High dose treatment for haematologic malignancies: from rituals to evidence based practice
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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.

Chapter 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 patients 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
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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 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.
References


