High dose treatment for haematologic malignancies: from rituals to evidence based practice
Mank, A.P.M.

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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.
References


