Health-related quality of life after stem cell transplantation – The first year

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ABSTRACT

High-Dose Chemotherapy (HDC) followed by Stem Cell Transplantation (SCT) has been proven to be beneficial for a variety of haematological diseases, solid tumours and immune disorders. Despite improved care and treatment, SCT continues to produce significant long-term complications with impaired functioning and distressing symptoms. In this thesis the overall aim was to improve our knowledge about how SCT patients experience different types of transplantations and the effect it may have on their Health-Related Quality of Life (HRQoL) during the first year after SCT. Semi structured interviews were performed and two questionnaires, the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) and the module, High-Dose-Chemotherapy (HDC-19), were administered. Health-related quality of life after allogeneic SCT following Reduced Intensity Conditioning (RIC) and MyeloAblative Conditioning (MAC) were compared. Both groups showed a similar pattern of development over time in functioning and symptoms, albeit more severe in the MAC group. One year after SCT there were no significant differences between the groups in global Quality of Life (QoL). However, RIC patients improved in global QoL back to baseline earlier compared to MAC patients. When allogeneic and autologous patients were compared, RIC patients seemed to recover in the same way as autologous patients and these two groups were closer in their scoring compared to MAC patients. The results emphasize the need to separate the two allogeneic groups when evaluating HRQoL after SCT. Symptoms related to the digestive system like; dry mouth, sore mouth, appetite loss and change of taste together with fatigue were among the most frequent reported symptoms throughout the SCT period for all three groups. In the MAC group, symptoms of dry mouth and change of taste even increased, and one year after SCT these symptoms were more pronounced compared to baseline. Four themes emerged from the data analysis of the interviews and illustrate how the participants described their life from discharge until one year after SCT; *obstacles on the road to normality, to be part of a normal life, the chance to be cured overshadow everything and new values in life*. The patients described that they felt restricted in life and had problems to manage the response from family and friends. Stem cell transplantation had changed their opportunities in life, meaning that plans for the future had to be altered, sometimes in a negative way. Stem cell transplantation is a demanding procedure that affects the patients HRQoL over a long period of time. Alleviation and management of distressing symptoms and impaired functioning are some of the most important tasks for the health care providers in order to contribute to a better health and life situation for SCT survivors.

Keywords: health-related quality of life, stem cell transplantation, myeloablative conditioning, reduced intensity conditioning, symptoms, functioning

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ABBREVIATIONS

QoL	Quality of Life
AUC	Area Under the Curve
CR	Complete Remission
CARES-SF	Cancer Rehabilitation Evaluation System Short Form
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
FACT-G	Functional Assessment of Cancer Therapy-General
GvHD	Graft-versus-Host Disease
GvL	Graft-versus-Leukaemia
GvM	Graft-versus-Malignancy
HADS	Hospital Anxiety and Depression Scale
HDC	High Dose Chemotherapy
HDC-19	The module questionnaire High-Dose-Chemotherapy-19
HRQoL	Health-Related Quality of Life
ICC	Intra-Class Correlations
MAC	MyeloAblative Conditioning
MFI	Multidimensional Fatigue Inventory
NHP	Nottingham Health Profile
PR	Partial Remission
RD	Related Donor
RIC	Reduced Intensity Conditioning
SCT	Stem Cell Transplantation
SF-36	Medical Outcome Study Short Form Health Survey
SIP	Sickness Impact Profile
SRM	Standardised Response Means
TBI	Total Body Irradiation
URD	UnRelated Donor
VOD	Veno-Occlusive Disease
WHO	World Health Organisation

CONTENTS

INTRODUCTION

High-Dose Chemotherapy (HDC) followed by Stem Cell Transplantation (SCT) is an aggressive therapeutic option for haematological diseases, certain solid tumours and immunologic disorders [1-5]. The number of long-term survivors after SCT is increasing, and consequently also the number of patients living with long-term complications associated with SCT. These affect many organs, for example skin, eyes, mouth, intestine, lung and liver, as well as psychological and social well-being [6-11]. Patients' report a wide range of psychological concerns following SCT that may occur early after discharge from hospital, and continue for many months. The most frequent reported are depression, anxiety, memory and concentration difficulties [12]. Fear has been found to be a common reaction among SCT patients – fear of cancer recurrence and fear for the future [10, 12]. Other long-term psychological effects include lowered self-esteem and a general dissatisfaction with life [10, 13]. Patients may also experience difficulties in financial situations, family roles and relation with friends [10].

The chance to survive and be cured after SCT differs, depending on the diagnosis, the patient's age and stage of the disease. In general, early treatment and younger age are advantageous to long-term survival [4]. Autologous transplantations are thought to be less dangerous compared to allogeneic SCT, with less treatment related morbidity and mortality. On the other hand autologous SCT entail a greater risk of relapse compared to allogeneic procedures [14]. Survivors of SCT may experience significant life-altering side effects because of the prolonged and extensive nature of their treatments [15-17], and often health care professionals fail to understand the depth of the trauma the patient might have experienced [16]. Patients undergoing SCT require considerable supportive nursing care following transplantation and Health-Related Quality of Life (HRQoL) assessment can help to identify rehabilitation needs and requirement for interventions [18].

The outcome measures of SCT were initially focused on survival, control of underlying disease and morbidity related to treatment [19]. During the last decades the focus has changed to also involve psychosocial adjustment, HRQoL, effects on the donor and the family and cost effectiveness [19-23]. Studies concerning HRQoL, including frequency and difficulties related to side effects, are important and provide a greater understanding of the impact of illness and treatment and have the potential to improve health care [21, 24]. However, even if this field of research is expanding, most studies are retrospective and based on small samples [21]. It has been argued that prospective designs with follow-ups are better methods to assess the variations in HRQoL during the periods of treatments and rehabilitation [25, 26]. The present thesis focuses on HRQoL among SCT patients during the first year after transplantation.

BACKGROUND

Haematological malignancies

Haematological malignancies are rare diseases and can be identified by the primary hematologic component that is affected: Red Blood Counts (RBCs), White Blood Counts (WBCs), platelets, or the coagulation system. The major abnormalities in haematology are quantitative in nature, with either excessive or deficient production of one of the hematopoietic constitutes [27]. Symptoms at diagnose varies between the different diagnoses but fever, weight loss, infections, fatigue and pain are dominant. The most common diagnosis is Lymphoma with 2000 new cases per year, thereafter multiple myeloma and acute leukaemia with 500 and 400 new cases per year respectively.

Management of haematological malignancies

Treatment has undergone major changes over the last 20 years. Chemotherapy is still basic treatment, but several new treatment options have been added; monoclonal antibodies, thyrosine kinase inhibitors, proteasome inhibitors and anti-aniogenesis drugs. The new treatment modalities have all led to a prolonged survival, but also to substantially more cure. However, stem cell transplantation is now standard treatment in certain phases of haematological malignancies [4]. For some patients, the aim of the stem cell transplantation is to extend the time to relapse of the disease, but for patients with leukaemia and lymphoma, the aim is also to cure.

Stem cells can either be derived from bone marrow, peripheral blood or cord blood [4]. Stem cell transplantations are divided into autologous and allogeneic depending on the source of the stem cells. Autologous SCT means that the patient's own stem cells are re-infused [28] and allogeneic SCT that the patients receive stem cells from a donor [14]. Stem cell transplantation has been defined as "any procedure where haematopoietic stem cells of any donor-type and any source are given to a recipient with the intention of repopulating and replacing the haematopoietic system in total or in part" [4]. The choice between autologous or allogeneic stem cell transplantation is dependent on the underlying disease, and to a lesser extent, the patient's status.

Incidence of stem cell transplantation

In 2008 there was over 30 000 SCT in Europe (allogeneic 39% and autologous 61%) [3]. The proportion between allogeneic and autologous SCT in Sweden was nearly the same. In 2008, 225 patients had an allogeneic SCT and over 600 patients an autologous SCT. Main indications for allogeneic SCT were acute and chronic

leukaemia and for autologous SCT the main indication was multiple myeloma and lymphoma [3]. The numbers of allogeneic SCT are steadily increasing, thanks to reduced conditioning regimen transplantations in fragile patients. Since 2006, approximately 40% of stem cell transplantations have use reduced conditioning regimens [3]. Unfortunately, reduced conditioning regimen transplantations have failed to demonstrate a real survival advantage compared to myeloablative conditioning transplantations. The reduction in toxicity seems to be gained at the price of an increased incidence of relapse [29].

Treatment and caring procedures in stem cell transplantation

The SCT starts with the conditioning regimen, including intensive high-dose chemotherapy with or without Total Body Irradiation (TBI). Conditioning is given with three main objectives "creation of space", immunosupression and disease eradication. The term "conditioning" in SCT means to prepare the patient for its transplantation [30]. Patients are admitted to the hospital 3-8 days before transplantation depending on conditioning regimen. Complications due to chemotherapy and myelosuppression range from minimal to life-threatening, where nausea, vomiting, mucositis, loss of appetite and weight, fatigue, bleeding, fluid and electrolyte imbalance and frequent infections are the most common [6, 8]. Patients receiving allogeneic SCT experience additional complications as infections related to extended immunosupression and neutropenia (neutrophil count $\leq 0.5 \times 10^9$/L) and are therefore placed in protective care during this period [9, 11]. Patients receiving allogeneic SCT also have a risk for Veno-Occlusive Disease (VOD) [11] and Graft-versus-Host Disease (GvHD) [9, 11]. A majority of the patients have previous experiences from other treatments of the disease, such as chemotherapy and radiotherapy, and symptoms related to this. During the hospitalisation period, the main purpose of the nursing care is to guide and support the patient trough the SCT and to detect and minimize the acute complications and ease the symptoms. Side effects and issues during the SCT are numerous and occur across many HRQoL domains – such as physical, social, emotional, and psychological [10].

Patients undergoing autologous SCT are discharged from the ward 2-3 weeks after transplantation while those undergoing allogeneic SCT remain for 3-4 weeks. After autologous SCT the patient meet the physician for follow-up one month after SCT and thereafter when needed. The follow-up visits for patients after allogeneic SCT are more frequent. During the first month they visit the outpatient clinic twice a week and if there are no complications the visits become successively more sparsely. The transition from active treatment to post-treatment is crucial in preventing and detecting later complications and establishing long-term health [15]. For many patients the transition from patient to survivor is a time of uncertainty. The old "normal" life may never return, rather a new "normal" life has to begin [8].

The concept of health-related quality of life

Health-related quality of life rest on the concept of health as well as Quality of Life (QoL). In medicine, health is usually associated with objective indicators measuring the absence of disease, illness and sickness. It is more common to measure ill health because it is easier to measure deviations from health rather than to find indications of health itself [31]. The focus on objective data alone has been criticized in terms of the inability to capture factors relevant to health status, to the way people feel, and the context in which they live [31]. In 1946 the World Health Organization (WHO) accepted a more positive definition of health as not only the absence of disease and infirmity, but also a positive state of physical, mental and social well-being. WHO has argued that five health concepts are inherent in this definition: physical health, mental health, social functioning, role functioning and general well-being [31, 32].

Although health is highly valued by most people, it is only one of several components that build up a good QoL [31]. It depends on the individual experiences and expectations of his/her total life. Within the same individual, QoL can also fluctuate over time, because of developmental and environmental factors. A good QoL is usually expressed in terms of life satisfaction, contentment, happiness, goal fulfilment and the ability to cope. Because satisfaction with life, goal fulfilment or happiness are relative terms, circumstances that make one individual satisfied or happy do not necessarily produce the same feelings for another person [33]. The definitions may be classified into two main categories: objective and subjective. The former indicates essential ingredients in a good life, whereas the latter indicates the individual's own perception of it. WHO's definition of QoL from 1993 is: "Quality of life is defined as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [32, p 6]. It is a broad concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationships to prominent features of their environment [32].

Health-related quality of life is more specific and more appropriate to clinical research and practice as it points mainly to those aspects of life which are affected by health and treatments. Therefore, HRQoL can be considered synonymous with subjective health status assessment [34]. Health-related quality of life is, as well as QoL, multidimensional and proven difficult to define [31, 35]. Generally, HRQoL covers the subjective perceptions of the positive and negative aspects of patient's symptoms, including physical, emotional, social, and cognitive functioning [35]. Bowling [32] define HRQoL as optimum levels of mental, physical, role (work, parent, carer, etc.) and social functioning, including relationships, and perceptions of health, fitness, life satisfaction and well-being. Health-related quality of life

should also include assessment of the patient's level of satisfaction with treatment, outcome and health status and future prospective [32].

Health-related quality of life as an outcome variable

It is important that outcomes from cancer treatment include measures of HRQoL [34, 36-38], because, patient-reported outcome provide an understanding of the impact of illness from the patient's viewpoint [39, 40]. Reasons for measuring HRQoL in persons with cancer are to assess rehabilitation needs, as endpoints in evaluating treatment outcome and as predictors of responses to future treatments [41]. These measures also have a potential impact on the care environment because they provide information on patients' satisfaction about the quality of care provided [38, 42].

Assessment of health-related quality of life

A large number of HRQoL questionnaires have been developed and are available for use in research and clinical evaluations. These include generic, cancer-specific and domain-specific questionnaires [34, 42, 43].

Generic instruments, also called general instruments, are intended for use across a wide range of medical conditions. They are either unidimensional or multidimensional. The multidimensional instruments are composed of a number of subscales, each assessing a different HRQoL domain. The major advantage of generic instruments is that they allow comparison of results across patients with different diseases and conditions as well as with the general population. However, they may not adequately address those issues of relevance to specific diagnoses, such as disease symptoms and treatment side effects [34, 43]. Examples of generic questionnaires are the Sickness Impact Profile (SIP) [44], the Nottingham Health Profile (NHP) [45] and the Medical Outcome Study Short Form Health Survey (SF-36) [46].

The major advantage of the diagnose-specific instruments is that they are more likely to be responsive to disease-related changes in HRQoL [34, 43]. Examples of cancer-specific measures include the Cancer Rehabilitation Evaluation System Short Form (CARES-SF) [47], the Functional Assessment of Cancer Therapy-General (FACT-G) [48] and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [49]. EORTC QLQ-C30 is a widely used questionnaire to evaluate outcome in cancer diseases [50]. This 30-item questionnaire has been developed according to the so called modular approach for HRQoL assessment [43]. The "core" questionnaire (EORTC QLQ-C30) provides information about symptoms and problems commonly experienced by cancer patients in general. To obtain specific information in relation to different cancer diagnoses, several supplemental

diagnosis- and/or treatment-specific "modules" have been developed. The Head and Neck Cancer [51], Oesophageal Cancer [52], Breast Cancer [53], Colorectal Cancer [54] and Gastric Cancer [55] modules are some of the official and internationally validated modules available today. Detailed guidelines have been established by Sprangers and colleagues [56] on behalf of the EORTC for the development of such modules to supplement the core instrument EORTC QLQ-C30. The combination of a "core" instrument and a "module" allows for a sufficient degree of generalizability and specificity [34, 43].

Domain-specific instruments are designed to address one specific aspect of HRQoL (for example fatigue) in more details and are not always specific for cancer patients [43]. Examples of such questionnaires include the Multidimensional Fatigue Inventory (MFI) [57] and the Hospital Anxiety and Depression Scale (HADS) [58].

Variables related to health-related quality of life among SCT patients

Autologous versus allogeneic stem cell transplantation

Results from earlier studies have shown that a majority of patients experience an acceptable HRQoL one year or longer after SCT [22, 23, 59-63]. However, in spite of this overall positive picture, it has been shown that some areas remain impaired, such as physical functioning [60], and fatigue [25]. It has also been found that a number of patients are unable to return to work/education or perform certain daily tasks [62-64]. When compared, patients who have gone trough an autologous SCT tend to have a better HRQoL than patients who have gone trough an allogeneic SCT [60, 63, 65, 66]. There are, however, some exceptions to these general results. In a study by Hjermstad and colleagues [21] it was shown a significant difference in HRQoL between autologous and allogeneic patients at baseline. The autologous group reported more problems with emesis, appetite loss, dyspnoea, fatigue, sleep disturbance, constipation, physical, role and cognitive functioning and global QoL. As a possible explanation, it was suggested that the autologous patients were sicker than the allogeneic patients at baseline, or had undergone more chemotherapy of higher intensity over a longer period of time before SCT [21]. The development from baseline to the one year assessment showed, however, that the autologous group improved in functioning and had fewer symptoms whereas the allogeneic group had fairly the same scores after one year. At the one year assessment there was no significant differences between the two groups [21]. These results are in contradiction with other studies, where it was found that allogeneic SCT had a more negative impact on most HRQoL domains, compared to autologous SCT [60, 63, 65-68]. Watson and colleagues [68] compared autologous and allogeneic SCT

and found that physical, role and social functioning was significantly more impaired for allogeneic patients one year after SCT. This was also true for global QoL, fatigue, appetite loss, dry mouth and emesis [68].

Myeloablative conditioning versus reduced intensity conditioning

Reduced Intensity Conditioning (RIC) followed by allogeneic SCT has emerged as an alternative to conventional MyeloAblative Conditioning (MAC) [69-71]. The traditional allogeneic SCT includes myeloablative conditioning with high dose chemotherapy together with TBI to eliminate residual disease and recipient immunity in preparation for rescue of the patient with healthy donor derived hematopoietic stem cells [69, 72]. Over the years, the importance of immune reactions between donor-derived immunocomponent T-lymphocytes and host-type tumour cells has been recognized to be of major therapeutic importance in allogeneic SCT [69, 70]. The therapeutic principle governing RIC is the occurrence of a Graft-versus-Malignancy (GvM) effect. If no GvM effect develops then no therapeutic advantage is obtained [73]. One practical difference between MAC and RIC resides in the level of intensity of the conditioning regimen, resulting in less toxicity. Patients beyond the age limit of conventional allogeneic SCT (50-60 year) may therefore be candidates for this type of transplantation as well as patients that because of other medical conditions or the type of disease are poor candidates for HDC [11, 69, 70, 71, 73].

Medical research concerning SCT following RIC emphasizes that the treatment is less toxic [70, 72, 73], have lower incidence of infections [74] and that patients experience less mucositis [75] compared to MAC. There are also differences concerning GvHD. Acute GvHD after RIC commonly occurs 6-12 months after transplantation compared to a more immediate onset following conventional MAC. The onset of chronic GvHD may be slightly delayed [72]. However, patients receive chronic GvHD in the same amount as SCT patients following MAC, which in turn is a common cause of post transplant mortality [71, 73]. Reduced intensity conditioning reduces the treatment-related mortality [29, 76], but not with better overall survival due to an increased relapse incidence [29, 72, 77] and extensive chronic GvHD [71, 73, 78].

Psychosocial issues

Survivors after SCT have reported impairment on most of the commonly used indices of HRQoL domains of functioning i.e. physical, psychological and social functioning [20] A long-term goal of any treatment for a life threatening disease should include efforts toward reintegration into previous social and professional roles [62, 79], like returning to work [62]. Return to work has been shown to be significantly associated with better scores on most HRQoL domains among patients who have gone trough SCT [80]. However, the results are difficult to interpret, as it

is not clear whether patients return to work because of good HRQoL or whether HRQoL improves through the professional activity or the rewarding role of being self-supporting again [80]. It has been shown that patients who have gone trough an SCT have difficulties with readjustment to school and work, relation with family and social life [62, 63, 79, 81, 82]. Molassiotis and colleagues [63] found in their study that a fourth of patients after SCT were unable to return to fulltime work or studies. Similar results were presented by Andrykowski and colleagues [65] who found that a third of the patients were out of work or retired and they stated illness as a reason. This seems not to have changed over the years. Later studies showed that nearly half of the patients were unable to return to work after SCT [62, 79]. Edman and colleagues [22] could, however, show a more optimistic picture. In their study a majority (20 of 22) of patients who had gone trough SCT had returned to work or education 2-4 years after SCT [22]. To be unable to work is a source of worry among SCT patients, not only because it cause economic problems, it also affects the patient psychological with anxiety, sleep disorders, depression, impairments in social functioning, partnership and family life [59, 65, 79].

Symptoms

Patients receiving intensive therapies, such as SCT, may be at higher risk for developing multiple concurrent symptoms and side effects from therapy [18, 83]. The symptoms and side effects may further influence physical activity, perceived health status, and QoL [18, 84]. Fatigue has been reported as the most dominant physical symptom among SCT patients and a source of great disturbance in daily life [23, 25, 65, 79, 82, 85-87]. According to Glaus [88], most cancer patients experience fatigue as reduced physical fitness, weakness, extreme tiredness and an unusual need for rest. Maintaining or increasing levels of physical activity may play a role in reducing fatigue and improving HRQoL [18]. Other symptoms and problems that bother the patients after SCT is shortness of breath, nausea and vomiting, mouth problems, loss of appetite, sleeping difficulties, eyes dryness, skin problems, anxiety and weakness [22, 23, 65, 66, 87, 89, 90]. SCT patients also report sexual problems, sterility and problems with relationship [65, 23]. The influence of SCT on sexual function has been confirmed in several studies [23, 92-94]. Sexual dissatisfaction and difficulties were expressed as anxiety, pain, depression and the feeling of being physically incomplete [93]. Edman and colleagues [22] evaluated HRQoL after SCT, and the single problem most frequently reported was that the sexual activity was decreased.

Even as long as 2-5 years after SCT, patients report ongoing symptoms related to SCT [22, 25]. Since the number of long-term survivors after SCT is increasing, persistent residual treatment-related symptoms are more commonly occurring and pose a challenge for health care providers. Post-treatment symptoms can be a barrier to the resumption of pre-treatment functioning and also limit vocational activity and inhibit social recovery [83].

Graft-versus-host disease

Graft-versus-Host Disease (GvHD) is a major complication of allogeneic SCT [50, 68]. This is a cell-mediated rejection process where the immune-competent T-lymphocytes of the transplanted stem cells (graft) identify cells in the recipient (host) as foreign and attack them. It occurs in 40%-50% of all allogeneic SCT [95, 96] and can be divided into two types, acute and chronic [97]. Acute GvHD occurs within 100 days after engraftment of the stem cells and can be manifested in skin, gut and liver [96, 97]. The most frequently involved site of acute GvHD is the skin, where observed symptoms include a sometimes painful, pruritic and maculopapular rash. Gastrointestinal symptoms of acute GvHD include diarrhoea with or without anorexia, nausea and emesis [97]. If GvHD occurs after 100 days it is usually chronic. Clinical staging and grading of chronic GvHD is based on the severity of organ dysfunction and degree of organ involvement [96] and is described as limited (one organ site) or extensive (more than one site) [97]. Classic symptoms of chronic GvHD are skin changes resembling scleroderma and the sicca syndrome (i.e., extreme dryness of the skin, eyes and mouth). Other systems that could be affected of chronic GvHD are lungs, intestine, musculoskeletal, urologic, vagina and liver [7, 95, 97]. Although early mortality and morbidities have decreased substantially in SCT, chronic GvHD remains a major impediment to successful allogeneic SCT and continues to affect more than 50% of allogeneic SCT recipients [7].

Age and gender

There are different opinions in the literature concerning the influence of age and gender on HRQoL among SCT patients. Some studies show no significant impact on HRQoL owing to age [59, 98] or gender [59, 62, 79], while others found such relations. It has been shown that younger patients (62) and male patients had better HRQoL after SCT than before [23, 65, 90]. However, the opposite was found by Heinonen and colleagues [84]. The results from their study showed that patients receiving a transplant at younger age (< 40 years) had lower life-satisfaction compared to those at older age. One explanation might be that after SCT, younger patients find themselves more impaired in comparison with others in their age-group compared to older recipients [84]. Kopp and colleagues [66] found that male patients experienced significantly more pain after SCT than women. In a study where the authors examined gender-associated differences in the HRQoL after allogeneic SCT [99], it was shown that females perceived worse emotional well-being and more fatigue and had more problems with sleep compared to males. Males were found to experience less satisfaction with social support regardless of marital status. On the other hand, married males were more satisfied with their sexual life, more interested in sexual relationships, and more sexually active compared to married females [99].

Time since stem cell transplantation

Several studies have shown that HRQoL of SCT patients correlates positively with time since SCT [62, 66, 84, 86]. During the first year, after SCT, HRQoL is reduced, but thereafter improving with increasing interval to transplantation [62, 84]. Heinonen and colleagues [84] showed in their study that only 51% of the recipients where satisfied with HRQoL the first year after SCT, but this had increased to 81% after 5 years. Thus, there was an improvement in HRQoL after the first year post-transplantation.

RATIONALE

Health-related quality of life is a concept considered to be important for studying in health care. Most studies have focused on HRQoL for long time survivors, e.g. how the HRQoL was affected one year or more after SCT [22, 63, 65, 66, 82, 87]. Few studies are prospective and explore HRQoL during the first year after SCT [21, 64, 91, 100]. Because morbidity, relapse and mortality are significant during the first year after SCT [21, 64] it is of great importance to study HRQoL for this period. Knowledge of the patient's experience of a SCT and the effect on HRQoL can be used to refine the content and timing of educational and supportive interventions for patients undergoing SCT. Realistic information from caregivers about the often lengthy rehabilitation period is important. Knowledge about what to expect might help patients to reduce their frustration about shortcomings in their efforts to fulfil working and social roles [101]. Accurate information is also needed to adequately inform potential recipients and family members who are attempting to make a decision about transplantation [100].

AIMS OF THE THESIS

The overall aim was to improve our knowledge about how SCT patients experience different types of transplantations and the effect it may have on their HRQoL during the first year after stem cell transplantation.

Specific aims

I Field test a Swedish version of HDC-19 and to examine its validity, reliability and other psychometric properties in a group of patients undergoing SCT.

II Compare HRQoL during the first year after allogeneic SCT between patients who have received either reduced or full conditioning.

III Compare HRQoL during the first year between patients who have received either autologous or allogeneic SCT.

IV On the basis of patients' own narratives, describe how SCT patients perceive their HRQoL during the first year after SCT.

METHODS

Design

This thesis consists of a prospective, longitudinal study (papers I-III) and a qualitative interview study (paper IV) with the purpose of describing patient's experience of stem cell transplantation and the effect it may have on their HRQoL (Table 1).

Table 1. Presentation of design and methods for data collection and data analysis

Study	N	Objectives	Design	Methods for data collection	Method for data analysis
I	202	Field test a Swedish version of HDC-19 and to examine its validity, reliability and other psychometric properties in a group of patients undergoing SCT.	Field test of questionnaire	Questionnaire •HDC-19	Descriptive Validity, reliability, score distribution, responsiveness
II	57	Compare HRQoL during the first year after allogeneic transplant between patients who had received either reduced or full conditioning.	Descriptive, comparative, longitudinal	Questionnaires- •EORTC QLQ C-30 •HDC-19	Descriptive Development over time (Area Under the Curve) Mann-Withney U-test Fisher`s tests Fisher´s permutation test
III	202	Compare HRQoL during the first year between patients who received either autologous or allogeneic SCT.	Descriptive, comparative, longitudinal	Questionnaires- •EORTC QLQ C-30 •HDC-19	Descriptive Development over time (Area Under the Curve) Univariate Anova
IV	18	On the basis of patients' own narratives describe how SCT patients perceive their HRQoL during the first year after SCT.	Descriptive	Semi-structured interviews	Content analysis

Setting

The present studies were conducted at the section of Haematology, department of Medicine - Sahlgrenska University Hospital in Göteborg, Sweden, which serves 1.6 million inhabitants in the western part of Sweden. The first SCT at this department was performed in 1989 and now approximately 120 stem cell transplantations are performed each year. The distribution between autologous and allogeneic SCT is 75% autologous SCT and 25% allogeneic SCT and of these 30-50% receive reduced intensity conditioning (RIC).

Inclusion and exclusion criteria

Subjects included in study I-III consisted of patients who had been referred to the section of Haematology, department of Medicine at Sahlgrenska University Hospital and been accepted for SCT between the end of November 2000 to July 2004. Inclusion criteria were; age over 18 years, ability to speak and understand Swedish and no mental illness. In study IV the patients, except age and mental status, had to be within the first year after SCT to be included in the study.

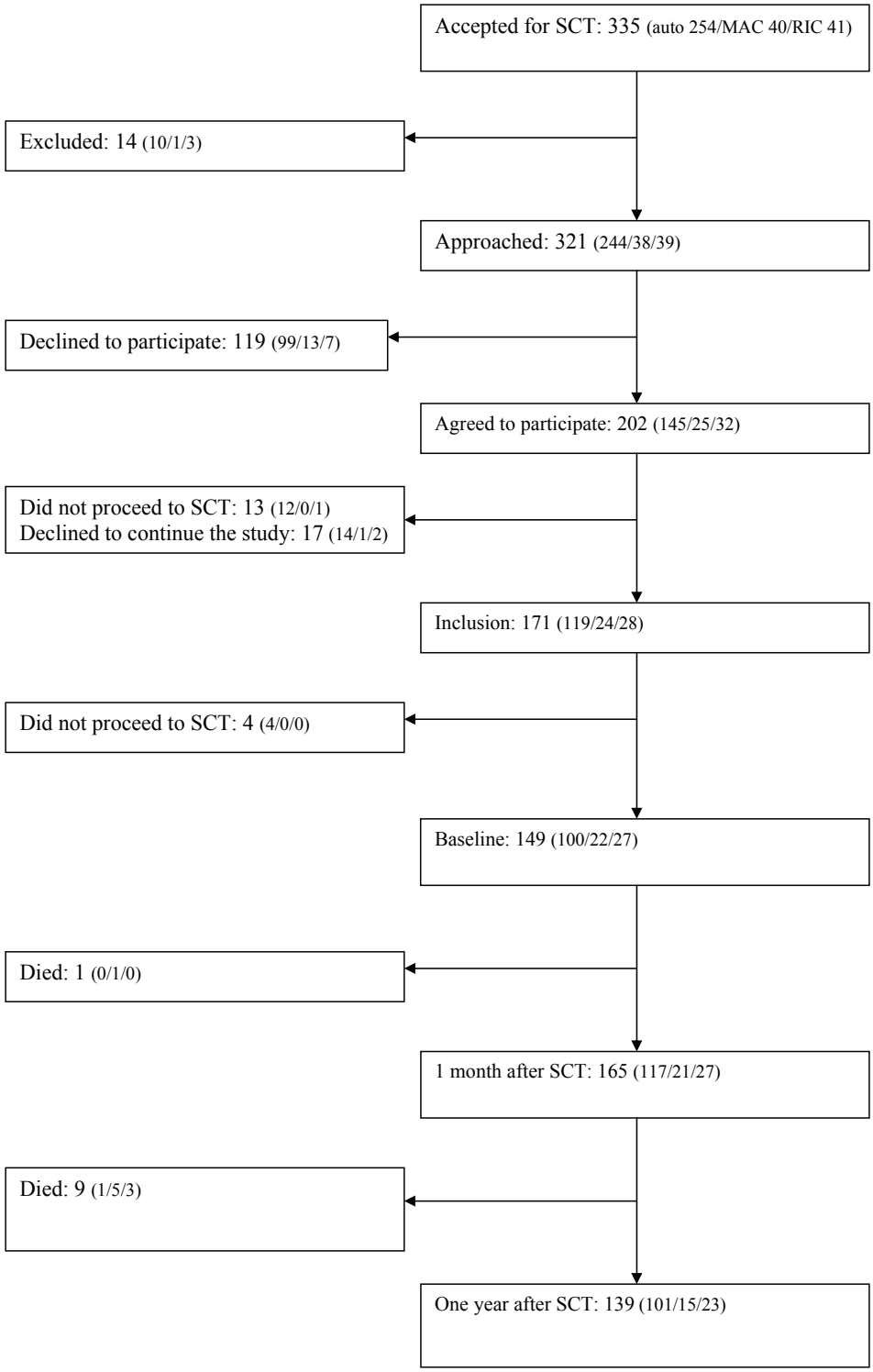
Sampling and participants

During the inclusion period, 335 patients were accepted for SCT (254 for autologous SCT and 81 for allogeneic SCT). Three patients were excluded because they were under 18 years, 8 did not speak or understand Swedish and 3 had mental illness. Of the remaining 321 patients meeting the inclusion criteria, 202 agreed to participate in the study. Figure 1 shows a flowchart of attrition from approach to the one year follow-up.

In study I and III the empirical data from both the autologous (145 patients) and allogeneic group (57 patients) were used. During the one year follow-up 17 patients declined to continue the study, 10 patients died and 17 patients did not proceed to SCT. In all, 139 (101 autologous, 23 RIC and 15 MAC) patients were followed during the first year after transplantation. In study II only the empirical data from the allogeneic group were used since the aim of the study was to compare HRQoL between allogeneic SCT after MAC versus allogeneic SCT after RIC. During the inclusion period, 81 patients were accepted for allogeneic SCT (40 for allogeneic SCT after MAC and 41 for allogeneic SCT after RIC). Of these, four did not fulfil the inclusion criteria. The remaining 77 patients were approached and 57 (73%) (25 MAC / 32 RIC) agreed to participate in the study. During follow-up, one MAC patient and two RIC patients declined to continue the study, six MAC patients and three RIC patients died and one RIC patient did not proceed to SCT. In all, 38 (15 MAC and 23 RIC) patients were followed during the whole follow-up period.

In study IV, data was gathered from 18 patients who were strategically selected to obtain variation regarding age, sex and source of stem cells (autologous or allogeneic). Only one patient who was approached had no wish to participate in the study.

Figure 1. Attrition of patients from approach to one year follow-up.



Data collection and procedure

After informed consent the patients were asked to complete two questionnaires, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (version 3.0) and High-Dose Chemotherapy 19 (HDC-19), at six occasions. The questionnaires were administered at inclusion (mean 49 days before transplantation), at admission to hospital (mean 8 days before transplantation) and at 30 days, 100 days, 6 and 12 months after transplantation. They were administered to the patients as inpatients when applicable or by mail after telephone contact. One reminder for each occasion was sent out when needed. Demographic and clinical data were obtained from medical records.

The assessment at admission to hospital was used as baseline for most patients. However, for 18 patients the assessment at inclusion was used as baseline. The reason for this was that the interval between inclusion and hospital admission for transplantation was very short for these patients (in average four days). Therefore it was decided that these 18 patients should not be requested to fill in questionnaires in connection to their hasty admission.

Questionnaires study I-III

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Health-related quality of life was measured using a Swedish version of the EORTC QLQ-C30 (version 3.0) [49]. The EORTC QLQ-C30 is a core questionnaire i.e. designed to cover a range of domains relevant for a broad spectrum of cancer patients. It consists of 30 items, covering six scales measuring physical, emotional, social, cognitive, role functioning, and global QoL. Three symptom scales measuring fatigue, pain, and nausea/vomiting, and 6 single items measuring financial impact and the symptoms dyspnoea, sleep disturbance, appetite loss, diarrhoea, and constipation (see appendix I). The time frame is the past week. All items are rated on a 4-point response scale ranging from 1 (not at all) to 4 (very much), except the two items measuring general health and QoL (global QoL), which have visual-analogue scales from 1-7. All scales and single items are transformed to a percentile scale from 0-100. Higher scores on the functioning, global QoL scales represent better health whereas high scores on the symptom scales and single items indicate a higher level of symptoms and/or problems [49, 102].

High-Dose Chemotherapy 19 (HDC-19). It is recommended that the EORTC QLQ-C30 core questionnaire is supplemented by a questionnaire module specific to particular cancers or treatments [56]. For this purpose a preliminary High-Dose Chemotherapy module (HDC-19) was developed by Hjermstad and colleagues [90] in order to assess specific HRQoL issues relevant to patients undergoing HDC followed by SCT. The factor structure and psychometric properties of a Swedish

version of this module was tested in the first paper of this thesis (see data analyses and results below). The module consists of 19 questions covering circulation, mouth and skin symptoms, pain, anxiety, sexuality, social support and perspectives regarding future health (see appendix II). It has 4-point response scales and is scored according to EORTC guidelines [49, 56, 90]. Items focusing on sexuality, future health perspective and social support constitute functioning scales and items focusing on symptoms form symptom scales. As in the EORTC QLQ-C30, functioning scales are calculated so that higher scores represent better functioning, whereas higher scores on the symptom scales represent higher levels of symptoms. All scales were transformed to a 0-100 scale.

Study IV (interviews)

The general purpose of the present thesis was to increase our knowledge how STC patients perceive their HRQoL during the first year after STC. In line with this purpose the qualitative descriptions in study IV and the quantitative data obtained in study I-III complement each other.

According to Kvale [103] the conversation is fundamental for human interaction. Through the conversation we learn to understand other humans, we learn about their experiences, feelings and expectations and about the world they live in [103]. The qualitative research interview is included in the professional conversation and is used in the exploration of the meanings of social phenomena as experienced by individuals themselves in their natural context [103, 104]. An interview is a conversation with a structure and a purpose. The interview is a way for the interviewer to obtain thoroughly tested knowledge through carefully asked questions [103].

The patients in study IV were approached by mail, given an information sheet detailing the aims of the study, the procedure and ensuring confidentiality of their responses. After one week the patients were contacted by phone, enabling the patients to ask questions and obtaining further information about the study, if needed. After informed consent an appointment for the interview was made. All interviews, except one, took place in a private room at the hospital in connection with visiting the outpatient clinic. The remaining interview took place in the patient's home. The interviews lasted approximately between 30 and 60 minutes.

The interviews began with the following question: "Please describe how the stem cell transplantation has affected you from the start of the conditioning until today"? The open nature of this question gave the patients freedom to portray their own story, after which the interview focused on elements of the given story. In order to influence the persons positively to tell more about their experiences, the interviewer were silent during most of the interview, just nodding and saying Yes, I see, Can you tell me more about……, How did you feel about that…..? and so forth. The

interviews were performed by the first author, who also transcribed all interviews. Before analysing, the first author listened to all interviews while reading the transcription in order to be able to make corrections and possible additions (pauses, laughter and sighs) to the text.

Data analyses

Study I

Tests of internal structure between items. Principal component analyses with varimax rotation were performed to examine for potential multi-item scales among the 19 items in the HDC-19 module. Three strategies were used to determine the number of tentative factors to retain - Cattell's scree plot, absorption of variance and face validity of factors [105]. The tentative multi-item factor structure that best fitted a compromise of these criteria across all assessments was then tested by means of multi-trait scaling analysis [106]. This technique is based on item-scale correlations and examines convergent and discriminatory validity.

Reliability. Test-retest reliability was examined with Intra-Class Correlations (ICC) between the assessments at inclusion and baseline, since relatively stable health could be expected during this period [107]. The internal consistency of multi-item scales was assessed by Cronbach's alpha.

Score distributions. Score distributions of both HDC-19 multi-item scales and single items were examined. These analyses also included proportions of missing values, proportions of respondents scoring at maximum (ceiling) or minimum (floor) levels and the extent that the full range of possible scores was used.

*Clinical validity***.** Clinical validity was examined with two methods. First, known-groups comparison was performed to assess the ability of the HDC-19 to discriminate between mutually exclusive groups of patients expected to differ in clinical status. Second, changes in HDC-19 scores over time were compared with changes in EORTC QLQ-C30 'global QoL'. Three categories of mutually exclusive groups were elaborated based on clinical experience: 1) patients with multiple myeloma versus lymphoma; 2) patients in Complete Remission (CR) versus Partial Remission (PR); 3) patients receiving stem cells from Related Donors (RD) versus patients receiving stem cells from UnRelated Donors (URD). Lymphoma patients were expected to have more symptoms compared to multiple myeloma patients because they had received more chemotherapy in their conditioning related to SCT. Patients in CR before SCT were expected to experience fewer symptoms compared to patients in PR because of a better starting-point, i.e. the latter had often received more chemotherapy of higher intensity over a longer period. Patients with RD were expected to have fewer problems after SCT than URD patients because of a higher risk for GvHD and infections in this latter

group. The known-group comparisons were performed on the assessments one month after transplantation because the highest levels of symptoms and problems were expected at this time.

Responsiveness. This was examined by computing dependent t-tests (p-values) and Standardised Response Means (SRM) between baseline and the subsequent assessments. The SRM is defined as the ratio of the mean change to the SD of that change [107]. Commonly the thresholds suggested by Cohen [108] are used to define what is regarded to be small (0.2-0.5), moderate (0.5-0.8) and large (above 0.8). Most changes in health perceptions were expected to occur between baseline and the two subsequent assessments (one and three months after transplantation, respectively).

Study II-III

As a summary measure of how HRQoL developed over time, the Area Under the Curve (AUC) was calculated. The AUC is the area between the longitudinal profile and the horizontal axis representing a zero score for each individual [107]. The AUC gives a summary measure of each patient's longitudinal experience as a single quantity. It was calculated for all scales of both questionnaires across all 5 measure points. Apart from differences in AUC, significances between treatment groups were only tested at baseline, one month and 12 months after SCT. The reason for this simplification was that the assessments 3 and 6 months after SCT followed the improving trends observed from 1 to 12 months after SCT and thus, did not add any information beyond the latter ones. It also reduced the number of tests performed.

To compare HRQoL between the two allogeneic groups of patients who had received MAC or RIC in study II, Mann-Withney U-test was used. Changes over time between baseline and one month and 12 months after SCT, respectively, were examined for both groups. In these dependent tests, Fisher`s test for paired comparison was used [109]. Differences in change scores between the MAC and RIC groups were examined with Fisher´s permutation test [109]. The relation between global QoL and relapse and GvHD was examined with Fischer´s exact test.

The results from study II indicated that, the RIC group regained global QoL faster compared to the MAC group. As a result of these findings and because of earlier research [110], in study III we choosed to divide the allogeneic group, with consideration to reduced (RIC) or full (MAC) conditioning. This means that three treatment groups were compared in study III (autologous, RIC and MAC). Univariate ANOVA with post hoc tests according to Tukey was used to test for differences in scores between these three groups.

To evaluate the clinical relevance of differences in HRQoL data measured by the EORTC questionnaire, it has been suggested that differences greater than 10 could be regarded as clinically important [40, 111, 112]. These limits were used to complement the statistically significant results as rough indicators of clinical important differences/changes.

Study IV

The method used for analyzing the data in study IV was content analysis, which is a research method that has come into wide use in health studies [113]. Krippendorff has defined it as "a research technique for making replicable and valid inferences from texts to the contexts of their use" [114, p 18]. Content analysis is appropriate when existing theory or research literature on a phenomenon is limited. Researchers avoid using preconceived categories instead allowing the categories and names for categories to flow from the data. Researchers immerse themselves in the data to allow new insights to emerge, also described as inductive category development [113]. Content analyse has a long history in research, dating back to the 18th century when it was used to analyse religious texts [113, 114]. Not until World War II it was named content analysis, when it was used in journalism to analyse documents, producing counts of words or phrases [114]. There are now several approaches to content analysis in literature, social sciences and critical scholarship. Thus, content analysis has evolved from its original use for analysis of the written word into a research method in its own right, which enables data to be analysed with respect to their expressive contents, symbolic qualities and meanings [114]. When performing content analysis it is important to decide whether the analysis should focus on manifest or latent content. Analysis of what the text says deals with the content aspect and describes the visible, obvious components in the text, referred to as the manifest content. In contrast, analysis of what the text talks about involves an interpretation of the underlying meaning of the text, referred to as latent content [115].

There is no single set of rules and procedures for content analysis. However, in study IV, the analysis was influenced by Graneheim and Lundman in their overview of concepts, procedures and interpretation [115]. All interviews (unit of analyse) were read repeatedly by the first author of that study to achieve immersion and a sense of the whole. The second and third authors of the study also read the transcribed interviews to obtain a general impression. The text concerning the research questions were than marked and taken into one text, i.e. meaning unit. The meaning unit were then condensed and labelled with codes. All codes were controlled back to the meaning unit and some codes were changed. Codes with similar content were marked with different colours and tentative themes were formed. The themes were discussed and revised several times by the three authors before they were finally sorted into four themes. Only the first theme was divided into subthemes.

ETHICAL CONSIDERATIONS

The research project was approved by the research ethics committee at University of Gothenburg (Dnr: S 404-00 and 339-09). All patients received both oral and written information that their participation was voluntary and that they could withdraw at any time without affecting their treatment or care and without the need to provide any reason for withdrawal. Confidentiality was guaranteed by coding the questionnaires. Collected data and personal data were stored separately according to the Swedish data protection law (116 SFS1998:204). Important considerations in all studies were respect for the individual's autonomy and to avoid the risk of causing emotional and psychological distress through interviews and questionnaires. The potential risk of participation in the studies was of psychological character and there was preparedness if the patient was reminded of distressing situations. If there was a need for conversational therapy the patient could always contact the first author who could arrange further help from the clinic.

RESULTS

Study I – psychometric tests of HDC-19

Demographic and clinical data

Mean age was 51 (19-70) years and 60% of the patients were male. The largest diagnostic groups were lymphoma (33%) and multiple myeloma (28%). Other diagnoses were acute leukaemia (15%) and chronic leukaemia (7%). One hundred and forty-five 145 (72%) of the patients had gone trough autologous SCT and 57 (28%) had gone trough allogeneic SCT.

Tests of internal structure between items

The principal component analyses suggested that 10 of the 19 items in the HDC19 could be reduced to 4 components. These components were named future health perspective (items 11, 12, 13), sexual functioning (items 17-19), joint and muscle pain (items 9, 10) and skin irritations (items 7, 8). Multi-trait scaling analysis showed that most item-scale correlation coefficients met the standards of convergent (> 0.40) and discriminant validity. The other 9 items were kept as single-item scales.

Score distributions

The most common symptoms were ‘feeling cold more easily’, ‘change of taste’, ‘dry mouth’ and ‘potency problems’ (among men). ‘Sexual functioning’ was low, but ‘future health perspective’ was relatively positive. The lowest levels of functioning and highest levels of symptoms were found one and three months after the transplantation.

Reliability tests

The test-retest reliability coefficients between the assessments at inclusion and baseline were very high for all scales, ranging from 0.96-1.00. The Cronbach’s alpha of the multi-item scales was also acceptable.

Clinical validity

Overall, the known-groups comparisons showed smaller differences between designated groups than expected. However, changes in the HDC-19 mirrored the changes in QLQ-C30 global QoL.

Responsiveness

Most changes were found between the assessments at baseline and one month after transplantation. This was particularly true for 'feeling cold more easily', 'dry mouth' and 'change of taste'. Moderate changes were noted for 'sexual functioning', sexual enjoyment', 'skin irritations', 'dizziness', 'increased mucous production, 'soreness in the mouth' and 'potency problems'. Smaller changes were observed between baseline and the assessment three months after transplantation. Although, functioning and symptoms largely tended to improve after 3 months, significant impairments were still found up to 12 months after transplantation for 'sexual functioning', 'joint and muscle pain' and 'change of taste'.

Study II – differences in HRQoL between full conditioning (MAC) and reduced conditioning (RIC)

Demographic and clinical data

Mean age was 38 years in the MAC group and 50 years in the RIC group. This age difference was statistically significant ($p \leq 0.001$). There were relatively more females in the RIC group (53%) compared to the MAC group (44%), but the difference was not significant. The largest diagnostic groups were acute myeloid leukaemia (36%) and acute lymphatic leukaemia (36%) in the MAC group, and acute myeloid leukaemia (28%) and chronic myeloid leukaemia (22%) in the RIC group. The incidence of acute GvHD grade 2-3 was higher in the MAC group (44%) compared to the RIC group (13%). In contrast, the incidence of chronic GvHD was similar in the two groups; 36% and 40% in MAC and RIC groups, respectively. No significant differences were found in global QoL between patients with and without GvHD, irrespective of whether this was acute or chronic.

Overall development of HRQoL over time

The highest symptom scores and lowest functioning scores were experienced one month after SCT. Thereafter the levels of symptoms decreased and levels of functioning increased, hence returning to baseline levels. However, the MAC group appeared to experience more symptoms and lower levels of functioning on most

scales. Because of the significant age difference between the groups, correlations between age and HRQoL data were specifically examined. Age correlated significantly with physical functioning and fear of sterility at baseline and one month after SCT. Older patients perceived lower physical functioning, and younger patients had more fear of sterility. To estimate the overall development of functioning and symptoms AUC values for both treatment groups were compared. The MAC group experienced significantly more impairment in social functioning and higher values on appetite loss, change of taste and financial problems.

In the continuing presentation of differences in scale scores from paper II and III we will report the clinically significant results (differences and changes of 10 scale scores or more). However, in most cases the clinical significance corresponded to statistical significances. For a more detailed report we refer to the original papers.

Differences in HRQoL between the groups one month and one year after SCT

In the comparisons between groups one month after SCT, differences with clinical significance were found for sleep disturbance, financial impact, skin irritations, soreness in mouth, and change of taste. For all these symptoms and problems the differences were in favour for the RIC group. One year after SCT, symptom scores had decreased and functioning had improved in both groups. The only difference between groups was dry mouth, which remained as more problematic for the MAC group compared to the RIC group.

Changes in HRQoL from baseline to one month after SCT

One month after SCT the MAC group had deteriorated in 20 of total 29 scales in the EORTC QLQ-C30 and HDC-19. The greatest differences were found for fatigue, sleep disturbance, appetite loss, change of taste, dry mouth, potency problems, physical functioning, role functioning, sexual functioning and global QoL. In the RIC group, differences with clinical significances were observed in 8 of the 29 scales: Fatigue, dyspnoea, appetite loss, felt cold more easily, change of taste, physical functioning, role functioning and global QoL. When comparing differences in change over time between the MAC group and the RIC group the greatest differences were found for cognitive functioning, sleep disturbance, soreness in mouth, dry mouth, change of taste and potency problems. In all cases the MAC group showed more deterioration.

Changes in HRQoL from baseline to one year after SCT

One year after SCT the MAC group still reported higher scores compared to baseline in 14 of 19 symptom scales. Differences in change scores were found for: Fatigue, pain, joint and muscle pain, dry mouth and potency problems. For the RIC

group, change scores had decreased and functioning had improved to baseline levels or better in 10 of 29 scales. Improvements with clinical significance were found for role functioning and future health perspective. In the comparison between groups there remained differences in change scores for fatigue, pain, sleep disturbance, dizziness, dry mouth and potency problems. For all these symptoms and problems the differences were in favour for the RIC group. There was also a difference between the groups in global QoL. The MAC patients rated their global QoL lower compared to baseline, whereas RIC patients valued their global QoL higher compared to baseline.

Study III - differences in HRQoL between autologous and allogeneic (RIC and MAC) SCT

Demographic and clinical data

Mean age was 54 years in the autologous group (60% male), 50 years in the RIC group (47% male) and 38 years in the MAC group (56% male). The age difference between groups was significant ($p<0.000$), the MAC group deviated significantly from the other two groups. For this reason age was used as a covariate in the ANOVA tests. The largest diagnostic groups in the autologous group were lymphoma (41%) and multiple myeloma (40%). In the allogeneic group (RIC and MAC) the largest diagnostic groups were acute leukaemia (28/72) and chronic leukaemia (28/8).

Overall development of HRQoL over time

The overall development followed the same pattern as in study II with highest symptom and lowest functioning one month after SCT for all three groups. Thereafter the levels of functioning increased and levels of symptom decreased. The MAC group, however, demonstrated lower functioning scores and higher symptom scores compared to the other two groups. Statistical significance tests of the AUC values showed that the MAC group experienced significantly more sleep disturbance, felt cold more easily, had more skin irritations, more of sore mouth and change of taste compared to the other two groups.

Differences in HRQoL between groups one month and one year after SCT

When comparing the groups one month after SCT differences with clinical significance was found for sleep disturbance, skin irritations, sore mouth, change of taste, dry mouth and potency problems. The MAC group differed from the two

other groups in most domains, i.e. they experienced more sleep disturbance, had more skin irritations and more problems with change of taste. The RIC group experienced significantly less change of taste, dry mouth and potency problems compared to the autologous group and the MAC group. One year after SCT differences with clinical significance was found for sleep disturbance and dry mouth. In both cases it was the MAC group that deviated from the other two groups, i.e. they showed significant more of sleep disturbance and dry mouth.

Changes in HRQoL from baseline to one month after SCT

From baseline to one month after SCT, the autologous group deteriorated in physical functioning, role functioning, global QoL, fatigue, nausea and vomiting, dyspnoea, appetite loss, diarrhoea, feeling cold more easily, increased mucous production, dry mouth and change of taste. The RIC group changed correspondingly in physical functioning, role functioning, global QoL, fatigue, nausea and vomiting, appetite loss, dyspnoea, feeling cold more easily and change of taste. In the MAC group, changes were observed in 20 of the 29 scales. The greatest differences with clinical significance in change score was found for physical functioning, role functioning, global QoL, fatigue, sleep disturbance, appetite loss, sexual functioning, feeling cold more easily, dry mouth, change of taste, and potency problems. When comparing the change scores between groups it was found that the MAC group tended to deviate from both the autologous group and the RIC group. Compared to the other two groups, the MAC group deteriorated significantly more during the first month after SCT in sleep disturbance, sexual functioning, sore mouth and potency problems. No differences in change scores were observed between the autologous group and the RIC group.

Changes in HRQoL from baseline to one year after SCT

Compared to baseline levels, the autologous group had improved in role functioning, social functioning, fatigue, appetite loss and change of taste. The RIC group had improved in role functioning, social functioning, dyspnoea and constipation. However, the MAC group still reported a deteriorated health in 10 of the 29 scales. Lower scores, with clinical significance, was observed for emotional functioning and global QoL as well as higher scores for fatigue, pain, joint and muscle pain, dizziness, dry mouth, changed taste, fear of sterility and potency problems. When comparing change scores between groups it was found that the MAC group still tended to show more deterioration over time compared to both the autologous and RIC group. Compared to the other two groups, the MAC group showed more change during the first year in pain, sleep disturbance, dizziness, dry mouth and potency problems.

Study IV – patient descriptions about their HRQoL

Demographic and clinical data

Study IV utilized data from 18 patients, 9 males and 9 females. The mean age for the patients was 52 year. Ten of the patients had gone through allogeneic SCT and 8 autologous SCT. The patients were 8-14 months post SCT with a mean of 11, 7 months.

Extracted themes

Four themes emerged in the data analysis. These were labelled; *obstacles on the road to normality, to be part of normal life, the chance to be cured overshadow everything* and *new values in life*. The themes illustrate how the patients described their life from discharge until one year after SCT. The first of the themes, *obstacles on the road to normality*, also included five subthemes, labelled; *physical, psychological* and *social restrictions, responses from family and friends* and *changed opportunities in life*.

Obstacles on the road to normality

Physical restrictions

Symptoms from the mouth, fatigue, GvHD in mouth, skin, intestine and genitals, pain and the increased risk for infections restricted the life of the patients. The physical symptom that caused most restrictions was fatigue. This symptom was a major hindrance for returning to work and only 44% of the patients were working half time or more. Fatigue was worse at discharge but all of the patients expressed some degree of fatigue even one year after SCT. Fatigue did not only restrict their ability to work but also their motivation to do things with friends and family. Most of their physical strength was spent on work, housework and visiting the out-patient clinic at the hospital. Restriction in food intake was described as a periodically occurring problem for most of the patients. One reason for this was GvHD with pain, dry and sour mouth, but also changes of taste and medication that made them nauseous. The patients could only eat very small portions and for some of the patient's, fluids was the only choice. Symptoms related to food intake lasted from weeks to months after discharge from the ward. The chemotherapy given to the patients in connection to SCT eventuate to a profound pancytopenia increasing the risk for infections over a long period. Furthermore, if the patients had an allogeneic SCT and because of that had to take immunosuppressive medication because of the GvHD, the risk for infections would be extended. The increased risk for infections restricted their lives and some patients avoided being with friends and/or relatives like grandchildren. Side-effects from medication were another thing that restricted

life. This was especially true for those who were treated with corticosteroids for longer periods, which caused sleep disturbance, weak skeleton, changed their appearance with swelling (especially the face), bruises and fragile skin and because of this they avoided the public.

Psychological restrictions

Some patients described that they became angry more easily, for no reason at all. They did not manage stress as well as before and they also described difficulties to concentrate. This also hindered their capability to work as they did before. Worries and thoughts of relapse were also perceived as a restriction to fully enjoy life and an obstacle to have a normal life.

Social restrictions

The social life was restricted in one way or another after SCT. All of them had medication for a varying period after SCT and this together with treatments not only restricted them socially but also constantly reminded them of the disease and the SCT. The patients experienced that some friends were scared of the disease and the SCT, they did not know what to say and for this reason they avoided the diseased. On the other hand, some patients felt that they had nothing in common with their friends any more and were reluctant to contact them.

Problems to manage the response from family and friends

To manage the period after SCT there was a need for the patient's to talk about and share the SCT experience with someone. However, negative response from family members and friends stopped some of them from talking about the SCT experience at home. The family did not want to be reminded or they did not share the same experience of the SCT period. The patient's were also afraid to upset their family and because of this they did not talk about their feelings or if they had symptoms that could be interpreted as signs of relapse.

Changed opportunities in life

Even if the SCT gave the patients a chance to live longer and even to be cured, the disease and its treatment had changed their opportunities in life, meaning that plans for the future had to be altered, for some in a negative way. Their visions and plans of a family, education or work could not be taken for granted any more. It was not only the disease and treatment that changed the opportunities, but people around them also thought of them as less capable to come anywhere in life.

To be part of a normal life

This theme described the patients longing back to the life they had before SCT. It was important to be part of a normal life and not giving up because of the disease, symptoms or late effects that followed the SCT. They were striving to do things that they wanted to do and not letting, for instance, fatigue rule their lives. On the road back to a normal life it was important for them to have someone to share their thoughts and worries with; what is normal, how you feel, what you do about it, how your children react and so on. Some of the patients obtained help from their family and friends but other preferred to talk to other patients or the nurses when visiting the out-patient clinic.

The chance to be cured overshadow everything

All of the patients expressed how grateful they were to still be alive. They were aware that without SCT they most likely had been dead by now. This belief made it easier to deal with problems - it was the price they had to pay to be alive. However, all side effects were not interpreted in a negative way. The patients who had gone through an allogeneic SCT were aware that GvHD had a Graft-versus-Leukaemia (GvL) effect that decreased the risk of relapse and increased the chance to be cured.

New values in life

The last theme that emerged from the data described how the SCT had changed their values in life. Life was not taken for granted any more and the patients had become more humble to life. They had learned to appreciate ordinary things more, things that before was taken for granted. The patients also described that it was important to have time of their own and to be surrounded with positive energy. They more actively choose to be with people who made them feel good, time was too valuable to spend on others problem.

DISCUSSION

Stem cell transplantation is a potentially curative treatment for various hematologic malignancies, certain solid tumours and immunologic disorders [3, 4]. Results are improving with the course of time and this has led to a reduced morbidity, mortality and accordingly increased life expectation. The number of patients surviving SCT has grown and because it is an exceedingly aggressive and demanding treatment, significant concerns related to HRQoL have been raised [86]. Such information has become an important outcome measure in health care to gain insight into the patients' perspectives of their disease and treatment since this type of information gives a more comprehensive evaluation of treatment outcome than survival and relapse-free intervals alone [117].

In this thesis we focused on the first year after autologous and allogeneic SCT to describe HRQoL and compare the different treatment groups with each other. Despite that results show a significantly reduced HRQoL within the first year after SCT [66, 68, 90] little attention has been paid for this period. The first year post-transplantation has shown to be essential for returning to normal life and to prevent delayed psychosocial adjustment [100]. Research concerning the way in which the patient perceive life after SCT gives important knowledge for health care providers and are prerequisites for providing realistic information and good nursing practice.

The impact of autologous versus allogeneic stem cell transplantation

Despite improvement in care and HRQoL of the recipient, allogeneic SCT continues to produce significant, long-term complications [97]. This was also shown in the present thesis. In study II where two different treatment groups before allogeneic SCT were compared (MAC versus RIC), the results indicated that they showed a similar pattern of development over time in functioning and symptoms, albeit more severe in the MAC group. One year after SCT the MAC group still reported a high incidence of symptoms, particularly dry mouth, pain, joint and muscle pain, fatigue and decreased potency. In spite of this, no significant differences in global QoL between the two groups were seen one year after SCT. However, RIC patients returned to baseline level earlier in global QoL. Compared to other studies the results from study II indicate that, the RIC group regains general health and QoL faster compared to the other treatment group [110, 118]. Bevans and colleagues [110] found no significant differences between MAC and RIC. Díez-Campelo and colleagues [118] compared patients who received RIC before SCT with autologous SCT. The later group experienced more symptoms and problems the first six months after SCT and than gradually improved while patients after RIC experienced more symptoms and problems from six months to one year

assessment. Because of these differences we found it important to divide the allogeneic group, with consideration to MAC or RIC, in the continuing work.

After SCT there is a gradual improvement in both autologous and allogeneic groups, but autologous patients seem to recover faster during the first 6 months [25, 119, 120]. This is in accordance with study III, with one unexpected result though. The RIC group tended to recover in the same way as the autologous group and the two groups was more alike in their HRQoL scorings compared to the MAC group. There were no significant differences in change scores from baseline to one month after SCT between the autologous and the RIC group. One possible reason for this could be that the RIC and autologous groups were relatively equal in age, mean age 54 and 50 years respectively, compared to 38 years in the MAC group. Another reason is that both autologous SCT and RIC are considered to be procedures associated with less toxicity related problems and lower treatment related mortality compared to SCT after MAC, and for this reason perhaps more comparable than RIC versus MAC [118]. Thus, the results from study III further emphasize the need to separate RIC and MAC when evaluating the effect on HRQoL after SCT. This knowledge about differences and similarities between treatments is important for health care providers when patients and their relatives are informed about SCT. More individual and realistic information might give the patient a better chance to be prepared how they will experience the SCT and what to expect during the rehabilitation period. Inappropriate information and, consequently, small possibilities for preparation, might contribute to a feeling of loss of control over one's life [121].

Symptoms interfering with daily life after SCT

Symptoms related to the digestive system like; dry mouth, sore mouth, appetite loss and change of taste were among the most frequent symptoms throughout the whole SCT period for all three groups (paper II-IV). In the MAC group symptoms of dry mouth and change of taste even increased, and one year after SCT these symptoms were more pronounced compared to baseline (paper II-III). One reason could be that this group of patients predominantly received TBI in their conditioning regimen. Patients undergoing chemotherapy and/or irradiation may experience sore mouth [122] altered taste and mouth dryness [85, 89, 123] which may have a significant impact on daily life. Other symptoms related to dry mouth described in the literature are absent or thick, ropy saliva, burning or a sore sensation on the tongue and cracked lips [123]. Change of taste also seems to be closely associated with dry mouth [85]. Mouth dryness is rated as one of the most distressing symptom by patients [22, 23, 89, 91]. Despite this, few studies have focused on this symptom or suggesting interventions that could give some relief for this long lasting problem [123]. The autologous group also experienced significantly more change of taste at baseline (paper III). One explanation might be that they had received more chemotherapy over a longer period before SCT compared to the

other two groups. It could be problematic for patients to resume eating when suffering from nausea, dry mouth, reduced or altered taste and smell, following the cancer treatment [85]. Patients undergoing SCT may because of this suffer significant weight loss due to decreased food intake, decreased absorption and increased metabolic demands [8, 85]. In addition to HRQoL, the ability to preserve or gain weight and to resume and maintain oral intake may have a significant impact on the outcome of therapy and QoL [85].

Fatigue was a further symptom that was common one month after SCT in all three groups (Paper II-III). This is the time when most of the patients are discharged from the hospital. For the majority of patients, discharge from hospital is synonymous with a return to "normal life" [124]. However, the reality has shown to be different. Fatigue has been found to be a common long-term effect of SCT [22, 23, 87, 91] and described as one of the most prevalent and debilitating symptoms related to cancer treatment in general [125]. Fatigue was also one of the most dominant symptoms reported by the patients in study IV. Even as long as one year after SCT it restricted their life and was seen as an obstacle on the way back to normal life (Study IV). It has also been shown that fatigue may interfere with daily life for many years after SCT and to reduce HRQoL [25]. In study IV fatigue was one important reason for not being able to work full-time. This finding corresponds well with other studies [22, 82, 91, 126]. In a study from Dow and colleagues [17] SCT patients described their attempts to maintain independence and argued that this was a sign of health. Independence was synonymous with the ability to work and be productive. Previous research also show that survivors become frustrated over not being able to return to work more quickly [82, 126] or over the lack of strength they experienced when returning to work [126]. Patients also asked for more explicit recommendations to maintain strength and activity tolerance [127]. Thus, it is evident that there is a need for health care providers to actively ask the patient about problems related to fatigue and inform them that fatigue is a long lasting symptom that could last for several years after SCT.

A major complication after allogeneic SCT is GvHD witch may have an impact on patients' HRQoL [50, 68]. In study II many of the symptoms that occurred one year after SCT may be related to chronic GvHD e.g. dry mouth, pain and joint and muscle pain. However, Watson and colleagues [68] found that symptoms consistent with GvHD also occurred in autologous patients. Thus, it's difficult to estimate the true impact of chronic GvHD [68]. The result in study II showed that the MAC group experienced more acute GvHD (44%) compared to the RIC group (13%). On the other hand, the incidence of chronic GvHD was similar in the two groups. Even if the patients in the MAC group were reporting symptoms associated with chronic GvHD in higher degree than patients in the RIC group there were no significant differences in global QoL between patients with and without GvHD. Several studies have discussed if GvHD have an impact on HRQoL and to what extent. Some researcher have reported that the presence of GvHD have a major influence

on patients' HRQoL [50, 118, 128], with relevant impact on role functioning, global QoL, fatigue [50, 128] and reduced sexual functioning [10, 65]. In other studies no relationship were found between GvHD and global QoL [21, 87], even if patient with chronic GvHD experienced impaired physical, role and social functioning [87]. The treatment of GvHD can be stressful and extremely debilitating and the psychological impact of GvHD treatment and HRQoL is important issues to investigate [97]. Most patients with long-term physical issues, such as chronic GvHD, complained of taking too many pills, in addition to the complaints regarding the medication side effects [10]. This was also true in study IV where medication and side effects where seen as both social and physical restrictions in life. Earlier research has shown that most of the patients hoped that within one year after transplantation they could live without medication [10]. However, there were not only negative aspects of GvHD, also the positive side of GvHD was expressed by the patients in study IV. Graft-versus-Leukaemia (GvL) that follows with GvHD has the ability to prevent relapse and has also been associated with a survival benefit [129]. Thus, the chance to be cured overshadowed many of the symptoms and problems due to GvHD (Study IV). This was also seen in a study by Byar and colleagues [101] in which the survivors were mostly grateful to be alive and because of this, symptoms and problems had less significance. Maybe this was one reason why no differences were found in global QoL between patients with or without GvHD in earlier studies [21, 87, 130]. It is possible that a decrease in global QoL could have been the result if the patients did not have any GvHD because their awareness of the increased risk of relapse when it is absent.

It is important to have in mind that patients experience multiple symptoms simultaneously as a result of disease and the SCT and not one by one. Recent research suggests that multiple symptoms or symptom clusters are extensive problem for the patient and have a major impact on patients' functional status and global QoL [131, 132]. Focusing only on a single symptom may not adequately capture the trajectory of disease and treatment-related symptoms over time and because of that the patients may not be provided the efficacy and breadth of symptom management available [131]. Another issue is the relationship between symptoms and HRQoL and if symptoms always cause changes in HRQoL. It is possible that some symptoms are causally related to low HRQoL while others are the effect of low HRQoL [40].

Accommodation to a new life

The uncertainty of recovering to the pre-transplant level of physical, social, vocational and psychological functioning appears to be one of the most difficult and distressing challenges facing transplant survivors [10]. This is unanimous with other studies suggesting that QoL means having a "normal life" as it was before the illness and the transplantation [82, 133]. This was also found in study IV, in which

the patients' described the importance of being a part of normal life, with work, school, friends and family. They tried to find a way to cope with the new situation and not letting symptoms and physical problems rule their lives. In the study from Sherman [10] it was suggested that patients' expected a "normal life" after SCT, with a shorter period of convalescence following transplantation. Problems following SCT were strongly underestimated and the discordance between pre-transplant expectations for returning to normal and current functional status was associated with great psychological distress [10]. Similar results were also shown in the study by Stephens [134] in which the participants described the long time to recover, but also described adaption to the new life. Thus, recovery was not always to reach the level of physical or psychological function as before SCT, but rather to a level of being able to live with the new life situation [134]. In their way to regain normal life, the patients in study IV, were supported in different ways by family, friends, other patients and health care professionals. This was difficult to do alone and they had a need to share their feelings, thoughts and worries.

Patients concern for the future and whether the disease would return have been found to be related to various aspects of well-being [12, 13, 59, 62, 82, 124]. It can result in psychosocial distress and some of the patients in study IV described how they become irritated and angry more easily, often without any obvious reason. For health care providers it is important to inform the patients that it is normal to react with anger and sadness bearing in mind the stressful situation in which they are living as well as the impending threat of relapse. There is also a need to encourage the patient to talk about this subject to assure them that it's nothing to feel guilty of.

In many ways the results in study IV confirmed the findings from the quantitative studies (Study II-III), with prolonged and distressing symptoms and decreased functioning. However, several patients described positive effects of their disease and the following SCT (Study IV). Some of them found new interests and values in life, which somehow resulted in a heightened appreciation of life. This change of value has been found in earlier studies as well [20, 82, 101, 126, 133-135]. Having survived SCT seemed to result in alteration in values. Patients appreciated small things and had learned not to take life for granted [124, 133]. Haberman and colleagues [126] described it as the patients had become 'philosophical' about their lives, and were thankful for a second chance. Another thing that many patients expressed in study IV, was the importance of having time of their own and to be with people who gave them positive feedback. In a way they had become more egoistic, time was too precious to spend on persons who gave nothing in return. This could be difficult to explain for family and friends. It could be that patients need support from the caring staff to accept this important and seemingly common way to cope with their situation.

The influence of age and gender on HRQoL

In concordance with other studies [11, 29] patients in the RIC group (study II) were significantly older compared to the MAC group (50 versus 38 years). In spite of this, age was not highly related to HRQoL in that study. This give support to the assumption that RIC might preserve HRQoL and by that bee offered to a larger group of patients compared to MAC. However, some problems are of natural reasons related to age. The MAC group (Study II-III) was younger and they perceived more worries about sterility and problems with declined potency and sexual interest during treatment compared to the other two groups. Patients in older age could of natural reasons suffer from more physical impairments [23, 68]. This was also seen in study II where physical function was reduced in the RIC group. An association between age and influence of general health has been reported in other studies [64]. Influence of age on HRQoL could be reflected in differences of health expectations between younger and older patients, i.e. discordances between other in their age-group and present experience [136]. Younger patients may have higher expectations of their health and consequently experience more impact on HRQoL even from modest changes in clinical conditions. In contrast, older patients may have lower expectations and, thus, may experience less deterioration under the same clinical circumstances [84, 136].

Time as a healing factor for improvement in HRQoL

Time is an important factor for improvement in HRQoL. It has been shown that HRQoL is significantly reduced the first year after SCT, improves with time and reaches the level of the general population after 3-6 years [23, 25, 62]. In this thesis (Study I-III), self-reported HRQoL was impaired during the first year of follow-up after SCT with the highest symptom scores and lowest functioning scores one month after SCT. Thereafter the levels of symptoms decreased and levels of functioning increased back to baseline or even better. This pattern was especially true for patients in the autologous and RIC groups, who improved from baseline to one year after SCT (Study II- III). However, in the MAC group no significant improvements were seen at one year assessment compared to baseline. In spite of this, most patients reported their HRQoL to be good one year after SCT (Study II-III). This has also been found in other studies [62, 66, 84, 86]. Here global QoL was significantly reduced the first year after SCT and improved with interval to transplantation. Such findings might be interpreted as a result from changes in patients' personal standards or values, or changes in the conceptualization of HRQoL, referred to in the literature as "response shift" [93, 137].

METHODOLOGICAL CONSIDERATIONS

The overall aim of this thesis was to improve our knowledge about how SCT patients experience different types of transplantations and the effect it may have on their HRQoL during the first year after SCT. To answer the research questions we used both quantitative and qualitative methods. This also strengthens the results and gives a more comprehensive picture of the issues studied.

Quantitative studies

When evaluating HRQoL with questionnaires, it is recommended to supplement a core questionnaire, in this case EORTC QLQ-C30, with a questionnaire module specific to particular cancers or treatments [56]. In 2000, when this work was initiated no specific questionnaires for evaluating HRQoL after SCT were available. Thus, it was decided to use the preliminary HDC-19, developed by Hjermstad and colleagues [90] for the purpose to evaluate HRQoL in a prospective study of autologous and allogeneic STC. This ad-hoc module was developed according to the guidelines set forth by the EORTC [56] and focused on physical symptoms and psychological problems related to SCT not covered by the core questionnaire. Since HDC-19 was only used in a Norwegian population and not field tested the purpose in study I was to translate the original Norwegian HDC-19 into Swedish and to examine its validity, reliability and other psychometric properties in a group of Swedish patients undergoing SCT. The EORTC guidelines, set up by Sprangers and colleagues [56], were followed in performing these evaluations. The results of study I gave support to the Swedish version of HDC-19 as it was found to be a reliable HRQoL measure for patients receiving SCT after HDC.

One limitation of the quantitative studies (paper I-III) was the small number of participants and the relative large group of patients who declined to participate during the study period (99 for autologous SCT and 20 for allogeneic SCT), but also the varying number of patients in the three groups (145 Autologous, 25 MAC and 32 RIC). However, this distribution reflects the treatment policy in both Sweden and in rest of Europe, where the majority of SCT are autologous [3]. The demographic differences between the study group and the 119 patients who declined to participate in the study were however small and insignificant. In the latter group, the mean age was 50 years compared to 51 years in the study group and 68% were male compared to 60% in the study group. Among clinical variables, the only significant differences were that a greater proportion among the non-participants had multiple myeloma (41% vs. 28% in the study group) and fewer had lymphoma (25% vs. 33% in the study group).

Because of the relatively small sample we chose to minimize multivariate analysis in study II-III. The small sample was also one of the reasons to simplify the analyses by excluding two of the assessment times in the tests (3 and 6 months post SCT). Thus, data for the treatment groups in study II and III were only examined at baseline, one month and 12 months after SCT. Further reason for this was that the assessments 3 and 6 months after SCT followed the improving trends observed from 1 to 12 months after SCT and, thus, did not add any information beyond the latter ones. It also reduced the number of tests performed. However, even if the chosen analyses imply a larger number of tests with mass-significance as a consequence, the overall pattern of the results suggested that the MAC group had more of symptoms and decreased functioning compared to the autologous and RIC groups.

Qualitative studies

Research findings should be as trustworthy as possible and every research study must be evaluated in relation to the procedures used to generate the findings [115]. The use of concepts describing trustworthiness in the qualitative research differs somehow from the quantitative research traditions, even if concepts related to the quantitative tradition, such as validity, reliability and generalisation, are used here as well [115, 138]. However, the concepts credibility, dependability and transferability are more common to describe various aspects of trustworthiness in qualitative work [115]. Graneheim and Lundman [115] also suggest that concepts linked to the qualitative tradition are the most applicable when reporting findings of studies using qualitative content analysis. Credibility deals with the quality of the data collected and refer to the confidence and the truth of the data. The data collection should be performed in such a way that the believability of the findings is enhanced [139]. Dependability refers to the stability of data over time and conditions [139]. To minimize the risk of inconsistency during data collection the interviews in study IV were performed during a short period of 6 weeks. Even if it is of great importance to ask the same questions to all participants, the interview is an evolving process during which new insights into the phenomena of study can emerge and subsequently influence follow-up questions [115]. Transferability refers fundamentally to the generalizability of the data, that is, to which extent the findings from the data can be transferred to other groups or settings [139]. To facilitate transferability we have accurately described the setting for study IV and how the participants were selected. Further on, through the presentation of the findings and appropriate quotations that illustrate the narratives the transferability were enhanced. Even if previous qualitative research concerning the effect on HRQoL after SCT predominately has focused on long term survivors, as long as 18 years after SCT, [13, 82, 124, 126, 133, 134] the results in these studies were quite similar to the themes that emerged in study IV. This strengthens the trustworthiness of the study. However, the findings in study IV must be evaluated in the light of the limitations. The sample size was relatively small, which may have prohibited the

development of other themes prevalent in SCT patients. Even if the study period only cover the first year after SCT some memories effects in the data may also have taken place. Perhaps a tendency to forget passed problems and instead focuses on the present and the future.

CONCLUSIONS

The overall aim of this thesis was to improve our knowledge, and describe patients' experience of stem cell transplantation and the effect it may have on their HRQoL during the first year after SCT. The following conclusions have been drawn from the four studies included in this thesis:

- This thesis gives support to earlier research that SCT is a demanding procedure that affects the patients HRQoL over a long period of time.

- Responsive instruments such as the HDC-19 can be helpful in measuring symptoms and functioning related to SCT after HDC and a good complement to the EORTC QLQ-C30 when evaluating HRQoL.

- There was no significant difference in global QoL between the three groups one year after SCT. However, both autologous and RIC patients regained health and functioning earlier compared to MAC patients.

- There were significant differences between MAC and RIC patients as well as similarities between the autologous and RIC patients in functioning and symptom experience. These results emphasize the need to separate RIC and MAC when evaluating HRQoL after allogeneic SCT.

- There is a need for more studies that evaluate the long-term effects and HRQoL after RIC. The fact that RIC patients receive chronic GvHD in the same amount as MAC patients may influence HRQoL, one year or longer following SCT.

- The symptoms that affected patients mostly, both physical, psychological and social, was fatigue and symptoms from the mouth, e.g. mouth dryness, altered taste and sore mouth. These symptoms were a hinder to go back to work and live a normal life. Fatigue and symptoms from mouth are well known and still there seems to be a lack of knowledge about interventions to relieve the effect of these symptoms.

- There were both negative and positive effects of GvHD on patients HRQoL. Graft-versus-Host Disease not only gave long lasting symptoms and a treatment that reminded them of the disease but was also a hope of cure.

- The first year after SCT was a time of restrictions and isolation. Some patients did not dare to meet their grandchildren due to infections, other expressed that they had noting in common with their friends or, they could not share their worries with their family. Due to physical changes they did not have a wish to be with people and because of the disease they had a label on them as sick.

- The patients had become more humble to life and expressed their need to spend time of their own. They had become more selfish and this was not always easy to handle.

- The chance to be cured overshadowed most of the symptoms, problems and impaired functioning that the patients experienced after SCT. Quality of life was life it self.

CLINICAL IMPLICATIONS

The results from the present study have clinical implications for the care of these patients over the whole SCT process, from the first contact and information about SCT, during the hospitalization and in the post-transplant care when preparing the patient for a life after SCT. According to the results, full restoration of health is unlikely for a majority of SCT patients. Consequently it is important to communicate this during the pre-SCT period and to continue this specific information to encourage realistic expectations for post-SCT functioning throughout the post-SCT recovery period.

The results show that patients undergoing SCT require considerable supportive nursing care during the SCT period and the following year. Nursing professionals, both clinicians and researchers, need to strive for effective symptom management to improve successful outcomes following the intensive treatment. One way is to have specialized nurses, to prevent and manage the expected and unexpected complications of SCT. Particular attention has to be given to help patients adjust back to life, and the management and monitoring of life-long effects. Specialized nurses can initiate a conversation about topics that are not routinely discussed or are underemphasized, such as spirituality, sexuality, and effects of treatment on fertility, long-term effects and complementary and alternative therapies.

Nursing care of SCT patients can be complex and demanding, as a result, the need for evidence-based practice guidelines is high. We believe that the results from this thesis are important for health care professionals to acknowledge, specifically when designing guidelines and interventions to support and improve the care for SCT patients.

SVENSK SAMMANFATTNING

Hälso-relaterad livskvalitet, inklusive problem relaterade till biverkningar av given behandling anses mer och mer viktiga att studera. Resultat från sådana studier ger en större förståelse för vilken inverkan sjukdom och behandling har för patienten samt ger möjlighet att förbättra omvårdanden i samband med t.ex. en stamcellstransplantation. Traditionellt har indikatorer på vårdkvaliteten för stamcellstransplantationer baserats på återfall och överlevnad. Även om detta fortfarande är primärt är det otillräckligt för att utvärdera fysisk, psykisk och social funktion samt de symtom och problem som uppstår till följd av en stamcellstransplantation. Det övergripande syftet med denna avhandling var att förbättra vår kunskap hur patienterna upplever olika typer av stamcellstransplantationer och hur den påverkar deras hälso-relaterade livskvalitet under det första året efter en transplantation.

Avhandlingen består av fyra delarbeten. I de tre första ingick patienter som accepterats för en stamcellstransplantation och som senare genomgick en transplantation vid sektionen för hematologi, Sahlgrenska Universitetssjukhuset i Göteborg under åren 2000 - 2004. Under det första året efter stamcellstransplantationen besvarade patienterna två frågeformulär, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C-30) och High-Dose Chemotherapy (HDC-19), vid sex olika tillfällen. Frågeformulären berörde fysisk-, psykisk-, social, emotionell-, och kognitiv funktion, generell hälsa och livskvalitet samt symtom och problem relaterade till högdos cytostatika och efterföljande stamcellstransplantation.

I delarbete ett testades en svensk version av HDC-19 med avseende på validitet, reliabilitet och andra psykometriska egenskaper enligt EORTC:s riktlinjer. Den svenska versionen av HDC-19 uppvisade acceptabel reliabilitet och validitet, vilket innebär att den kan användas som tillägg till EORTC QLQ C-30 för att utvärdera specifika symtom och problem relaterade till stamcellstransplantation.

I delarbete två jämfördes hälso-relaterad livskvalitet mellan de patienter som fick full konditionering i samband med stamcellstransplantation mot patienter som fick reducerad konditionering. Resultaten visade att båda grupperna upplevde sämst funktion och flest symtom under den första månaden efter stamcellstransplantation för att sedan successivt förbättras. Dock var symtomen påtagliga och funktionen sämre för de patienter som genomgått full konditionering i samband med stamcellstransplantation. Ett år efter stamcellstransplantationen var funktion och symtombild den samma som innan start av konditionering eller bättre för patienterna som genomgått reducerad konditionering i samband med stamcellstransplantationen medan patienterna som genomgått stamcells-transplantation efter full konditionering fortfarande besvärades av nedsatt funktion

och flera symtom. Trots detta bedömde båda grupperna att de hade en god generell hälsa och livskvalitet ett år efter stamcellstransplantationen. De symtom som besvärade patienterna mest, oavsett grupp, var trötthet och symtom relaterade till mun och mag-tarmkanalen. Muntorrhet, till exempel, var ett symtom som till och med förvärrades bland de patienter som fått full konditionering. Avstötningsreaktionen mellan de nya stamcellerna och patientens immunförsvar, Graft-versus-Host Disease (GvHD), är en komplikation av stor betydelse för de patienter som genomgår en allogen stamcellstransplantation och många av de symtom som besvärade patienterna kan relateras till denna reaktion. Graft-versus-Host Disease finns i både akut och kronisk form. Det var betydligt fler patienter som fick akut GvHD efter full konditionering. Däremot var det ingen större skillnad i kronisk GvHD, 40 % av patienterna som fick reducerad konditionering jämfört med 36 % för dem som fick full konditionering. Trots besvärande symtom var det ingen skillnad i generell hälsa eller livskvalitet mellan de patienter som fick eller inte fick GvHD.

I delarbete tre jämfördes funktion, symtom och generell hälsa och livskvalitet mellan patienter som genomgått autolog stamcellstransplantation med patienter som genomgått allogen stamcellstransplantation. Med tanke på resultaten från delarbete två och tidigare forskning så delades den allogena gruppen med hänsyn till full respektive reducerad konditionering. Resultaten visade samma utveckling av symtom och funktion som i delarbete två, det vill säga att patienterna mådde som sämst en månad efter stamcellstransplantation för att sedan successivt förbättras. Det som överraskade var att patienter som genomgått autolog stamcellstransplantation samt de patienter som genomgått allogen stamcellstransplantation efter reducerad konditionering låg mycket lika i bedömning av symtom och funktion. Patienter som genomgått stamcellstransplantation efter full konditionering visade däremot, precis som i delarbete två, att de hade mer besvärande symtom och sämre funktion jämfört med de andra två grupperna under hela det år som patienterna följdes.

I delarbete fyra intervjuades 18 patienter ett år efter stamcellstransplantation. Syftet var att komplettera de kvantitativa studierna med patienternas berättelser hur en stamcellstransplantation påverkade deras hälsorelaterade livskvalitet. Genom innehållsanalys av intervjuer framkom fyra teman som handlade om *hinder i det dagliga livet*, de kände sig begränsade både fysiskt, psykiskt och socialt. Stamcellstransplantationen gav förändrade livschanser på ett oönskat sätt och de hade problem med att bemöta omgivningens reaktioner. *Önskan att vara delaktig i ett normalt liv* var stor och *chansen att bli frisk överskuggade alla* de symtom och funktionsnedsättningar som transplantationen orsakat. Patienterna beskrev också att det man gått igenom gav *nya värden i livet*, både att man blev mer ödmjuk men även att man värdesatte egen tid i större utsträckning.

Kunskap om patientens erfarenhet av en stamcellstransplantation och hur den påverkar hälsorelaterad livskvalitet är värdefull och kan bland annat användas för att förbättra innehåll och tidpunkt av information och interventioner för patienter som genomgår en stamcellstransplantation. Genom att ge individuellt anpassad information, som dessutom är realistisk, kan man minska den frustration som många patienter känner för den långa återhämtningsperiod som följer en stamcellstransplantation och som kan försvåra återgången till ett normalt liv.

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EORTC QLQ-C30 (version 3)

Vi är intresserade av några saker som har med Dig och Din hälsa att göra. Besvara alla frågor genom att sätta en ring runt den siffra som stämmer bäst in på Dig. Det finns inga svar som är "rätt" eller "fel". Den information Du lämnar kommer att hållas strikt konfidentiell.

Var vänlig fyll i Dina initialer:
När är Du född? (Dag, Månad, År):
Dagens datum (Dag, Månad, År): 31

		Inte alls	Lite	En hel del	Mycket
1.	Har Du svårt att göra ansträngande saker, som att bära en tung kasse eller väska?	1	2	3	4
2.	Har Du svårt att ta en lång promenad?	1	2	3	4
3.	Har Du svårt att ta en kort promenad utomhus?	1	2	3	4
4.	Måste Du sitta eller ligga på dagarna?	1	2	3	4
5.	Behöver Du hjälp med att äta, klä Dig, tvätta Dig eller gå på toaletten?	1	2	3	4

Under veckan som gått:

		Inte alls	Lite	En hel del	Mycket
6.	Har Du varit begränsad i Dina möjligheter att utföra antingen Ditt förvärvsarbete eller andra dagliga aktiviteter?	1	2	3	4
7.	Har Du varit begränsad i Dina möjligheter att utöva Dina hobbys eller andra fritidssysselsättningar?	1	2	3	4
8.	Har Du blivit andfådd?	1	2	3	4
9.	Har Du haft ont?	1	2	3	4
10.	Har Du behövt vila?	1	2	3	4
11.	Har Du haft svårt att sova?	1	2	3	4
12.	Har Du känt Dig svag?	1	2	3	4
13.	Har Du haft dålig aptit?	1	2	3	4
14.	Har Du känt Dig illamående?	1	2	3	4
15.	Har Du kräkts?	1	2	3	4
16.	Har Du varit förstoppad?	1	2	3	4

Fortsätt på nästa sida

Under veckan som gått:		**Inte alls**	**Lite**	**En hel del**	**Mycket**
17.	Har Du haft diarré?	1	2	3	4
18.	Har Du varit trött?	1	2	3	4
19.	Har Dina dagliga aktiviteter påverkats av smärta?	1	2	3	4
20.	Har Du haft svårt att koncentrera Dig, t.ex. läsa tidningen eller se på TV?	1	2	3	4
21.	Har Du känt Dig spänd?	1	2	3	4
22.	Har Du oroat Dig?	1	2	3	4
23.	Har Du känt Dig irriterad?	1	2	3	4
24.	Har Du känt Dig nedstämd?	1	2	3	4
25.	Har Du haft svårt att komma ihåg saker?	1	2	3	4
26.	Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Ditt familjeliv?	1	2	3	4
27.	Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Dina sociala aktiviteter?	1	2	3	4
28.	Har Ditt fysiska tillstånd eller den medicinska behandlingen gjort att Du fått ekonomiska svårigheter?	1	2	3	4

Sätt en ring runt den siffra mellan 1 och 7 som stämmer bäst in på Dig för följande frågor:

29. Hur skulle Du vilja beskriva Din hälsa totalt sett under den vecka som gått?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

30. Hur skulle Du vilja beskriva Din totala livskvalitet under den vecka som gått?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

HDC-19

En del patienter upplever att de har några av följande symtom eller problem. Var vänlig och ange i vilken grad som du besvärats av dessa symtom eller problem under den senaste veckan. Sätt en ring runt den siffra som best beskriver ditt tillstånd.
I formuläret används cancer som ett samlingsnamn för samtliga elakartade blodsjukdomar (leukemi, myelom, myelodysplastiskt syndrom m.m.)

Under den sista veckan	**Inte alls**	**Lite**	**En hel del**	**Mycket**
31. Har Du lätt för att frysa?	1	2	3	4
32. Har Du varit yr?	1	2	3	4
33. Har Du haft ökad slemproduktion i mun och svalg?	1	2	3	4
34. Har Du haft sår i munnen?	1	2	3	4
35. Har Du haft muntorrhet?	1	2	3	4
36. Har Du haft smakförändringar?	1	2	3	4
37. Har Du haft klåda på huden?	1	2	3	4
38. Har Du haft torr hud?	1	2	3	4
39. Har Du varit stel i lederna?	1	2	3	4
40. Har Du haft muskel- eller skelettvärk?	1	2	3	4
41. Har Du varit orolig för att få återfall av din cancersjukdom?	1	2	3	4
42. Har Du varit orolig för att få någon annan form av cancer?	1	2	3	4
43. Har Du varit orolig för Din hälsa med tanke på framtiden?	1	2	3	4
44. Har Du haft någon att prata med om din oro?	1	2	3	4
45. Har Du varit orolig för att Du kan komma att bli steril?	1	2	3	4
46. Besvaras endast av män: Har Du haft några problem med potensen?	1	2	3	4

Under den sista månaden:	**Inte alls**	**Lite**	**En hel del**	**Mycket**
47. I vilken utsträckning har Du varit intresserad av sex?	1	2	3	4
48. I vilken utsträckning har Du varit sexuellt aktiv?	1	2	3	4

Besvara endast nästa fråga om du varit sexuellt aktiv!

49. I vilken utsträckning har sex varit till glädje för dig?	1	2	3	4