80)	Too little 2(4)	Much too little -

Table 3. figure of importance from 1 to 10

	Mean (Range)	Missing (%)
1. Diagnosis	7.8 (5-10)	2 (3.9)
2. Hospital	7.6 (5-10)	1 (1.9)
3. Stem Cell Transplantation	8.3 (6-10)	-
4. Side effects	8.0 (6-10)	-
5. Recovery	7.8 (5-10)	-
6. Going Home	7.8 (5-10)	-

the CD-Rom to other patients. Patients appreciated getting information by means of an interactive system. This finding is in accordance with findings of Bader [19] and Lambing [20].

Patients' perceptions of the videos of fellow patients were more variable. Some liked it, whereas others did not. One might assume that these latter patients were less in need of social comparison and/or possibly perceived information from fellow patients as too personal or frightening.
The SCT Module was given the highest score. We speculate that it is the most acute and pressing issue for patients at that moment.

A few limitations of this study should be acknowledged. First, a one group, post-test only design was used. Due to the absence of a pre-test, and a control group condition we cannot draw any conclusions regarding he program's effectiveness. Second, the interactive CD-Rom was provided to patients in the context of a study project. Consequently, patients may have received more personal attention, information and education than they would have had under other circumstances. This may have influenced the results. Third, a new means of patient education was tested and patients were told they were the first to receive and view this innovation. As a result, a so-called bias-by-novelty effect may have occurred.
Despite the positive evaluation of the interactive CD-Rom some questions remain. We do not know how long and how often the patients have utilised the CD-Rom? Moreover, we do not know the exact influence of the friends and family members on the patient evaluations.

Conclusion

The interactive CD-ROM on SCT is well accepted by patients and they appreciated getting information by means of an interactive system. Most

patients would recommend the interactive CD-Rom to other patients in the same situation.
Development of interactive patient education that includes medical information and the subjective experiences of patients may enhance the quality of patient care.
Further developments of comparable support programs, and their evaluation, should be encouraged to promote well-informed cancer patients.

Practice Implications

The CD-Rom may be provided to all new patients eligible for a SCT. We must now establish the program's effectiveness, and develop a structure for timely updating. In the meantime, the CDROM may also be used in the education of medical and nursing professionals.
We plan to transform the CD-Rom into web-based education. One of the advantages would then be broad availability to all SCT patients in The Netherlands.

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Chapter 9

Safe early discharge for patients undergoing high dose chemotherapy with or without stem cell transplantation a prospective analysis of clinical variables predictive for complications after treatment

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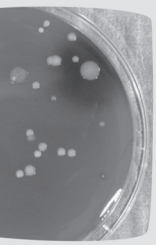

Abstract

Introduction: To identify which patient groups can be safely discharged early. Until recently the standard of care for patients with hematological malignancies who have been treated with high dose chemotherapy has been to hospitalize them until neutrophil recovery and clinical improvement. Over the past years, a more liberal approach has resulted in a tendency to discharge patients earlier. However, currently it is unclear which clinical variables are important and which patient groups are most suitable to be discharged early.

Methods: Prospective cohort study. The study group of 55 patients underwent 82 admission periods for a total of 2269 patient days, which could be classified into four categories: acute myelogenous leukemia induction treatment or consolidation treatment, and autologous or allogeneic stem cell transplantation. The variables were subsequently analyzed for their association with each treatment group.

Results: The median duration of admission was 27 days. The incidence of fever (82.9%) and use of i.v. antibiotics (79.3%) was high in all treatment groups. The only statistically significant differences between groups were found for Performance Status and mucositis. In the patient group undergoing consolidation chemotherapy for AML, the PS was better and mucositis was less severe. The decline in PS and the severity of mucositis were as expected most obvious 10-14 days after the start of chemotherapy.

Conclusion: Patients undergoing consolidation chemotherapy appear to be the most suitable candidates for early discharge, especially in the first week post chemotherapy treatment. Early discharge can also be considered in patients with a good performance status in the autologous stem cell transplantation group, directly after transplantation.

Relevance to clinical practice: An important factor in developing an early discharge program is a good infrastructure, both at home and in the hospital.

Introduction

In recent years there has been a tendency to shorten the duration of the hospital stay and to treat patients with hematological malignancies in an outpatient setting or day care facility. Before embarking on such a program of early discharge in patients undergoing high dose chemotherapy, it is important to analyze which 'patient groups' are most suitable and which clinical conditions are most relevant for early discharge.

Background

Younger patients with Acute Myeloid Leukemia (AML), Non Hodgkin Lymphoma (NHL), Multiple Myeloma (MM) or other hematological malignancies are often treated with several cycles of high dose chemotherapy leading to profound neutropenia. For many decades, the standard of care has been to hospitalize these patients until neutrophil recovery and clinical improvement [1, 2, 3, 4]. Studies performed at the end of the last century assessing infection and mortality show that myeloablative therapy and Stem Cell Transplantation (SCT) can be safely completed without protective isolation or the need to confine patients continuously in a hospital [5, 6, 7]. This more liberal view, together with increased political and economic demands to reduce costs, coupled with the wish to improve quality of life for patients, resulted in changes in admissions policies [8]. In an attempt to shorten the duration of hospital stay the earlier discharge of patients, or the option of home based treatment has been promoted [9]. Interestingly, several studies have shown the benefits of early discharge in terms of reduction of the incidence of bacteremia and of infection with resistant hospital-acquired pathogens when compared to patients treated in the hospital [10, 11, 12, 13]. In addition, increased oral intake of food has been observed [14]. Home care can be arranged in many different ways, e.g. with community-based professionals [15], a mixed inpatient-outpatient model [16] or a selective discharge program [6, 17]. Treatment outside the hospital during neutropenia is a feasible, well-accepted and cost-saving option [18] but clinical predictors for the length of hospital stay were not studied and subsequently the selection of patients for whom this approach is safe is unclear. In a prospective study Pastura et al. concluded that "to appear ill" is one of the factors associated with longer lengths of hospital stay, but "to appear ill" is a highly subjective measurement [19]. Hermann and Svahn also performed

studies on early discharge criteria with comparable results but remarkably, mucositis was not used as a criterion in either one of these studies [12,20]. Before changing our policy on in- and outpatient treatment, we studied clinical variables that could be helpful for making this selection: the incidence of fever, the use of intravenous (IV) therapeutic antibiotics, the severity of mucositis, the need for total parental nutrition (TPN) and the Performance Status (PS). The purpose of this study was to identify the frequency of these variables in different patient groups, in order to identify patients who can be safely discharged early.

Patients and Methods

This prospective cohort study took place between March 2005 and March 2006 in the Academic Medical Centre of the University of Amsterdam, a tertiary referral hospital in the Netherlands. All patients aged ≥ 18 years who were treated for a hematologic malignancy with high dose chemotherapy were eligible for this study. Treatment categories were:

1 induction chemotherapy for AML,
2 consolidation chemotherapy for AML,
3 autologous SCT for multiple myeloma (MM) or relapsed lymphoma,
4 myeloablative allogeneic SCT for AML, Acute Lymphatic Leukaemia (ALL) and MM.

All patients received infection prophylaxis consisting of oral ciprofloxacine, oral amphotericin-B and intravenous penicillin-G. In case of fever empiric broad spectrum antibiotics were started (vancomycin and ceftazidim i.v.) and adjusted according to the results of blood cultures. Patients were not discharged until the neutrophil count was > 0.5 x 109/ L and the patient's clinical condition was satisfactory, including absence of fever or bleeding, or need for i.v. therapy. The admission periods were categorized into:

1 the number of days a patient received chemotherapy,
2 the number of neutropenic days with an Absolute Neutrophil Count (ANC) count below 0.5 x 10^9/ L
3 the number of days the patient needed to stay in the hospital for other reasons, such as mucositis.

The only exclusion criterion for this study was the inability to complete the whole treatment period on the ward, independent of the reason for withdrawal. According to Dutch law studies involving human subjects must undergo medical ethics review if they are subject to the Medical Research Act Involving Human Subjects [21]. Following these rules for this study, which

was an observational and only involved collection of data, we only needed approval from the patients, and approval from the medical ethics committee was not required.

Definition of clinical variables

In this study we used commonly used clinical variables deemed relevant for discharge [6, 12, 19, 20, 22].

Neutropenia

Peripheral blood samples or samples from the central venous catheter were taken three times a week and neutropenia was defined as a neutrophil count of $< 0.5 \times 10^9$/ L.

Performance Status

Performance on the WHO PS is scored from 0, normal activity without restrictions, to 4, completely disabled and/or fully dependent in activities of daily living (ADL) [23]. The PS was measured twice daily on different nursing shifts and the highest score was documented to be sure a possible short period of a worse PS (which could have impeded discharge) would have been missed. The score was dichotomized per day into < 2 (out-of-bed activity more than 50%) and ≥ 2. Patients with a score of 0 and 1 are considered to be independent in their daily activities and thus were considered to be eligible for discharge [23].

Fever and infection

Body temperature was measured twice daily. When the temperature was higher than 38.0°C, the temperature was measured more frequently. Fever was defined as a single oral temperature of ≥ 38.5°C or a temperature of ≥ 38.0°C for ≥ 1 hour.
Surveillance cultures (peri-anal and nasopharyngeal swabs) were taken once a week, and on indication other cultures (e.g. stool cultures or cultures of the central venous line insertion place) were taken. Blood cultures from the central venous catheter and peripheral blood were taken the first time the patient had a temperature of > 38.5 °C or when the temperature was repeatedly > 38.0 °C. Subsequent blood cultures were obtained when patients had high fever and chills or after 48 hours in the event of continuous fever.

Infectious episodes were classified into one of four groups: 1 microbiologically documented infection with bacteraemia; 2 microbiologically documented infection without bacteraemia; 3 clinically suspected infection without microbiological documentation; and 4 fever of unknown origin (FUO).

Therapeutic Intravenous Antibiotics

In case of fever patients were started on empiric broad spectrum i.v. antibiotics. If necessary the antibiotic treatment was adjusted e.g. on the basis of culture results or clinical condition of the patient, and if possible changed from i.v. to oral, or stopped.

Oral Mucositis

Oral Mucositis (OM) is defined as a disruption in oral mucosal integrity and is a common toxicity of high-dose chemotherapy and irradiation of the upper head and neck [24]. The severity of oral mucositis was evaluated according to the National Cancer Institute Common Toxicity Criteria [25] grading from 0, no symptoms to 4 for necrosis and / or alimentation not possible [26]. The score was dichotomized based on international agreement, to 0 to 1 for mild mucositis and 2 to 4 for more severe mucositis [27]. A score of 2 or more is a reason not to discharge patients because of the associated treatment and pain management.

Capability of food intake

The capability of oral food intake was scored on a four point scale: 0 (eating without limitations), 1 (eating with difficulty), 2 (only liquid nutrition possible) and 3 (no oral intake possible). Patients with a score of 3 were considered unsuitable for early discharge.

Total Parental Nutrition (TPN)

TPN was started when patients had insufficient oral intake for several days and/or weight loss > 10 % from the start of therapy. Use of TPN is a reason not to discharge because of handling of the Central Venous Catheter (CVC) and the risk of infection.

Statistical Analysis

Data were analyzed by descriptive statistical methods per patient and per admission period. Some patients underwent several courses of

chemotherapy; for every admission period the patient was considered in the analysis as a new patient and the admission periods were considered as independent. Patients were categorized into groups who underwent AML induction treatment, AML consolidation treatment, autologous SCT, or myeloablative allogeneic SCT. The number of days of chemotherapy treatment, neutropenia, and the number of days requiring hospital admission for other reasons, were analyzed in relation to the total number of days patients were admitted. The median number of days of admission per patient was compared with the score of the clinical variables (neutropenia, PS, fever, i.v. antibiotics, mucositis, oral intake, and TPN) for each of the treatment groups.
The Kruskal Wallis analysis for ordinal data and Chi^2 test for nominal data were used to test the differences between the four treatment groups; a p value of <0.05 was considered statistically significant. The development over time of the variables was shown by calculating and plotting the median score per admission during the first 4 weeks of the admission period. All data were analyzed with the statistical package S.P.S.S., version 12.0.

Results

A total of 58 patients underwent 86 cycles of chemotherapy. Three patients were excluded from the analysis, because they had to be transferred to the intensive care unit due to infectious complications with respiratory failure (two on day 6, and one on day 18 after start of the chemotherapy). Two of them recovered and one patient died of respiratory failure due to congestive heart failure and pneumonia occurring at day 8 after the start of the chemotherapy. All three were part of the induction chemotherapy group.
A total of 55 patients were included in the analysis. Patient characteristics and diagnoses are shown in table 1. These 55 patients underwent 82 treatment cycles and spent in total 2269 days in hospital. The majority of the patients were male (N= 38) with a median age of 49 years (range 18-72). The most frequent diagnoses were: AML/MDS (N= 25), NHL (N= 14) and MM (N= 12).
Table 2 shows the number of episodes and the median number of days in hospital in relation to the different variables. The median number of days in hospital was 27 with a range of 17-56. There was no significant difference in the number of days of admission between the four groups. As expected, all patients had a prolonged period of profound neutropenia. The median duration of admission until a neutrophil count of > 0.5 X 10^9/ L was 17

Table 1. Patient Characteristics

Number of patients	55
Male / Female	38 / 17
Median Age (Range)	49.0 (18-72)
Person days	2269
Diagnosis	
AML/MDS	25
NHL	14
MM	12
ALL	4
Number of admission periods	82
Induction chemotherapy	29
Consolidation chemotherapy	23
Autologous SCT	24
Allogeneic SCT (Myeloablative)	6

days with a range of 14 to 48 days. The incidence of fever and subsequent use of empiric broad spectrum antibiotics was high in all groups and not significantly different between the groups. Overall fever was observed in 82.9 % (N= 68) of admission episodes, with a range of 38.0 °C to 41.5 °C, and during 79.3 % of episodes (N= 65) broad spectrum i.v. antibiotics had to be given. In 69 cases (84.1%) of all episodes an episode of neutropenic fever was observed. In 25 episodes a microbiologically documented infection was present (30.5%). Bacteremia was present in 17 cases; with coagulase negative Staphylococci being the most frequently cultured microorganisms (Table 3). There were no significant differences (P= 0.28) concerning fever, the presence of positive blood cultures or the use of i.v. antibiotics between the four groups.

The majority of patients (71.6%) at some point during the admission period had a PS of ≥ 2, indicating a low level of activity and independence. The proportion of patients with a PS of ≥ 2 was significantly different between the treatment groups (P< 0.05). In the consolidation chemotherapy group, the proportion of patients with a PS of ≥ 2 was the lowest (56.6%) while it was 100% in the allogeneic SCT group. The proportion of patients with a mucositis score of ≥ 2 (39 patients; 47.6%) was also significantly different between the treatment groups , with 21.7% in the consolidation chemotherapy group versus 41.3%, 75% and 66.7% in the induction chemotherapy group, autologous SCT and allogeneic SCT group respectively

(p=0.02). The median duration of severe mucositis was four days in the autologous SCT group versus 6.5 days in the allogeneic SCT group Overall 33 patients (40.2%) had a period during which oral food intake was not possible. The smallest number of patients without food intake was seen in the consolidation chemotherapy group (7 patients, 30.4%); the highest in the autologous SCT group [n= 14 (58.3%)] (P < 0.05). The use of TPN was necessary for 26 patients (31.7%); however, there were no significant differences (P= 0.43) between the treatment groups.

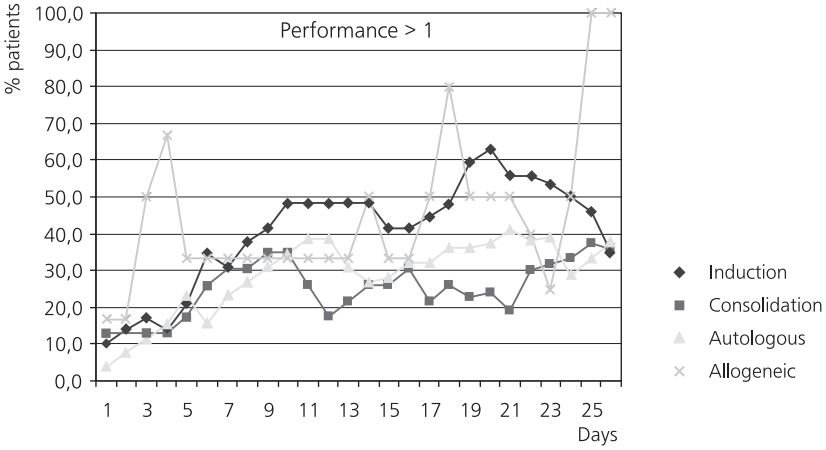

Figure 1. Development of performance status over time Percentage of patients with a performance status of ≥2 per treatment group on each admission day.

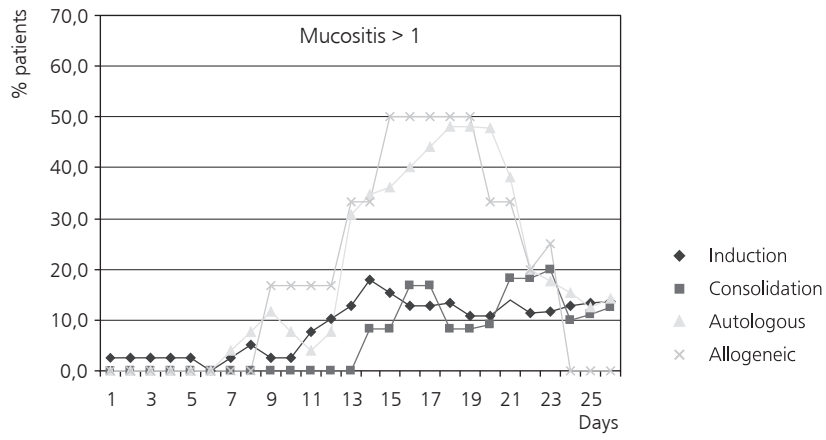

Figure 2. Development of mucositis 1 over time Percentage of patients with mucositis grade ≥2 according to CTC criteria per treatment group on each admission day.

Table 2: Course of discharge criteria by type of treatment

	All episodes N= 82
Median days of admission (Range)	27 (17-56)
Neutropenia	
Median number of days until a neutrophil count > 0.5 * 10^9/ L (Range)	17 (8-48)
Performance Status	
Number of episodes with performance status ≥ 2 (%)	59 (71.6)
Median number of days with PS ≥ 2 (Range.)	8 (0-48)
Fever, Infection and Antibiotics	
Number of episodes with fever ≥ 38.5°C (%)	68 (82.9)
Median number of days with fever ≥ 38.5°C (Range)	3 (0-19)
(1) microbiologically documented infection with bacteremia (%)	25 (30.5)
(2) microbiologically documented infection without bacteremia (%)	8 (9.8)
(3) clinically suspected infection without microbiological documentation (%)	5 (6.1)
(4)fever of unknown origin (FUO) (%)	37 (45.1)
Number of episodes with therapeutic i.v. antibiotics (%)	65 (79.3)
Median number of days with therapeutic i.v. antibiotics (Range)	8.5 (0-36)
Oral Mucositis,Oral Intake and TPN	
Number of episodes with Mucositis	39 (47.6)
Median number of days with Mucositis ≥ 2 (Range)	0 (0-15)
Number of episodes with no oral intake (%)	33 (40.2)
Median number of days with no oral intake (Range)	0 (0-15)
Number of episodes requiring TPN (%)	26 (31.7)
Median days of use of TPN (Range)	0 (0-32)

The development over time of the PS and the mucositis score in the first 28 days is shown in fig. 1 and 2. Starting on day 7, the proportion of patients with a PS > 1 is clearly higher in the Induction group and lower in the consolidation chemotherapy group, indicating that those patients on the basis of PS would be eligible for early discharge. The appearance of more severe mucositis (CTC score 2-4) is more obvious in the autologous and allogeneic SCT group, especially from day 13-22. (figure 1, 2).
Overall, we found statistically significant differences between the 4 treatment groups for PS, mucositis and oral intake, which were all better in the patients undergoing AML consolidation chemotherapy. However, also in the other treatment groups PS and mucositis were acceptable especially during the first week after chemotherapy.

	Induction N= 29	Consolidation N= 23	Autologous SCT N= 24	Allogeneic SCT N= 6	P
	28 (17-46)	28.5 (19-56)	24 (19-40)	23 (21-33)	
	18 (10-48)	20 (8-26)	17 (9-27)	19.5 (10-28)	
	24 (82.6)	13 (56.6)	16 (66.7)	6 (100)	< 0.05
	10 (0-26)	5 (0-48)	11 (0-37)	9 (3-20)	
	26 (89.7)	19 (82.6)	18 (75.0)	5 (83.3)	0.28
	6 (0-19)	3 (0-15)	2 (0-13)	1.5 (0-4)	
	8 (27.6)	9 (39.1)	7 (29.2)	1 (16.7)	
	2 (6.9)	1 (4.3)	4 (16.7)	1 (16.7)	
	1 (3.4)	1 (4.3)	3 (12.5)	0	
	13 (44.8)	13 (56.2)	10 (41.7)	5 (83.3)	
	24 (82.6)	18 (78.3)	18 (75.0)	5 (83.3)	
	12 (0-31)	8 (0-36)	6 (0-22)	14.5 (0-26)	
	12 (41.3)	5 (21.7)	18 (75.0)	4 (66.7)	0.02
	0 (0-15)	0 (0-13)	4 (0-14)	6.5 (0-15)	
	8 (27.6)	7 (30.4)	14 (58.3)	4 (66.7)	< 0.05
	0 (0-15)	0 (0-6)	1.5 (0-15)	1 (0-8)	
	11 (37.9)	6 (26.1)	7 (29.2)	2 (33.3)	0.43
	0 (0-32)	0 (0-32)	0 (0-24)	0 (0-21)	

chapter 9

Discussion

The aim of this study was to define criteria for safe early discharge after high dose chemotherapy in four different treatment groups; AML induction therapy, AML consolidation therapy and autologous and allogeneic SCT. For this purpose we studied the incidence and development over time of neutropenia, performance status, fever, infections, use of i.v. antibiotics, and oral mucositis to determine whether these factors differ between the groups.

No statistically significant differences were found between the four treatment groups regarding the duration of neutropenia and the incidence of fever or use of broad spectrum i.v. antibiotics. The high incidence of fever (84.1% of 82 episodes) is not surprising and comparable to other studies.

Table 3. Neutropenic fever and infection (N= 82 episodes)

	No.
Episodes of neutropenic fever	69 (84.1 %)
(1) microbiologically documented infection with bacteraemia	25 (30.5 %)
Staphylococcus, coagulase negative	15
Enterobacter cloacae	2
Escherichia coli	2
Pseudomonas aeruginosa	2
Fusobacterium nucleatum	1
Difteroids	1
Enterococcus	1
(2) microbiologically documented infection without bacteraemia	8 (9.8 %)
Aspergillus fumigatus	2
Proteus mirabilis	1
Herpes zoster	1
Other fungal isolates	1
Candida albicans	1
(3) clinically suspected infection without microbiological documentation	5 (6.1 %)
Herpes simplex virus	2
Aspergillus	2
Pneumocystis carinii	1
(4) fever of unknown origin (FUO)	37 (45.1 %)

Also, the percentage of microbiologically documented infections with or without bacteraemia was comparable to data reported in the literature [28]. We did however find a significant difference with respect to PS, mucositis, and the capability of oral intake, all of which were more favourable in the consolidation chemotherapy group. Furthermore, 3 patients undergoing AML induction chemotherapy had to be transferred to the ICU, because of septicaemia. One of the possible causes for the more severe infections observed in this group is the fact that these patients often already have prolonged neutropenia at the start of chemotherapy and are in a poorer general condition. Therefore in our opinion patients undergoing induction chemotherapy should not be discharged early. The small size of the allogeneic SCT group makes it difficult to draw conclusions concerning these patients, but considering the duration of severe mucositis and the poor PS, probably these patients are also not good candidates for early discharge. Patients undergoing consolidation chemotherapy appear to be the most suitable candidates for early discharge. Early discharge can also be

considered in patients with good PS in the autologous SCT group, directly after the stem cell reinfusion because although also these patients are at risk for severe mucositis, this usually does not develop until day 12. The high incidence of fever suggests that many of these patients will at some point need to be readmitted; however, since the protocols for the treatment of neutropenic fever are rapidly changing from i.v. to oral antibiotics, in the near future more patients after a short observation period could probably be treated in the outpatient setting [29].

Conclusion

In conclusion, our data suggest that of all patients with hematological malignancies treated with high dose chemotherapy, patients undergoing consolidation chemotherapy for acute leukaemia are the most suitable candidates for early discharge, whereas early discharge can also be considered in patients with a good performance status in the autologous SCT group, directly after the stem cell reinfusion. Currently, we are performing a prospective study of early discharge with ambulatory care in these patient groups.

Relevance to clinical practice

An important factor in developing an early discharge program is a good infrastructure, both at home and in the hospital. Patients must come to the hospital or outpatient clinic several times a week to check for vital signs, temperature, PS, mucositis, to have blood samples drawn and to have their home situation evaluated. The cost effective use of trained and experienced nurses coupled with the need to have hospital beds available in case of an emergency is crucial in such a program. It is also important that patients have 24 hour access to a volunteer aid who can take care of them and who can bring them to the hospital if necessary.

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Conflict of interest

The authors declare no conflicts of interest, research funding or other support.

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Chapter 10

Ambulatory treatment after high dose chemotherapy with or without autologous stem cell transplantation is safe and feasible: a prospective evaluation of 6 years of home care

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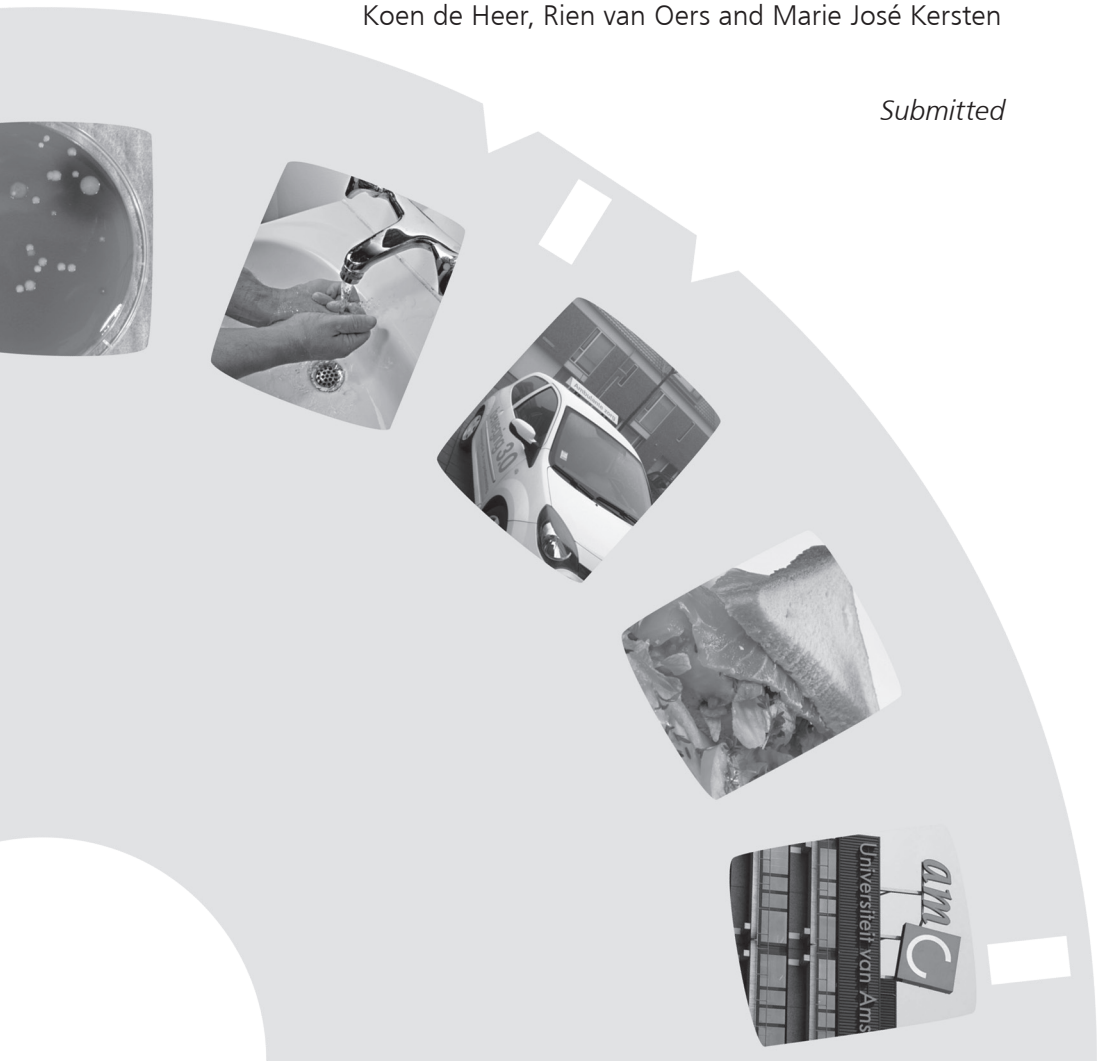
Submitted



Abstract

Background: A prospective, non randomized clinical study was undertaken to examine the safety and feasibility of ambulatory care in patients undergoing consolidation chemotherapy for acute leukemia, or autologous stem cell transplantation for lymphoma or myeloma.

Design and Methods: Patients fulfilling the eligibility criteria were discharged into ambulatory care the day after the last chemotherapy administration, or the day after reinfusion of the stem cells. Patients were seen at the ambulatory care unit 3 times a week.

Results: During the study period, 224 patients were admitted for 283 chemotherapy cycles. 101 patients (116 cycles) were considered not to be eligible for the ambulatory care program, mostly because of their medical situation, the lack of a caregiver, or the travel time to the hospital. The 123 patients in the ambulatory care group, who underwent 167 cycles of high dose chemotherapy, were able to spend more than 70% of the neutropenic phase at home. In 44% of the cycles, patients were never readmitted to the hospital. There was no treatment related mortality during the ambulatory care period. The median costs per day for the ambulatory care group were less than 50% of the costs for the hospital group.

Conclusions: This study demonstrates the safety, feasibility and economic benefit of managing carefully selected patients in an ambulatory care setting after high dose chemotherapy with or without autologous SCT for several diagnoses. Patients and their caregivers felt safe and comfortable at home, and the vast majority preferred home care to in-hospital treatment.

Introduction

High dose chemotherapy with or without autologous stem cell transplantation (SCT) is standard practice for many hematologic malignancies. The main risks of intensive chemotherapy, with its subsequent prolonged pancytopenia, are infectious complications and bleeding.[1]
The toxicity and mortality associated with high dose chemotherapy have been reduced by several factors, such as the use of mobilized peripheral blood stem cells instead of bone marrow, the administration of granulocyte colony-stimulating factor, improved prophylactic and empiric antibiotic regimens, and a more proactive management in preventing opportunistic infections.[2] Although protective isolation to prevent infections has long been the accepted standard of care for these patients, the necessity of keeping patients in hospital after myelosuppressive chemotherapy or SCT until full neutrophil recovery is under discussion.[3-4].
Health care issues, quality of life and more efficient use of hospital resources have led to several projects implementing outpatient or home care even during high-risk phases of treatment. Ambulatory treatment has the potential to decrease patient exposure to multidrug-resistant organisms in the hospital and to provide a more comfortable environment for patients and their family.[5]
Ambulatory treatment should obviously first of all be safe regarding the risk of infection and it should not negatively affect overall survival. [6] High dose chemotherapy with or without SCT is an expensive medical procedure. [7]
According to several studies hospital admission costs account for 58 to 78% of the total costs of high dose chemotherapy. Therefore, a shift from inpatient to outpatient treatment could lead to a substantial decrease in costs. [8-10]
Over the last 20 years different models for outpatient treatment have been developed for selected patients groups, e.g. following SCT. Patients were visited, and if necessary, treated at home or patients were seen in an ambulatory care setting in the hospital, in a separate unit or a hotel accommodation connected to the hospital. Some studies employing home-based [11-16] or ambulatory treatment [17-21] have shown ambulatory care to be safe. However, most of these studies were performed in a single hematologic malignancy with a limited amount of patients.
Support, education, perception, expectations and feeling safe at home instead of being hospitalized are important topics in the development of an ambulatory care program. [22] The psychosocial impact of at-home versus in-hospital treatment in SCT showed significantly higher scores for emotional wellbeing and global quality of life in the ambulatory care group. [23]

In a previous study we have defined requirements for eligibility for ambulatory care after high dose chemotherapy [24]. We found that, compared to induction treatment for AML, high risk myelodysplastic syndrome (HD-MDS) and myeloablative allogeneic SCT, relatively few complications were seen after consolidation chemotherapy for AML, HD-MDS and after autologous SCT in patients with relapsed lymphoma and MM. We therefore considered these patients to be the most suitable candidates for ambulatory care. In the present study we prospectively examined the safety in patients receiving high dose chemotherapy with or without autologous SCT support for consolidation in AML, Acute lymphoblastic leukemia (ALL), relapsed lymphoma and Muliple Myeloma.

Design and Methods

Study design

A prospective nonrandomized clinical study, with a study group (ambulatory care) and a control group (patients not eligible for ambulatory care, treated in the hospital).

Patients and Requirements for ambulatory care

All consecutive patients admitted to the Hematology Department of the Academic Medical Centre in Amsterdam (Netherlands) between September 2005 and September 2011 with a hematologic malignancy (AML, MDS, ALL, NHL, and MM) undergoing treatment with high dose chemotherapy were considered for participation in the ambulatory care project. Patients with acute leukemia were not eligible during the first induction cycle. Eligibility criteria for ambulatory care included: WHO PS $\leq$ 2, travel time from home to the hospital less than 60 minutes, availability of an educated caregiver for 24 hours a day, and patient understanding and acceptance of the procedures. At the time of actual discharge into ambulatory care, the following additional eligibility criteria were checked: patients should have no fever nor uncontrolled symptoms, adequate oral intake, no mucositis $\geq$ CTC grade 2 [25], no uncontrolled diarrhea and/or vomiting, and no cardiac or respiratory distress. In addition, patients had to feel safe to leave the hospital. If ambulatory care was not possible patients were included in the control group.

Ambulatory care

Before starting this project an ambulatory unit was organized to provide assistance to up to four patients simultaneously. Specialized nurses (C.S and K.B.) were trained to educate the patients and caregivers, to check fulfillment of the requirements for ambulatory care and to perform the check-ups at the ambulatory care unit. Subsequently more nurses were educated by training-on-the job. All patients and their caregivers were informed about the procedures before making the choice between ambulatory care and hospital care. At home patients were instructed to check their own vital parameters including temperature, oral intake and body weight daily, and to return to the hospital immediately in case of fever and/or other signs of infection, bleeding or any other complication. If necessary, patients could consult the hematology nursing staff 24 hours per day. Patients were discharged into ambulatory care on the day following the last administration of chemotherapy or, in the case of ASCT, on the day after reinfusion of the stem cells.

Patients visited the ambulatory care unit 3 times a week for monitoring of vital signs such as weight, temperature, pulse and blood pressure. In addition, oral intake was discussed with the patients, the mouth was inspected for signs of mucositis, the central venous catheter (CVC) was checked and, if necessary, cultures of the central venous line were taken. Surveillance cultures (peri-anal and nasopharyngeal swabs) were taken once a week, and on indication other cultures were performed (such as stool cultures). The complete blood count was checked and platelet and red blood cell transfusions were given when required. Patients were seen by a physician at least weekly and more often if necessary. Visits generally took 1-2 hours if no red blood cell or platelet transfusions needed to be given. During the period of neutropenia in hospital, patients were nursed preferably in a single room. Strict hygiene procedures including hand washing and the use of hand alcohol were followed by all personnel. Patients were discharged from ambulatory care or from the hospital to the outpatient department as soon as neutrophils had recovered to > 0.5 * 10^9/l and their clinical condition was considered to be satisfactory.

Infection prophylaxis and supportive care

All patients were given the same infection prophylaxis, which was started on the first day of high dose chemotherapy, and continued until neutrophil recovery. *Gram negative prophylaxis* consisted of ciprofloxacin 500 mg orally or 400 mg intravenously (i.v.) b.i.d. or, if ciprofloxacin-resistant gram negative

bacteria were present in the surveillance cultures, colistin orally 200 mg q.i.d. and cotrimoxazole 960 mg b.i.d. *Gram positive prophylaxis* consisted of oral feneticilline 250 mg q.i.d or penicillin 1 million units i.v. q.i.d. from day 7 after start of the chemotherapy or day 1 after ASCT. In case of penicillin allergy, clarithromycine 500 mg b.i.d. was prescribed. *Antifungal prophylaxis* consisted of amphotericin B oral suspension 500 mg q.i.d.. [26]The efficacy of the prophylaxis was checked by weekly surveillance cultures of the perineum and throat.

Indications for readmission

Patients were readmitted in case of temperature ≥ 38.5 C, uncontrolled nausea, vomiting or diarrhea, mucositis grade ≥ 2, requirement of total parenteral nutrition (TPN), hemodynamic instability, pneumonia, cardiac and/or respiratory distress or any other situation which could not be handled at home. If necessary, a hospital bed was always available.
In the event of fever, patients were fully evaluated by a physician. Blood cultures were taken both from a peripheral vein and from the CVC. Other appropriate cultures were taken on indication, and a chest X-ray was performed.
As soon as the situation had stabilized and the patient no longer required intravenous antibiotics, he or she could be discharged into ambulatory care again.

Empiric antibiotic regimen

In case of fever, patients were treated empirically with vancomycine 1000 mg i.v. b.i.d and ceftazidime 1000 mg i.v. t.i.d, or with other antibiotics based on results of the surveillance cultures (e.g. gentamycin or meropenem). Patients with persistent fever despite i.v. antibiotic therapy after 72 hours underwent evaluation for invasive aspergillosis by high resolution CT scan and galactomannan antigen testing in serum. If abnormalities were found, a bronco-alveolar lavage was performed for galactomannan antigen testing and culture of the broncho-alveolar fluid.

Definitions and diagnostic criteria

Neutropenia: absolute neutrophil count (ANC) < 0.5 x 10^9 /L.
Fever: a single oral temperature of ≥ 38.5°C not related to transfusion or drug administration [27]
Infection: Episodes of neutropenic fever (NF) were classified into four groups: 1. fever of unknown origin (FUO): fever without signs and symptoms

of inflammation at anatomic sites and no identification or recovery of pathogens, 2. clinically suspected infection (e.g. pneumonia) without documentation of a pathogenic microorganism (CDI), 3. microbiologically documented infection (MDI) with or without bacteraemia. This group included infections with coagulase-negative Staphylococcus (CNS), in which case at least two positive blood cultures were required, *4.* invasive pulmonary aspergillosis (IPA), further classified according to the revised european organization for research and treatment of cancer and infectious diseases mycoses study group (EORTC/MSG) criteria which revised the definition of proven, probable or possible. [28]
Performance status: the performance status (PS) was scored according to the WHO score (from 0, normal activity without restrictions, to 4, completely disabled and/or fully dependent in activities of daily living (ADL). [29]
Mucositis: The severity of oral mucositis was evaluated according to the National Cancer Institute Common Toxicity Criteria version 3.0, grading from 0 (no symptoms) to 4 (necrosis and / or alimentation not possible). [30] A score of 2 or more was considered to be a reason not to discharge patients because of the associated treatment and pain management.

Calculation of costs

For the purpose of the study, we looked at costs of admission versus costs of ambulatory visits. The costs were calculated from the day of the start of the (possible) ambulatory care until the day of discharge to the outpatient department. In-hospital hematological admission in our hospital is charged at € 491, - per day. A visit to the ambulatory care unit for a regular check-up was calculated at € 65, - . In case of blood transfusions, visits lasting more than 2 hours were considered to be day care and were charged at € 423,- per visit. This calculation does not include the costs of diagnostic procedures, laboratory services, medication, blood products and overhead costs, since they were expected to be similar for both groups. Also, loss of income to patients and caregivers and costs of daily living at home were not included in the analysis.

Patient satisfaction

The first 64 patients who participated in the ambulatory care group were invited to complete an anonymous questionnaire after completion of the whole procedure. On a psychometric 5-point symmetric Likert scale, patients specified their level of agreement or disagreement for a series of

21 statements. [31] This questionnaire covered the following topics: logistics, information, communication and patient perception.

Statistical methods

The incidence and types of complications requiring readmission to hospital, and the number of hospital days saved by this policy have been prospectively evaluated.
Results were compared with those observed in the control group of patients who were treated in the hospital.
The following factors were descriptively analyzed for home care versus hospital care: number of days until neutrophil recovery, (re-)admission, fever and infection, performance status, mucositis, nutrition, weight difference between start and end of the treatment, platelet and erythrocyte transfusions and patient satisfaction. All analyses were carried out using SPSS version 18 statistical software (SPSS Inc, Chicago, IL).

Results

Reasons for inclusion in the ambulatory care or hospital group

Two hundred and twenty four patients undergoing two hundred and eighty three cycles of high dose chemotherapy (with or without ASCT) were included in the study. 123 patients (167 cycles) were included in the ambulatory care group and 101 patients (116 cycles) were included in the hospital group.
The most common reason for a patient during a particular cycle not to be included in the ambulatory care program was that he or she was considered to be medically unfit (63 cycles), most frequently because of fever. Logistic reasons (lack of a caregiver, travel time to the hospital) and patient preferences (53 cycles) were the other most prevalent reasons for not including patients in the ambulatory care program (figure 1).

Baseline characteristics

The patient characteristics including diagnosis and treatment are described in table 1, with AML/ high risk MDS being the most frequent diagnosis. There was no difference in the male to female ratio between both groups but there was a difference in age, with a higher median age in the hospital group of 57 years (range 19-72) versus 49 years (range 18-68) in the ambulatory care group. The included treatment modalities also show several

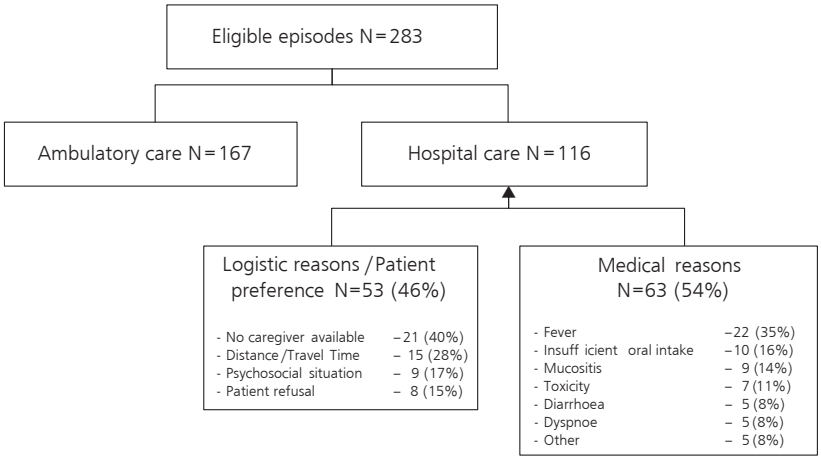


Figure 1. Eligible episodes

Table 1. Patient Characteristics

	Ambulatory care	**Hospital group**
Patients	123	101
Male / Female (%)	73(59.3)/ 50(40.7)	54(53.5)/ 47(46.5)
Median Age (Range)	49 (18-68)	57 (19-72)
Diagnosis		
AML/high risk MDS	37/10	40/6
NHL	34	8
MM	24	44
ALL	13	1
Lymphoma	4	2
CML	1	-
Cycles	167	116
Consolidation AML/MDS	57	54
ALL intensive chemotherapy	19	2
NHL intensive chemotherapy	41	3
High Dose Melfalan, autoSCT	23	48
Beam, autoSCT	27	9

striking differences. In both groups, the most commonly included treatment was consolidation chemotherapy for AML (34% of all cycles included in the ambulatory care group and 46% in the hospital group). However 75% of all 36 BEAM cycles and 93% of all 44 patients treated with high dose chemotherapy for NHL were treated in the ambulatory care group, whereas

68% of 71 patients were treated with high dose melphalan for MM were treated in the hospital group (table 1).

Readmissions in the ambulatory care group

In 73 cycles (44% of all cycles), patients treated in the ambulatory care group were never readmitted. Of the 108 readmissions, 82 were single readmissions; in 10 cycles patients were readmitted twice and two patients had to be re-admitted three times. Fever was the most frequent reason for readmission (58%), followed by mucositis (14%), diarrhoea (7%) and respiratory distress (6%). In 17 % of the readmissions, there were multiple reasons for readmission.

In the ambulatory care group 71 % of the 2812 days which would otherwise have been spent in the hospital could be spent at home. If readmission was necessary, the median day of readmission was day 8 (range 2-27) while the median duration of readmission was 6 days (range 1-22). The highest risk of readmission was observed following consolidation treatment for AML (72%) and following BEAM/autologous SCT (70%). The risk of readmission for patients treated with high dose chemotherapy for ALL, NHL, and MM was 37%, 44% and 39%, respectively.

Outcome variables (mucositis, weight loss, fever and infections)

In table 2 the outcome variables, including fever and infection are summarized. The total number of patient days in the ambulatory care group was 2812 days, with a median of 14 days per cycle (range 6-40). Many of the patients needed platelet transfusions (84%) and red blood cell transfusions (79%).

In 62 % of the cycles one or more febrile episodes occurred. In approximate two-third of the febrile episodes, the febrile episode was classified as FUO (fever of unknown origin) An overview of the different micro-organisms which were identified is shown in table 2. From the 27 gram-positive isolates, 70% (19) coagulase negative staphylococci were isolated, and 2 Streptococcus Mitis. From the Gram-negative isolates Escheria coli (4) and Pantoea spec. (1) found. In seven cases possible IPA was determined, in one case probable. The median number of days using IV antibiotics was 3 days with a range of 0-32 days.

Two patients from the ambulatory care group had to be admitted temporarily to the ICU and both recovered fully. One patient was admitted for 48 hours because of hemodynamic instability following a CNS bacteremia, and the second patient for 24 hours because of a severe

Table 2. Outcome variables including fever and infections in the ambulatory care group (N= 167 cycles)

Total number of days in ambulatory care	2812
Median days of ambulatory care (range)	14 (6-40)
Days with PS ≥ 2 (%)	460 (16.4)
Days with mucositis ≥ 2 (%)	143 (5.1)
Days with no oral intake (%)	82 (2.9)
Days requiring TPN (%) (range)	78 (2.8)
Median weight loss (kg.)	- 1.4
Cycles requiring platelet transfusions (%)	140 (83.8)
Cycles requiring red blood cell transfusions (%)	132 (79.0)
Fever	
Cycles with fever (%)	103 (61.7)
Consolidation AML/MDS (%)	42 (73.7)
ALL intensive (%)	9 (47.4)
NHL intensive (%)	23 (43.9)
Autologous HDM (%)	11 (52.2)
Autologous BEAM (%)	18 (66.7)
Number of days with fever ≥ 38.5 C (%)	491 (17.4)
Episodes of Neutropenic Fever	110
Infections and micro-organisms identified	
FUO	62
MDI	37
Gram + isolates	27
CNS	19
Gram – isolates	7
Anaerobic	3
CDI	3
IPA Proven/ Probable/ Possible	0/1/7
Days number of I.V. antibiotics were required (%)	812 (28.8)
Median number of days on I.V. antibiotics (Range)	3 (0-32)

anaphylactic reaction to a platelet transfusion. No deaths occurred in the ambulatory care group, whereas 3 patients died of treatment-related complications in the hospital group.

Calculation of costs and use of hospital beds

In the hospital group, the total costs were calculated at € 991.820,- (2020 days of admission at €491,- per day. The cumulative costs for the 2812 patient days in the ambulatory care group were considerably lower at

€ 505.184,- (783 days of admission at € 491.- per day; 182 days of day care at € 423.- per day and 673 regular visits to the ambulatory care unit at € 65.- per visit. The median costs per day were also lower for the ambulatory care group: € 180,- per day versus € 490,- in the hospital group. When comparing costs for relatively homogeneous group of AML/MDS patients undergoing consolidation chemotherapy, the median costs for the 1278 patients days in the ambulatory care group were € 209.- per day, versus € 491,- per day for the 1160 admission days for the hospital group. Apart from these direct cost savings shifting to ambulatory care treatment also meant more patients could be treated at our department: patients who otherwise would have been hospitalized were actually at home for 2029 days, implying that at a median duration of admission including chemotherapy and neutropenic phase of 22 days, 92 more patients could be admitted for high dose chemotherapy in this time period.

Patient satisfaction

Sixty four patients out of the first 89 patients in the study (72%) sent back the questionnaire. Four of the answers reflecting the topics logistics, information, communication and patient perception are shown in figure 2. All patients felt safe at home regarding the risk for infections and did not regret the decision to be treated at home. All patients, except for one, were positive about the logistics of ambulatory care. However, 15% of the

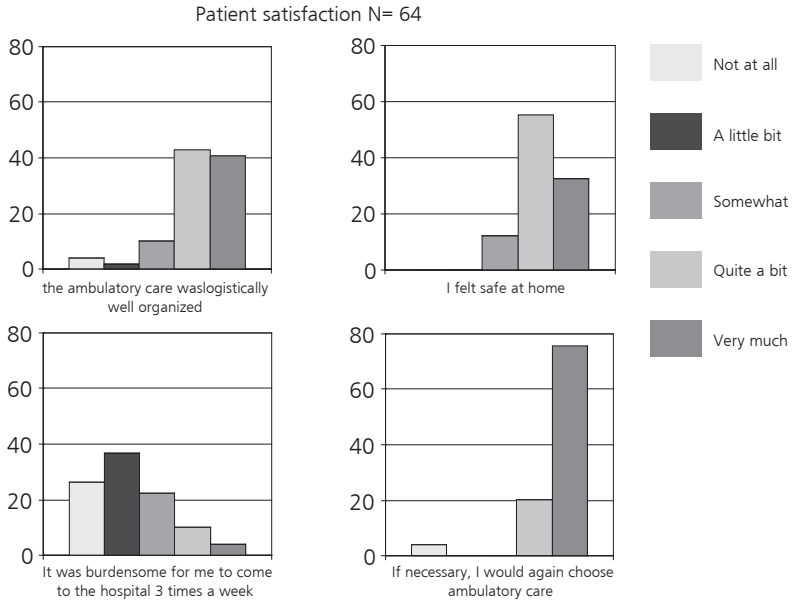


Figure 2. Patient satisfaction

patients and their caregivers felt it to be somewhat burdensome to come to the hospital for a check-up 3 times a week. Except for one patient all patients would choose again for ambulatory care if necessary, and would advise it also to fellow patients.

Discussion

In this prospective study of patients with AML, ALL, NHL and MM receiving high dose chemotherapy with or without autologous stem cell support, we examined whether ambulatory care could be a safe and more patient-friendly alternative for hospital care.

All patients who were potentially eligible were carefully evaluated for ambulatory care using a series of both medical and psychosocial criteria, and an analysis of the situation at home.

Ultimately, in approximately 70% of the eligible cycles patients could be treated at home, and they were able to spend more than 70% of the days which normally would have been spent as an in-patient in their home environment. Although readmission was necessary in 56% of the cycles, which is comparable with other studies[11, 14, 16, 19] , none of the patients had life threatening complications and there was no treatment-related mortality. Several outcome variables, such as number of days with fever, mucositis, weight loss and use of TPN appeared to be more favorable in the patients treated at home versus the patients who stayed in hospital, we were reluctant to perform a formal comparison. The main reason for this caution is the fact that since this was not a randomized trial, and patients were selected on the basis of medical and logistic criteria, there were some striking differences in the patient categories between the groups. Patients who ended up in the ambulatory care group were younger and more often had NHL or ALL, whereas in the hospital group patients were older and more often had myeloma. This meant that also the treatment (e.g. BEAM versus HDM) was different, and that it was thus impossible to have paired groups for analysis. Secondly, the strict and cautious selection of the patients which we applied might have provided bias in this study, because patients in better medical condition were more likely to be treated in the ambulatory care project.

Nonetheless, it is clear that ambulatory care is cost saving, and, importantly, that better use can be made of hospital resources, because more patients requiring intensive hematologic care could be treated at our hematology department.

Results of the patient survey showed that patients feel safe, confident and comfortable at home and that the vast majority would again choose for ambulatory care if necessary, or would recommend it to other patients. It was however considered to be somewhat burdensome to come to the hospital 3 times per week. Also, we found it to be important to give intensive support also to the caregivers, who felt it to be a great responsibility to care for their spouses/family members.
We found it to be extremely important that the team of physicians and nurses is well trained and experienced, and that a lot of time and effort is spent to educate the patients and their caregivers, both before and during the ambulatory treatment.
In conclusion, this study demonstrates the safety and feasibility of managing carefully selected patients in their home environment following high dose chemotherapy with or without autologous stem cell support. Ambulatory care is a cost saving and excellent alternative for hospital care, which, importantly, is also greatly appreciated by patients.

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Chapter 11

Summary, general discussion and Implications

Summary

The main objective of the research presented in this thesis was to gather evidence on the effectiveness of a number of procedures routinely performed in patients receiving high dose chemotherapy for hematologic malignancies. This was done both by performing systematic reviews and by performing clinical studies, and focused on different aspects of supportive care for this vulnerable patient group. The ultimate goal was on the one hand to promote medical and nursing interventions of proven evidence based benefit, and on the other hand to restructure or discourage ineffective interventions, which should both lead to improvement of the quality of care.

In **chapter 2** we describe the results of a prospective study in patients treated with nephrotoxic chemotherapy. To prevent renal toxicity these patients receive hyperhydration and are at risk of fluid overload. Measuring fluid intake/output is labour-intensive and often unreliable because of incomplete data, and represents an occupational hazard for nurses and other health-care workers handling cytotoxic body excreta. Our hypothesis was that bodyweight can be used as a more simple and reliable parameter for fluid overload. In a cohort of 591 combined observations of bodyweight and fluid intake/output, there was a rather low correlation between the two parameters, with an earlier and higher increase in bodyweight than in fluid balance. In only four cases (0.6%) fluid overload would have been missed if fluid intake/output would no longer have been registered. None of these patients suffered from clinical consequences. We concluded that bodyweight can be used as the only parameter for monitoring fluid overload in patients treated with hyperhydration during nephrotoxic chemotherapy. The results of our study were subsequently implemented as a hospital guideline and medical and nursing protocols were changed and simplified.
Chaper 3 outlines a subsequent retrospective study which explored factors accounting for adherence to the guideline described in chapter 2, seven years after its introduction. To assess long-term adherence, fluid balances and medical orders were checked in all patient charts on the oncology/ hematology, gynaecology and pulmonology wards during a 6-month period. In this time period 178 cycles of chemotherapy were administered for which hyperhydration was necessary. According to the routine of calculating the fluid balance three times every 24 hours, 534 fluid balances could have been calculated. However, only eight fluid balances were actually calculated, either because of the inability to weigh a patient or for the purpose of monitoring

a high-output stoma. In all other cases bodyweight was used. Focus group interviews held with nurses and questionnaires issued to hematologists and oncologists revealed that both groups applied the guideline correctly in almost 100% of the cases.

The role of protective isolation was studied in **chapter 4.** In the literature we found mostly older prospective randomized studies which contradict each other on the usefulness of protective isolation. We therefore decided to stop protective isolation, following a campaign for optimal hygiene and more specifically detailed instruction for a correct use of hand alcohol and proper hand washing. Following implementation of this guideline we monitored the incidence of febrile neutropenia, infections and use of systemic antibiotics during a three year time period, and compared these with the findings in the preceding three years, when isolation was still common practice. No significant differences in infections or mortality were found. We concluded that abandoning protective isolation combined with increased hygienic measures in the nursing of patients with severe neutropenia did not increase the risk of infections. These results improved the quality of care and patient satisfaction, and reduced costs.

Chapter 5 describes an intervention study which compared knowledge about mucositis and skills in handling it in two groups of nurses, before and after oral care education. Two hematology units with comparable patient categories from two different university hospitals were involved. The knowledge test consisted of a 32-item questionnaire including open-ended and multiple-choice questions, and 8 photographs of the mouth illustrating different stages of oral mucositis. Observation skills were evaluated with a list consisting of 44 observations points. Oral care education sessions were given in only one hospital and follow-up tests were performed in both hospitals. Nursing records were examined and observations of nurses performing oral care were made at baseline as well as at follow-up. 31 nurses in the intervention group (education) and 29 nurses in the control group participated in the knowledge test both at baseline and at follow-up. Knowledge about oral hygiene at baseline varied widely between nurses in both groups. In the intervention group, but not in the control group, a significant increase was demonstrated in the scores for knowledge and skills after education. Furthermore, nurses who followed the education session implemented the oral care protocol considerably better than those who did not. Education in oral care has a positive influence on the knowledge and skills of nurses who care for patients at risk for oral mucositis.

A detailed European survey described in **chapter 6** examined the use of a low bacterial diet (LBD) in patients treated with high dose chemotherapy.

Two hundred and forty-eight questionnaires were distributed, with 108 responses (44%) from 20 European centers and 9 non-European centers. Although 88% of the 108 hospitals who completed the questionnaire had guidelines, there were enormous differences in both the guidelines themselves and the way in which they were implemented. The conditions for starting or stopping LBD were diverse. The restrictions on food products sometimes contradicted each other. This survey highlighted the fact that there is currently no standard for a LBD.

In the subsequent Cochrane review (**chapter 7**) three randomized studies were identified, comparing LBD with a standard diet in 192 adults and children with different types of cancer, mostly hematologic malignancies. Other interventions, such as antimicrobial prophylaxis, hygiene practices and definitions of the different outcome parameters also differed between the studies. All of the studies had methodological flaws, which is why unfortunately performing a meta-analysis on the included studies was not possible. For all outcome parameters no statistically significant differences between the study groups were observed. There was therefore no evidence from individual studies showing that the use of a LBD could prevent infections.

In **chapter 8** we explored the acceptability of an interactive CD-ROM for patients undergoing stem cell transplantation, which was developed as a supplement to oral and written information. An overall evaluation of this interactive CD-ROM showed a high level of acceptance: 90.2% (N=51) of the patients found the CD-ROM interesting, clear and useful, and valued the opportunity to receive extra information. The content with five chapters concerning different phases from diagnosis until home care, the integrated interviews with fellow patients, and the computer-based, interactive method of the CD-Rom where all well received by patients. Most patients would recommend the CD-Rom to other patients in the same situation. Computer-based education may enhance patient education and thus quality of patient care.

Traditionally, patients are admitted to the hospital during the pancytopenic phase, with or without protective isolation.Health care issues, quality of life and more efficient use of hospital resources have led to several projects implementing outpatient or home care even during these high-risk phases of treatment. In a prospective analysis described in **chapter 9**, we identified patient groups which could be eligible for ambulatory care. A group of 55 patients who underwent 82 admissions were classified into four treatment categories: induction treatment, consolidation treatment, autologous stem cell transplantation or myeloablative allogeneic SCT. Patient characteristics

and toxicities of treatment were subsequently analyzed for their association with each treatment group. Statistically significant differences between groups were only found for performance status and mucositis. Patients undergoing consolidation chemotherapy and autologous stem cell transplantation appeared to be the most suitable candidates for early discharge. These results were used for the development of an ambulatory care program.

In **chapter 10** a six year prospective, non randomized clinical study is described on the safety,feasibility and patient perspective of ambulatory care. In this time period 224 patients were admitted for high dose chemotherapy (283 cycles) who theoretically qualified for the ambulatory care program (consolidation chemotherapy for acute leukemia, high dose chemotherapy for NHL, or autologous SCT for NHL or MM). Of these patients, 101 patients (116 cycles) were considered not to be eligible for the ambulatory care program, mostly because of their medical situation. The lack of a caregiver or the travel time to the hospital only played a minor role. The 123 patients who could be included in the ambulatory care program were able to spend 70% of the time which would otherwise have been spent in the hospital at home. In 44% of the cycles, patients were never readmitted to the hospital. Different outcome variables, such as fever and infections were evaluated. There was no treatment related mortality during the ambulatory care period. The median costs per day for the ambulatory care group were less than 50% of the costs for the hospital group. Patients and their caregivers felt safe and comfortable at home, and the vast majority preferred home care to in-hospital treatment. Ambulatory care is safe regarding the risk of infection and other complications of high dose chemotherapy when applied in a carefully selected patient group, and patients feel more comfortable at home.

General Discussion

Concluding Remarks

In this thesis we have described several studies on different aspects of supportive care in patients receiving high dose chemotherapy for hematologic malignancies. To put the results into perspective the most important conclusions are listed, some general comments are made, and implications for clinical practice and directions for future research are discussed.

Most important conclusions:

1. Bodyweight can safely be used as the only parameter for monitoring fluid overload in patients treated with nephrotoxic chemotherapy requiring hyperhydration.
2. Abandoning protective isolation is safe, provided appropriate hygienic measures are taken.
3. Education in oral care has a positive effect on knowledge and skills of nurses who care for patients at risk for oral mucositis.
4. There are many differences across Europe in the indications for and content of low bacterial diets.
5. There is no evidence demonstrating that the use of a low bacterial diet prevents infections.
6. An interactive CD-ROM as a supplement to oral and written information is highly appreciated by patients and fulfills their information needs.
7. Ambulatory care appears to be most suitable for patients undergoing consolidation chemotherapy for acute leukemia, or autologous stem cell transplantation for MM or lymphoma.
8. Ambulatory care is feasible, can yield an economic benefit, and is safe with regard to infections as long as the patients are carefully selected.
9. In the vast majority of cases, patients treated in ambulatory care and their caregivers feel safe at home, and would recommend this procedure to fellow patients

General comments

Providing highly complex care and at the same time minimizing the risk of life threatening adverse events is crucial for patients treated with high dose chemotherapy for a hematologic malignancy. Nurses play a key role

in ensuring the proper and safe administration of these therapies and they are often the first to identify signs of side effects. Most of the interventions for managing these patients however continue to be based on tradition and rituals rather than on evidence, and there are large variations in prophylaxis and monitoring strategies among hospitals (1). Many studies have focused on infection prevention and treatment. Optimizing supportive care can improve outcome, which was the main reason for the research presented in this thesis.

Methodological issues

Because in the studies reported in this thesis consecutive patients from the target populations have been included (chapter 2, 3, 4, 9, and 10), we believe that the results obtained can be extended to a larger population of patients with hematologic malignancies. However, there are some methodological limitations that should be mentioned. The first limitation is the fact that most studies, such as the intervention study comparing ambulatory care with hospital care were not randomized (chapter 4, 9 and 10). In this study, the decision as to whether or not a patient was included in the ambulatory care group was made through careful selection of the patients by the hematologist in collaboration with the nursing staff, the patients themselves and their caregivers. The main reasons for patients being allocated to the hospital care group were fever or other medical reasons such as insufficient oral intake. As a consequence the more fit patients were allocated to the ambulatory care group, which resulted in an imbalance in age, diagnosis and treatment between the groups. For this reason, we could not perform a formal statistical analysis of the differences in outcome between the groups. Ideally, a randomized study should be performed in patients eligible for ambulatory care to detect important clinical differences (2). The selection of these patients should be based on clear screening criteria which are reproducible and clinically applicable (3).
The second limitation was the validity and reliability of the tools and questionnaires used in several studies (chapter 3, 4, 5, 6 and 9), some of which were specifically designed for these studies and have not been formally validated in the relevant patient groups. As to g reliability: the response rate of 71% (N=101) for the protective isolation survey (Chapter 4) is relatively high, while the response rate in the low bacterial diet survey (Chapter 6) of 44% (N=108) seems rather low. However, according to a systematic review performed by Asch this is comparable to published surveys of physicians and allied health professionals, showing a mean response rate

of around 50% (4). We conclude that both studies give good insight into the current situation in Europe with regard to protective isolation and the use of a low bacterial diet, and could lead to a platform to standardize these practices.

Implications for clinical practice and future research

Considering the methodological issues mentioned above it is fair to conclude that some of the results obtained in our studies might not necessarily be generalizable to everyday clinical practice. However, they certainly are far beyond tradition and rituals. This will hopefully lead to discouragement of the use of ineffective interventions that are based solely on custom or tradition (5). To obtain more solid evidence well-designed clinical trials are required, which ideally should be randomized controlled trials (RCT). However, due to the difficulties in randomization because of practical and ethical aspects, in some cases rigorous observational studies may well be an acceptable alternative to RCT's. With the results of these trials, guidelines can be developed which are evidence-based. Establishing evidence based guidelines should however not be considered to be the end of the "journey", and implementation is an important step to obtain optimal long-term adherence. This requires a systematic approach, a positive attitude to change, a sense of urgency, and support and education and a long-term follow-up policy (6). As of today several guidelines and procedure/practice changes have already y been successfully implemented in the Academic Medical Centre as well as in other centers.

Future research opportunities in the field of supportive care include prevention of complications, psychosocial issues, providing information, and the use of nurse-led services. For instance more research should be done on the role of the caregiver, and on providing better support to this important group.

Until definitive evidence is available clinicians can use consensus-based guidelines but it is important that they continue to identify clinical practices that require additional research.

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chapter
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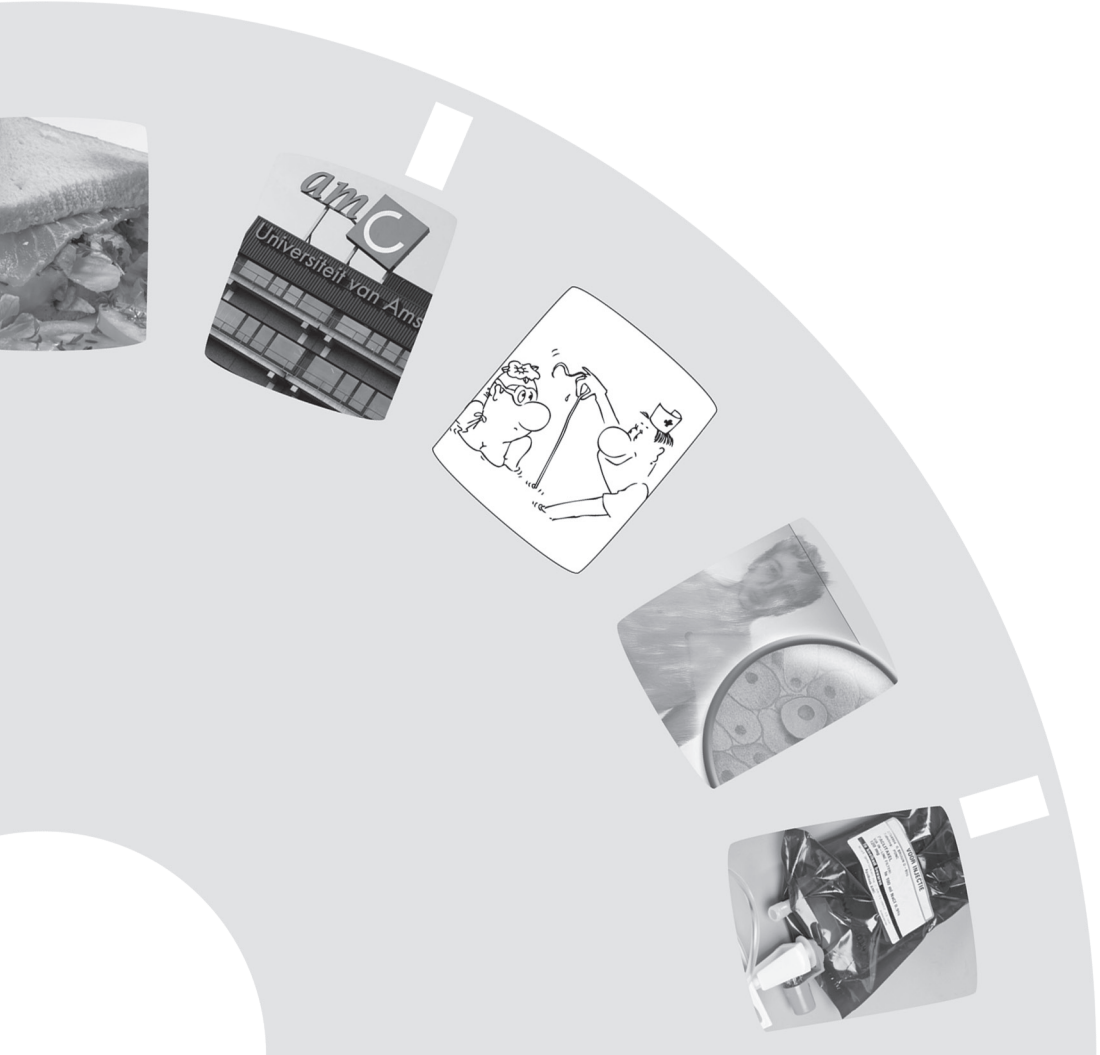
Chapter 12

Nederlandse samenvatting
(Dutch Summary)



Nederlandse samenvatting (Dutch Summary)

De belangrijkste doelstelling van de onderzoeken die in dit proefschrift beschreven worden is bewijsmateriaal/evidence te verzamelen t.a.v. de doeltreffendheid van een aantal routinematige procedures binnen de hematologie. Deze handelingen, soms ook als rituelen gekenschetst, worden uitgevoerd bij patiënten worden die behandeld worden voor hematologische maligniteiten zoals Leukemie, Hodgkin of Multipl Myeloom en hierbij hoge dosis chemotherapie toegediend krijgen. Dit werd gedaan zowel door systematische overzichten als door klinische studies uit te voeren. We concentreerde ons op verschillende aspecten van de ondersteunende zorg bij patienten met een verlaagde afweer en daardoor verhoogd risico op infecties. Het uiteindelijke doel was bewijs aan te tonen welke medische en verpleegkundige handelingen doelmatig waren en deze te bevorderen en anderzijds ondoelmatige handelingen aan te passen of evt. te stoppen. Uiteindelijk doel is verbetering van de kwaliteit van zorg met positieve consequenties wat betreft veiligheid en doelmatigheid voor zowel de patient, gezondheidszorginstelling en de gezondheidzorg.

In **hoofdstuk 2** beschrijven wij de resultaten van een prospectieve studie bij patiënten die met nephrotoxische chemotherapie wordt behandeld. Om schade van de nieren en blaas te verhinderen krijgen deze patiënten grote hoeveelheden intraveneus vocht (hyperhydratie) toegediend om geforceerd diurese te bewerkstelligen. Hierbij is er een gevaar op overvulling en decompensatio cordis en dus belasting van het hart. Bij gebrek aan een “gouden standaard”, wordt om dit te monitoren en evt. op tijd actie te ondernemen zowel de vochtbalans als het gewicht gecontroleerd. Meten van vloeibare opname/output (vochtbalans) is arbeidsintensief en kan onbetrouwbaar zijn wegens onvolledige gegevens. Daarnaast hebben deze handelingen een beroepsrisico tot gevolg voor verpleegkundigen en andere gezondheidszorg werkers die met cytotoxische lichaamsafscheidingen omgaan. Onze hypothese was dat het lichaamsgewicht als eenvoudiger en meer betrouwbaar parameter voor controle op overvulling kan worden gebruikt. In een cohort van 591 gecombineerde observaties van lichaamsgewicht en vochtbalans, was er een lage correlatie tussen de twee parameters, met een eerdere én hogere verhoging van lichaamsgewicht dan bij de vochtbalans. In slechts vier gevallen (0.6%) zou de mogelijke overvulling gemist zijn als de vochtbalans niet meer zou zijn geregistreerd.

Bij geen van deze patiënten waren er klinische consequenties. Wij concludeerden dat het lichaamsgewicht als enige parameter kan worden gebruikt voor de controle van decompensatie bij patiënten die met hyperhydratie tijdens nephrotoxische chemotherapie wordt behandeld. De resultaten van onze studie werden ingevoerd als aangepaste ziekenhuisrichtlijn en de medische en verpleegkundige protocollen werden veranderd en vereenvoudigd.

Hoofdstuk 3 beschrijft een retrospectieve studie die factoren onderzocht die van invloed kunnen zijn op het blijven volgen van de richtlijn zoals beschreven in hoofdstuk 2. Dit is vergeleken met een andere gelijktijdig ingevoerde richtlijn, zeven jaar na invoering van beide richtlijnen. Om de continuïteit van het opvolgen van de richtlijnen op de langere termijn te beoordelen, werden de medische en verpleegkundige dossiers gecontroleerd op het voorkomen van vochtbalansen op de afdelingen oncologie/ hematologie, gynaecologie en longziekten in een periode van 6 maanden. In deze periode werden 178 cycli van chemotherapie gecontroleerd waarbij hyperhydratie noodzakelijk was. Volgens de routine van het berekenen van de vochtbalans drie maal per 24 uur, konden theoretisch 534 vochtbalansen berekend worden. Nochtans, werden slechts acht vochtbalansen berekend, of wegens het onvermogen om een patiënt te wegen of voor de controle van een hoge-output bij een stoma. In alle andere gevallen werd alleen het lichaamsgewicht gebruikt. Ook zijn er interviews met vragenlijsten en groepsgesprekken gehouden met verpleegkundigen en artsen. Beiden volgden de richtlijn correct en waren tevreden over de toepassingen.

De rol van beschermende isolatie bij neutropene patiënten werd bestudeerd en beschreven in **hoofdstuk 4**. In de literatuur vonden wij merendeels oudere prospectieve studies die elkaar in het nut van beschermende isolatie tegenspraken. Wij beslisten de beschermende isolatie te stoppen, na een campagne voor optimale basis hygiëne, en een gedetailleerde scholing voor een correct gebruik van handen wassen en handalcohol. Na implementatie van deze richtlijn controleerden wij het effect hiervan tijdens een driejarige periode, en vergeleken deze met de bevindingen in de voorafgaande drie jaar, toen de isolatie nog praktijk was. Patiëntengegevens wat betreft koorts, mortaliteit, infecties, gebruik systemische antibiotica etc. zijn vergeleken tussen beide periodes. Geen significante verschillen in infecties of mortaliteit werden gevonden. Wij concludeerden dat het stoppen van beschermende isolatie, met verhoogde hygiënische maatregelen in de verpleging van patiënten met neutropenie verantwoord was. Deze resultaten hadden tot

gevolg, hogere kwaliteit van zorg, grotere patiëntentevredenheid, en lagere kosten.

Hoofdstuk 5 beschrijft een interventiestudie die kennis en vaardigheden in de observatie en behandeling van mucositis bij twee groepen verpleegkundigen, in twee verschillende ziekenhuizen, voor en na scholing vergeleek. Twee hematologie afdelingen met vergelijkbare categorieën patiënten van twee verschillende universitaire ziekenhuizen werden geïmplementeerd. De kennistest bestond uit een lijst met 32 vragen met inbegrip van open en meerkeuzevragen, en 8 foto's van de mond die verschillende stadia van mondelinge mucositis illustreerden. Vaardigheden van de observatie werden met een lijst geëvalueerd die uit 44 observatiepunten bestaat. De scholing werd gegeven in één ziekenhuis en de controletests werden uitgevoerd in de beide ziekenhuizen. Rapportage van de observaties van de verpleegkundigen die de mondzorg uitvoerden werden geregistreerd voor en na het scholingsprogramma, eveneens in op beide hematologieafdelingen. 31 verpleegkundigen in de interventie groep (onderwijs) en 29 verpleegkundigen in de controlegroep namen aan de kennistest deel, zowel bij de nulmeting als bij de follow-up. De kennis over mondzorg bij de nulmeting verschilden sterk tussen verpleegkundigen in beide groepen. In de interventiegroep, maar niet in de controlegroep, werd een significante verhoging aangetoond van de scores voor kennis en vaardigheden na het gevolgde onderwijs. De verpleegkundigen die de scholing volgden voerden de mondinspectie en zorgprotocol aanzienlijk beter uit dan zij die niet de scholing hadden gevolgd. Geconcludeerd werd dat het onderwijsprogramma t.a.v. mondinspectie en het verpleegkundig handelen een positieve invloed heeft op de kennis en de vaardigheden van verpleegkundigen die voor patiënten met een verhoogd risico op mucositis zorgen.

Een gedetailleerd Europees onderzoek dat in **hoofdstuk 6** wordt beschreven, onderzocht het gebruik van een bacteriearm dieet bij patiënten die met hoge dosis chemotherapie worden behandeld. Twee honderd achtenveertig vragenlijsten werden verspreid, met 108 reacties (44%) van 20 Europese centra en 9 niet-Europese centra. Hoewel 88% van de 108 ziekenhuizen die de vragenlijst voltooiden richtlijnen had, waren er grote verschillen zowel wat betreft de richtlijnen zelf als de manier waarin zij werden uitgevoerd. De voorwaarden om een bacteriearm dieet te starten of te stoppen waren zeer divers. De beperkingen op 18 geselecteerde voedingsmiddelen spraken elkaar soms tegen. Dit onderzoek benadrukte

het feit dat er momenteel geen norm voor een bacteriearm dieet is. In het vervolg hierop werd in een Cochrane review (**hoofdstuk 7**) drie gerandomiseerde klinische studies geïdentificeerd, waarbij bacteriearm dieet met een standaarddieet werd vergeleken. Het ging hierbij om 192 volwassenen en kinderen met verschillende soorten kanker, meestal hematologische maligniteiten. Andere acties, zoals antibiotische profylaxe, hygiëne maatregelen en definities van de verschillende eindpunten verschilden tussen de studies. Alle studies hadden methodologische gebreken, wat daarom een meta-analyse op de geïncludeerde studies niet mogelijk maakte. Voor alle eindpunten werden geen statistisch significante verschillen tussen de studiegroepen waargenomen. Er is dan ook geen bewijs vanuit de verschillende studies aangetoond dat het gebruik van een bacteriearm dieet besmettingen kan verhinderen.

In **hoofdstuk 8** onderzochten wij de meerwaarde van een interactieve Cd-rom voor patiënten die in de toekomst een stamceltransplantatie (SCT) zullen ondergaan, dit als aanvulling op de mondelinge en geschreven informatie die al gebruikt wordt. Een algemene evaluatie (N=51) van deze interactieve Cd-rom toonde een algemeen zeer positieve score. De patiënten vonden de Cd-rom, duidelijk en nuttig, en zeer prettig om op deze wijze extra informatie te ontvangen. De inhoud met de vijf hoofdstukken betreffende verschillende fasen van diagnose tot het naar huis gaan, de geïntegreerde interviews met medepatiënten, en de interactieve methode van Cd-rom werden allen zeer goed beoordeeld door de patiënten. De meeste patiënten zouden Cd-rom ook aan andere patiënten in de zelfde situatie adviseren. De patiëntenvoorlichting en dus ook de kwaliteit van de zorg is duidelijk hierdoor verbeterd en een nuttige aanvulling op reeds bestaande mondelinge en schriftelijke voorlichting.

Traditioneel, blijven patiënten opgenomen in het ziekenhuis tijdens de pancytopene fase, met of zonder beschermende isolatie. Gezondheidszorg aspecten, kwaliteit van leven en het efficiëntere gebruik van het ziekenhuismiddelen hebben geleid tot verscheidene projecten waarbij patiënten steeds meer buiten het ziekenhuis behandeld en gecontroleerd worden, ook in de periode van verlaagde afweer. In een prospectieve analyse die in **hoofdstuk 9** wordt beschreven, identificeerden wij verschillende patiënten categorieën die voor ambulante zorg in aanmerking zouden kunnen komen. Een groep van 55 patiënten die 82 hoge doses chemotherapie ondergingen werd geclassificeerd in vier behandelingscategorieën: inductie behandeling,

consolidatiebehandeling, autologe SCT of myeloablatieve allogene SCT. De patiënten karakteristieken en de toxiciteit van behandeling werden geanalyseerd per behandelingsgroep. Statistisch significante verschillen tussen groepen werden slechts gevonden voor zelfredzaamheid en mucositis. De patiënten die consolidatie chemotherapie en autologe SCT ondergaan waren de meest geschikte kandidaten voor ambulante zorg. Deze resultaten werden gebruikt voor de ontwikkeling van een ambulant zorgprogramma.
In **hoofdstuk 10** word in een zesjarige prospectieve, klinische studie de veiligheid en de haalbaarheid van ambulante zorg en het patientenperspectief beschreven. Tijdens deze periode werden 224 patiënten geïncludeerd voor hoge dosis chemotherapie (283 cycli) die theoretisch voor het ambulante zorgprogramma in aanmerking kwamen (consolidatie chemotherapie voor AML, hoge dosischemotherapie voor NHL, of autologe SCT voor NHL of MM). Van deze patiënten, werden 101 patiënten (116 cycli) niet geschikt geacht voor het ambulante zorgprogramma, hoofdzakelijk wegens hun medische situatie. Het gebrek aan een mantelzorger of de te lange reistijd naar het ziekenhuis speelde een minder belangrijke rol. De 123 patiënten die wel in het ambulante zorgprogramma kwamen konden 70% van de tijd thuis doorbrengen waarbij zij anders in het ziekenhuis opgenomen zouden zijn. In 44% van de cycli, werden de patiënten helemaal niet in het ziekenhuis heropgenomen. De verschillende de resultatenvariabelen, zoals koorts en infecties werden geëvalueerd. Er was geen verwante mortaliteit tijdens de ambulante zorgperiode. De gemiddelde kosten per dag voor de ambulante zorggroep waren minder dan 50% van de kosten dan voor de ziekenhuisgroep. De patiënten en hun mantelzorger voelden zich comfortabel en veilig thuis, en de overgrote meerderheid verkoos ambulante zorg boven ziekenhuis behandeling. Concluderend: Ambulante zorg is veilig betreffende het infectierisico en andere complicaties van hoge dosis chemotherapie mits toegepast in een zorgvuldig geselecteerde groep, het is kostenbesparend en de patiënten voelen zich thuis veilig en comfortabel.

Chapter 13

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Dit promotietraject is niet volgens de gangbare route verlopen zoals bij de meeste promovendi. Na al meer dan 5 jaar bezig geweest te zijn met zorg, onderwijs en onderzoek rondom de behandeling van deze intensieve patiënten groep kwam de vraag van anderen naar voren “zou je niet eens gaan promoveren?” Opleidingen gevolgd, patientenzorg, daarnaast vooral druk met nationale en internationale organisaties maakte het dat het daarna toch nog een aantal jaren geduurd heeft, maar hier ligt dat toch het resultaat. Een aantal studies die niet in “de la” terecht zijn gekomen maar al inmiddels daadwerkelijk ook iets veranderd hebben in de dagelijkse praktijk. Uiteraard was dit zeker niet gebeurd met de druk van enkelen en hulp van velen. Er zijn dan ook zoveel mensen die ik wil bedanken terwijl ik gelijk al weet dat ik mensen ga vergeten zeker als je zoveel mensen kent van binnen maar ook van buiten het AMC, nationaal en ook internationaal.

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Raad van bestuur, medische en verpleegkundige staf

Het Academisch Medisch Centrum en de Universiteit van Amsterdam "adopteerde" het EBP paradigma waarbij de board van directors een specifieke richting gaven om een strategie te ontwikkelen om EBP richtlijnen te ontwikkelen en te implementeren. Dit gaf ons als afdeling hematologie en F6zuid, en mij als uitvoerende, de mogelijkheden om twee maal een gecombineerde medisch/verpleegkundige richtlijnen studie uit te voeren met de eerder beschreven positieve resultaten. Hiervoor wil ik Prof. Marcel Levi in het bijzonder bedanken, mede omdat hij ook vertrouwen had in de afronding van mijn promotie en het open staan voor een verpleegkundige onderzoekslijn in het AMC. Dat geldt uiteraard ook voor alle verpleegkundige bestuurders van de interne divisie uit verleden en heden, in naam bedank ik Marian Mens, omdat ik ook het vertrouwen en de mogelijkheden heb gekregen om hierin tijd en energie te steken.
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De afdeling

F6Z is vanaf het moment dat ik 25 jaar geleden begon altijd een bron van inspiratie voor nieuwe ontwikkelingen geweest. Het feit dat ik de mogelijkheid ook gekregen heb om deze functie uit te voeren zegt al genoeg. Het is een afdeling waar altijd weer uitdagingen liggen en men op zoek is naar verbeteringen. Het feit dat deze afdeling in een korte termijn 2 accreditaties, JACIE en JCI, met glans hebben "doorstaan" zegt al genoeg.
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Curriculum Vitae

Arnoldus Petrus Maria Mank werd geboren op 14 juli 1956 te Nieuwer-Amstel, het huidige Amstelveen. Na het voltooien van de Middelbare school volgde hij van 1985 tot 1988 de Inservice opleiding tot A-verpleegkundige in het Academisch Ziekenhuis der Vrije Universiteit te Amsterdam. Na enige jaren werkervaring werd de opleiding tot B-verpleegkundige in de Academisch Ziekenhuis van de Universiteit van Amsterdam gevolgd van 1980 tot 1983 en daarna werkzaam tot 1987 als B-verpleegkundige en later als teamleider in Provinciaal Ziekenhuis Santpoort te Santpoort. Vanaf 1987 is Arno werkzaam in het Academisch Medisch Centrum op afd. F6 zuid, oncologie/hematologie, eerst als teamleider en daarna als verpleegkundig onderzoeker. Tussendoor diverse opleidingen gedaan zowel op management niveau als vakinhoudelijk. Van 1990 tot 1992 heeft hij de AMC-opleiding Klinische Epidemiologie en Biostatistiek gedaan en in 2003 gedeeltelijk de Masterstudie Evidence Based Practice.
Verder was en is Arno nog steeds inhoudelijk en bestuurlijk actief binnen diverse verpleegkundige en onco-/hematologische verenigingen, zowel nationaal binnen de VenVN oncologie en SIG Hematologie als internationaal in de European Bone and Marrow Transplant Nurses Group (EBMT-NG). Bij de EBMT aanvankelijk via de research committee, later op bestuurlijk niveau, m.n. als president van 2010 tot 2012. Verder is Arno actief als reviewer voor enkele tijdschriften en zit ook in diverse werkgroepen en adviescommissies.
Wat betreft het onderwijs is Arno actief als docent en begeleider binnen het AMC en aan diverse (oncologie) opleidingen en bij nationale en internationale scholingsprogramma's, zoveel mogelijk gebruik makend van de EBP gedachtegoed.
Als resultaat van deze activiteiten heeft, naast diverse nationale en internationale publicaties en enkele tientallen presentaties, dit ook twee prijzen opgeleverd, één nationale prijs voor een richtlijn voor CVC's en één internationale prijs; de Excellence in Patient Education Award van de European Oncology Nurses Society (EONS) voor de ontwikkelde Cd-rom zoals beschreven in hoofdstuk 8.
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