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Frequent and long-term follow-up of health-related quality of life following allogeneic haematopoietic stem cell transplantation

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Health-related quality of life (HRQL) was evaluated in 94 patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT) after myeloablative (MAC, n = 18) or reduced intensity conditioning (RIC, n = 76). HRQL was assessed with the EORTC QLQ C-30 during the inpatient period as well as during the following 3 years, i.e. at baseline and 12 times thereafter. Functional status and global quality of life decreased from baseline to weeks 2 and 3, especially role and social functions. Symptoms increased significantly during the first 3 weeks, particularly appetite loss, nausea and vomiting, diarrhoea and fatigue. It took at least 1 year for HRQL to return to the baseline level. The only function that improved significantly 3 years after HSCT was role function. Patients treated with MAC experienced significantly worse HRQL at baseline than patients treated with RIC, as well as more pain, sleep disturbance and appetite loss in weeks 3 and 4. Patients with extensive chronic graft-versus-host disease experienced reduced HRQL. These results provide a clinically useful overview of patients' HRQL during and after HSCT and indicate when they require increased support. The results demonstrate the importance of close follow-ups during the first year after HSCT to improve preventive or supportive interventions.

Keywords: quality of life, symptom, stem cell transplantation.

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INTRODUCTION

Patients receive various conditioning treatments [i.e. chemotherapy with or without total body irradiation (TBI)] before haematopoietic stem cell transplantation (HSCT). The aim of the conditioning regimen is to create space for the transplanted stem cells, to induce immunosuppression and to eliminate the disease (Juliusson et al. 2003; Gratwohl & Carreras 2012). The conditioning was initially myeloablative conditioning (MAC; Gyurkocza & Sandmaier 2014), which means high-dose chemotherapy with or without TBI. However, due to serious side effects, only young patients were eligible for HSCT, since severe toxicity increases with age (Socie et al. 2003; Diaconescu et al. 2004). In the late 1990s, reduced intensity conditioning (RIC) was introduced and developed (Bacigalupo et al. 2009; Cremer et al. 2011) with the main purpose of reducing toxicity to allow older people and those with compromised health to benefit from HSCT (Juliusson et al. 2006; Gyurkocza & Sandmaier 2014). Choice of the MAC or RIC is primarily influenced by various risk factors, for example the stage of the disease and age (Ljungman et al. 2010). It is important to evaluate factors other than treatment response and survival when the treatment strategy is changed. Irrespective of treatment strategy, HSCT has a strong impact on patients' health-related quality of life (HRQL; Larsen et al. 2004; Bevans et al. 2008), with a high risk of different complications, such as graft-versus-host disease (GvHD; Pallua et al. 2010; Braamse et al. 2012).GvHDis a common complication after allogeneic HSCT and is caused by several factors that trigger the activation of donor T cells. The risk of developing acute GvHD is 30–50% for patients with a related donor and may be higher with an unrelated donor (Bhatia et al. 2007; Apperley&Masszi 2012). The risk is graded from1 to 4, where 1 ismild GvHD and 4 is a life-threatening condition involving all three organs (Skin, gut and liver). ChronicGvHDnormally occurs 100 days afterHSCT. Chronic GvHD affects significantly more organs than acute GvHD and is divided into limited and extensive chronic GvHD, depending on the number of organs involved and the severity of the attack on the affected organs (Apperley&Masszi 2012). This study started in 2001 when RIC was introduced at our department. At that time, none of the previous studies with a prospective and longitudinal design had fully covered the whole inpatient period as well as longterm follow-up in patients receiving MAC and RIC regimes (Decker et al. 1989; Larson et al. 1993; Mcquellon et al. 1997, 1998; Zittoun et al. 1999). Thus, the overall purpose of the present study was to explore the whole inpatient period and the following 3 years to evaluate HRQL with both MAC and RIC regimes over time. Specific aims were to identify symptoms during treatment, how they develop over time and how long they persist after HSCT.

METHODS

Design

This is a quantitative, descriptive, prospective and longitudinal study following patients during their entire inpatient period and up to 3 years thereafter.

Study population

During the inclusion period from September 2001 to January 2008, 110 patients were accepted for allogeneic HSCT. The inclusion criteria were adult patients receiving their first allogeneic HSCT and being able to understand the Swedish language. Three patients were not included due to language problems, seven due to a second HSCT, two due to syngeneic HSCT, one was too ill and three declined participation, which gives a study population of 94 patients.

Data collection procedure

All patients who met the inclusion criteria were invited to participate in the study when they arrived at the transplant unit. All patients received verbal and written information about the study from one of the authors (UF). After oral informed consent, the patient received the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC30) (Aaronson 1993). A total of 13 questionnaires per patient were distributed at baseline (before the start of conditioning), once a week during weeks 1–4, once a month during months 2 and 3, once during month 6, and then once every 6 months up to year 3 after HSCT. After discharge, questionnaires were sent to the patients together with a prepaid return envelope. The questionnaires were distributed and collected by one of the authors (UF). Late responders received new questionnaires as a reminder after 2–4 weeks. Questionnaires answered later than a month after deadline were not included in the analysis.

Conditioning treatment

Patients received conditioning therapy according to disease and risk level (stage of the disease, age of the patient, time interval from diagnosis to transplantation, Karnofsky score, histocompatibility and sex combination between donor and patient; Ljungman et al. 2010; Table 1). The patients treated with RIC received combinations of drugs with known effects against the specific disease entities at established doses; doses intended to reduce toxicity without impairing efficacy. Patients with acute leukaemia and aggressive lymphomas received FAM (Fludarabine, ARA-C, Melphalan; some patients with an addition of mitoxantrone and idarubicin) or FluBu (Fludarabine, Busulphan). Multiple myeloma (MM), lymphoproliferative and other diseases were treated with FCM (Fludarabine, Cyclophosphamide, Melphalan). Patients with aplastic anaemia received fludarabine, cyclophosphamide and antithymoglobulin (ATG). Most patients received subcutaneous alemtuzumab or intravenous ATG to prevent rejection and reduce the risk for GvHD (Table 1). Regardless of the conditioning regimens, most patients received cyclosporine A together with mycophenylate mofetil as GvHD prophylaxis (Juliusson et al. 2003).

Measuring health-related quality of life

To measure HRQL, the EORTC QLQ-C30 questionnaire (version 3) was used (Aaronson 1993). The instrument has been translated and validated in 81 languages and used in more than 3000 studies worldwide. It consists of 30 items divided into three major domains: functional status, symptom status and global health/QoL. Functional scales consist of physical function (five items) and apply to the ability to manage daily life, for example if the patient has trouble executing strenuous activities, such as taking long/short walks, if the patient must sit/lie down during the daytime and if they can manage their own personal hygiene. Role function (two items) involves areas related to work, daily activities and leisure activities. Emotional function (four items) covers areas of tension, anxiety, irritability and depression. Social function (two items) concerns whether the patients' physical function or medical treatment has interfered with their family life or social activities. Cognitive function (two items) is about problems concentrating and remembering. There are three symptom scales that measure fatigue (three items), which addresses whether the patient needed rest, felt weak and has been tired, or experienced nausea and vomiting (two items) and pain (two items), where the patient is asked to answer whether he/she has had pain and whether his/her daily activities were affected by pain. There are five single items measuring dyspnoea, insomnia, appetite loss, constipation and diarrhoea, and one item measuring financial impact. Global health/QoL consists of two items, the first question concerns overall health and the second question concerns the overall QoL. The functional and symptom scales/items comprise four levels (response alternatives: not at all, a little, quite a bit, very much). Overall QoL is measured on a 7-point scale, ranging from 1 (very poor) to 7 (excellent). For all items in the instrument, the patient makes an assessment of the past week. All scales and items are transformed according to the EORTC scoring manual into a 0- to 100-point scale. Higher scores for functional scales and QoL status indicate a high level of function and higher scores on the symptom scales and single items indicate more severe symptoms or impairments.

Statistical methods

The results are presented using descriptive statistics: count, proportion, mean and standard deviation (SD). Missing data in individual questionnaires were processed according to the EORTC scoring manual (Fayers et al. 2001). Since a large proportion of patients (47%) died during the study period, separate data analyses were made for the 34 patients who participated in all 13 follow-ups from baseline over the 3-year period. Furthermore, mean differences between baseline and the follow-ups in week 3, month 3, year 1 and 3 were assessed as a complement to the analysis performed in the entire patient

group. The Wilcoxon signed-rank test was performed in the total study population to test for differences in every item between baseline and the follow-ups in weeks 2 and 3 and year 3, and to test for differences in every item between the patients answering the questionnaire at week 3 (n = 86), month 3 (n = 80), year 1 (n = 50) and 3 (n = 34) with the baseline value. A P-value of <0.05 was considered significant. Regression analyses adjusted for gender and age were applied separately each time when differences between and within groups were examined (Hjermstad et al. 1998). When comparing groups, a $P < 0.01$ was regarded as significant. GvHD was scored according to the EBMT handbook (Apperley & Masszi 2012). Clinical data including GvHD were extracted retrospectively from medical records (Table 1). All statistical analyses were performed using IBM SPSS/PASW Statistics18 USA.

Ethical consideration

In accordance with the Declaration of Helsinki, patients received verbal and written information about the study stating that participation was voluntary and confidentiality was guaranteed. The patients who met the inclusion criteria gave their verbal consent to participate in the study. The study was approved by the Ethics Committee at Linköping University (Dnr 03-366).

RESULTS

The mean age of the 94 participants was 48 years, with an equal distribution of men and women. The majority of the patients had leukaemia (54%), an unrelated donor (55%), and were treated with RIC (83%). At HSCT, the disease was in complete remission (CR) in 61% of the patients, there was no CR (i.e. partial remission or minor response) in 15%, progressive disease in 7%, chronic phase in 7%, refractory in 3%, sensitive disease in 2%, aplasia in 2% and in one patient the disease status was unknown at the HSCT (Table 1). The study population was reduced by 60% from baseline to the 3- year follow-up (Fig. 1).The primary reason for not completing the study was death (47%), caused by relapse (30%), infection (32%) and GvHD (25%). The majority (92%) of the 38 patients who remained in the study at the 3-year follow-up were in CR. The number of missing individual questionnaires amounted to 4%, with one missing questionnaire at baseline, and four at the 3-year follow-up. The patients who died during the study (n = 44) had significantly lower values at baseline than the patients who survived over the 3-year period (n = 34) with regard to physical function (60 vs. 88, $P < 0.01$), global health status/ QoL (64 vs. 77, $P < 0.01$), fatigue (38 vs. 23, $P < 0.01$), appetite loss (17 vs. 2, $P < 0.01$), nausea and vomiting (13 vs. 1, $P < 0.01$). The survivors' results were almost identical to those of the entire study population regarding HRQL during the inpatient- and follow-up period. To illustrate this, the results are provided in a separate graph in Figures 2 and 3.

Functional status

The patients reported a significant reduction in physical, social, role, cognitive and emotional function during the first 3 weeks ($P < 0.01$). Patients' physical, emotional, cognitive and social function started to improve already at week 4, but for role function there was no improvement until the 2-month assessment (Fig. 2). Patients still experienced a significant impact on physical, role, cognitive and social function at the 3- month assessment, with the exception of emotional function which had returned to the same value as at baseline ($P < 0.05$; Table 2). Approximately, 6 months after transplantation, role function had improved to almost the same value as before transplantation. Physical, cognitive and social function had improved to the same value as at baseline at the 1-year assessment (Fig. 2). Role function was the only function that had improved significantly at the 3-year follow-up compared to baseline ($P < 0.05$; Table 2).

Symptom status

The patients experienced a statistically significant deterioration in nearly all symptoms during the first 3 weeks from baseline. The most troublesome ones were appetite loss, nausea and vomiting, diarrhoea, fatigue, sleep disturbance and pain ($P < 0.05$; Fig. 3). Dyspnoea was a greater problem after HSCT and reached the maximum value 2 months after HSCT (Fig. 3). Patients still experienced significant problems with almost all symptoms at the 3- month assessment ($P < 0.05$; Table 2). Baseline values were nearly reached at the 1-year assessment, but there were still some significant differences in nausea, vomiting and appetite loss (Table 2; Fig. 3).

Overall/global QoL

The patients experienced a deterioration in overall/global QoL from a mean of 69 points at baseline to 37 points at week 3 ($P < 0.05$), with a gradual return to the baseline value 1 year after HSCT (data not shown). Thereafter, the overall QoL assessment remained stable over the following years.

Differences between MAC and RIC

Patients treated with MAC had a 6-day longer inpatient period and a 3-day longer period of neutrophil counts $<0.5 \times 10^9$/L than patients treated with RIC. Patients in the MAC group were more affected by acute GvHD, but less by chronic GvHD, compared to the patients in the RIC group. Among the patients treated with MAC and RIC, 69% MAC and 42% RIC died. At baseline, patients treated with MAC had significantly worse scores with regard to fatigue (46 vs. 27, $P < 0.01$), nausea and vomiting (19 vs. 4, $P < 0.01$) than patients treated with RIC. At week 3, patients treated with MAC had worse scores with regard to pain (52 vs. 29, $P < 0.01$), and sleep disturbances (65 vs. 36, $P < 0.01$) than patients treated with RIC. At week 4, the same patients had worse scores with regard to appetite loss (72 vs. 39, $P < 0.01$) and diarrhoea (40 vs. 13, $P < 0.01$) than

patients treated with RIC. At month 2, the differences between the MAC and RIC groups had diminished. After month 3, the number of MAC patients was 7 or fewer, and thus further testing between MAC and RIC was not performed (Fig. 4).

GvHD and HRQL

Acute GvHD was reported in 57% of the patients. Grade 1 and 2 affected 39% of the patients. Grade 3 and 4 affected 18% of the patients. Chronic GvHD was reported in 53% of the patients. Limited chronic GvHD affected 20% of the patients, and extensive chronic GvHD affected 33% of the patients (Table 1). There were no significant differences in HRQL between patients with or without acute GvHD. However, patients with extensive chronic GvHD reported impaired physical function compared to patients with limited chronic GvHD and those with no chronic GvHD at the 1½-year follow-up (69 vs. 93 and 88, $P < 0.01$), at the 2-year follow-up (76 vs. 92 and 94, $P < 0.01$) and at the 2½-year follow-up after HSCT (66 vs. 91 and 96, $P < 0.01$). They reported a highly affected role function after HSCT compared to patients with limited chronic GvHD at the 1-year follow-up (36 vs. 72, $P < 0.01$), at the 1½-year follow-up (39 vs. 77, $P < 0.01$) and at the 2-year follow-up (49 vs. 83, $P < 0.01$). They also experienced an affected role function at the 1-year follow-up (36 vs. 74, $P < 0.01$), and at the 2½-year follow-up (44 vs. 86, $P < 0.01$), compared to the patients without chronic GvHD. Patients with chronic GvHD had a significantly worse overall QoL from month 6 after HSCT to the 1½- year follow-up as compared to those with no or limited chronic GvHD ($P < 0.01$), as shown in Figure 5.

DISCUSSION

The present prospective study on HRQL after allogeneic HSCT, with frequent evaluations covering the entire inpatient period and up to 3 years afterwards provides unique data on how HRQL parameters in the study population changed over time following allogeneic HSCT. Patients experienced a significant worsening of most functions and symptoms from baseline to weeks 2 or 3. Thereafter, there was a gradual improvement in their HRQL. Recovery after transplantation, which we view as a return to the baseline value, reached baseline at month 6 indicating that role function recovers quite rapidly. Almost all other assessment items had returned to the baseline value approximately 1–1½ years after the HSCT and remained stable thereafter. Similar results were found also when data from the 38 patients who survived and participated over the entire study period were separately analysed. Our results are consistent with those of other studies showing that it takes approximately 1 year after HSCT for patients to recover to the same level as before HSCT (Hjermstad et al. 2004; Grulke et al. 2012). At baseline, our results were fairly consistent with those of Grulke and co-workers' meta-analysis of 33 studies made in European countries, except for role function; which the patients in our study rated lower (45 vs. 62; Grulke et al. 2012). In Fayers et al. (2001) study, they suggest that there might be health and cultural differences between countries (Fayers 2001). Therefore, a possible explanation for the differences in role functioning could be unidentified cultural differences between Sweden and other European countries. Some of the decreased physical function during the inpatient period is probably due to a temporarily limited ability to perform physical activities, rather than any inherent inability to be physically active. At the 3-month assessment, the patients still rated their physical capacity as diminished, indicating that for most patients it takes at least this much time to recover after transplantation. Previous studies have shown that physical activities during and after HSCT have beneficial effects on patients' HRQL (Defor et al. 2007; Jarden et al. 2009; Baumann et al. 2010). Therefore, it is important for physiotherapists and nursing staff to find activities that encourage physical activity despite hospitalisation and isolation. For instance, virtual computer games can be used to increase the level of physical activity level during the inpatient period. This form of activity has been used in the rehabilitation of patients with stroke and could also be suitable for patients undergoing allogeneic HSCT (Lewis et al. 2011). Role function was the only function that improved significantly during the 3 years after HSCT. Similar results were also reported in a study on patients undergoing autologous HSCT (Frodin et al. 2011), and in a meta-analysis by Grulke et al. (2012). In their study, Syrjala et al. (2004) found that 33% of patients with a history of work outside the home had returned to full-time work after 3 years. This indicates that the majority of patients will only return to their normal lives after HSCT over a period of years, and also indicates that some patients will never return to a regular job. The symptoms mostly affected during the inpatient period were appetite loss, nausea, vomiting, and fatigue, followed by diarrhoea, sleep disturbance and pain. These results correspond well with the clinical picture of the toxicity of the given treatment. Our results are comparable with the results from the meta-analysis by Grulke et al. (2012), and results reported by Bevans et al. (2008). In our study, many of the patients experienced appetite loss, fatigue, dyspnoea and diarrhoea up to 6 months after HSCT. These symptoms could be due to several factors, such as gastrointestinal GvHD, infection, depression and malnutrition (Mattson 2007; Martin-Salces et al. 2008). These symptoms can lead to severe weight loss, which can be devastating for the patient's recovery. It is therefore important to monitor diet and eating habits after discharge. Approximately, half of the patients in our study were affected by acute or chronic GvHD. Of those, 25% died due to GvHD. Patients who had extensive chronic GvHD had significantly impaired physical and role function and global QoL compared to those who had no or limited chronic GvHD. This result is consistent with results from other studies and points to the importance of providing appropriate support for patients affected by extensive chronic GvHD and implementing actions that increase their HRQL (Lee et al. 2006; Pallua et al. 2010; Pidala et al. 2011). This support might entail providing information about the benefits of self-care to reduce the problems of chronic GvHD, such as increased physical activity to prevent stiffening joints, which can be common in chronic GvHD (Chen 2014). The original reason for introducing RIC as an alternative to MAC was to reduce acute toxicity, while at the same time sustaining tumour control, safe engraftment and early full donor chimerism (Juliusson et al. 2003). Our RIC regimen thus included a relatively high dose of melphalan, and was more intense than many other RIC regimens, but still within the limits specified by Bacigalupo et al. (2009). The mean age of our RIC patients was similar to several other RIC studies, ranging between 45 and 52 years (Diez-Campelo et al. 2004; Bevans et al. 2006; Andersson et al. 2009; Cohen et al. 2012). In our centre, 46% of all AML patients aged between 40 and 59 years went through allogeneic HSCT as compared to 22% at other centres in Sweden, resulting in an improved 55% long-term survival of all AML patients in this age group (Juliusson et al.

2012). To the best of our knowledge, there are only five earlier studies that investigated HRQL in patients treated with RIC (Diez-Campelo et al. 2004; Bevans et al. 2006; Andersson et al. 2009, 2010; Cohen et al. 2012). Bevans et al. (2006) compared HRQL with SF-36, FACT-G and BMT in patients undergoing allogeneic HSCT with RIC or MAC regimes during the first 100 days after transplantation. They analysed data using mixed linear modelling, adjusting for baseline HRQL differences. HRQL was significantly improved (<0.01) in both groups with higher scores at day 100 compared to days 0 and 30. There was no difference between groups during early recovery. At 2 years, all survivors reported HRQL similar to or better than at baseline (Bevans et al. 2006). Andersson et al. (2009) also compared patients going through allogeneic HSCT with RIC and MAC regimes. HRQL was measured using EORTC QLQ C-30 and module high-dose chemotherapy (HDC-19). They found no difference between the two groups at baseline, whereas at 1 month after HSCT, MAC patients had significantly more sleep disturbances, financial problems, and mouth and taste problems. At the 1-year followup, patients who received MAC still had problems with dry mouth (Andersson et al. 2009). Our results differ from Bevans et al. (2006) and Andersson et al. (2009) since our patients treated with MAC had significantly more fatigue and nausea and vomiting even at baseline compared to patients treated with RIC. A possible explanation for the difference at baseline is that some MAC patients in this group had more limited time than RIC patients to recover from previous chemotherapy before the transplantation. However, due to the small study population in our MAC group the result must be interpreted with caution. At weeks 3 and 4, the patients treated with MAC also reported significantly more pain, sleep disturbances, loss of appetite and diarrhoea than the RIC patients. Pain during the early phase of our study was probably due to mucositis, which is a common side effect after MAC, but it also affects some patients treated with RIC (Ohbayashi et al. 2008; Takahashi et al. 2010). When performing studies on vulnerable patients, ethical considerations are crucial. The patients in our study were asked to fill out the questionnaire, even at times when clinical experience indicated that they could feel most negatively affected depending on the acute toxicity after conditioning. This could be regarded as troublesome for the patient, but any negative effects are probably outweighed by the patients' interest in reporting their symptoms. Since the researcher (UF) has taken an active part in the distribution and collection of the questionnaires, there is a risk that the patients had an emotional relationship with the researcher. The advantage of the researcher distributing the questionnaires is that the response rate is probably higher. The researcher (UF) has not had an active part in the daily care of the patients in the study. Since the study started, no patients have discontinued participation due to the questions being too offensive or too difficult to answer.
The strength of this study is the use of frequent and regular follow-ups during both the inpatient period and the 3- year follow-up which provide valid data illustrating fluctuations in patients' HRQL, giving a good overall clinical picture of how the patients felt during and after allogeneic HSCT, and strengthens the validity and transferability of the results.

LIMITATION

A limitation of our study is the 60% decrease of our study population from baseline until the 3-year follow-up, leaving a study population of 38 patients at the end of the study. The most common reason for not remaining in the study was death (47%), followed by relapse (30%), infections (32%) and GvHD (25%). This distribution reflects the fact that many patients had HSCT for advanced disease with a high risk of complications. Patients who died had reported values indicating greater impairment in some variables at baseline compared to patients who survived, demonstrating that the patients who died were already in worse general condition before HSCT than the patients who survived. To further validate our results, we made an analysis of the 34 surviving patients who answered all the questionnaires throughout the study period. This analysis showed that HRQL followed the same pattern among the survivors as the total study population. This further strengthens our results. The high mortality rates during the study were unfortunately unavoidable and emphasise the high risk involved with allogeneic HSCT. Our data are comparable with data in a study by Bhatia et al. (2007), who studied late mortality after HSCT. They found that relapse, chronic GvHD and infection were the primary reasons for death (Bhatia et al. 2007). A retrospective analysis using data from the EBMT database shows that 46% of patients transplanted with an allogeneic HSCT between 1990 and 2005 died; of these, 28% died from transplant-related causes (Gratwohl et al. 2009). This illustrates the challenge of conducting longitudinal studies in patients with severe diseases and poor survival. In the result section, we chose to report statistically significant differences; it may also be appropriate to take non-statistically significant differences into account in guiding clinical practice. In other words, small changes in HRQL that are not statistically significant must be considered as being of possible importance for individual patients (Polit & Beck 2008). Statistical significance is partly dependent on the size of the study population and related to the validity of the result, whereas non-significant differences could also suggest clinically significant findings. It has been recommended that a change in mean value of 10 points or more in the score should be defined as clinically significant, irrespective of the P-value (King 1996; Osoba et al. 1998; Maringwa et al. 2011). A limitation in our methodological approach is that the EORTC QLQ C-30 provides general knowledge of the patients' HRQL, but not a deeper understanding of the different aspects of the patients HRQL. For instance, patients are asked to answer whether they have diarrhoea. The response alternatives are not at all, a little, quite a bit and very much. This is a subjective evaluation about the patients' symptoms and can be interpreted in several ways; either the frequency or the amount of diarrhoea. However, it does not say anything about the distress that the symptom may cause. It would have been an advantage to also use instruments that explore in depth the areas more specific for patients going through HSCT such as 'the module High-Dose Chemotherapy (HDC 19)'. This module is directed to patients undergoing HSCT (Andersson et al. 2008), but was not available when we started the study.

Conclusion

It took at least 1 year for the patients' HRQL to return to the baseline level. The only function that had improved significantly 3 years after HSCT was role function. This is important information since it indicates the stages in the treatment period when the patient needs more support and illustrate the need for early and supportive intervention, particularly for appetite loss and chronic GvHD. Week 2 and 3 is the period in which patients undergoing allogeneic HSCT need the most supportive care.

The patients with MAC regimens experienced a worse HRQL at baseline than the patients with RIC regimens, and subsequently more pain, sleep disturbance and appetite loss in weeks 3 and 4. Although our patients treated with MAC s experienced worse HRQL, HSCT with RIC still had a great impact on HRQL, especially during the first year after HSCT. Patients with extensive chronic GvH experienced reduced HRQL.

Clinical implications

Based on the results of the study, there are several clinical implications. First, we recommend that healthcare professionals perform close follow-ups, using standardized assessment scales covering the most troublesome and frequent symptoms or impairments. Exercise programmes or virtual computer games could be used to increase patients' physical function during and after transplantation. Increased support during hospitalisation can provide faster recovery and may reduce the number of hospital days. The results will also help the healthcare personnel to inform patients and help the patients to understand what they have to expect during and after the transplantation, and that the recovery after the transplantation takes time for patients undergoing allogeneic HSCT. Since patients undergoing allogeneic HSCT have a severe disease with poor survival future, multicentre studies are recommended that will be able to reach adequate power. There is also a need for further prospective studies on HRQL focusing on the inpatient period in patients treated with RIC and also a need for studies investigating interventions for the most troublesome symptoms.

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Table 1. Patient characteristics

Number of patients (n)	94
Men/Women (n, %)	47/47 (50/50)
Age, mean (median)	48
MAC/RIC	40/49(41/53)
Marital status (n, %)	
Married/Cohabiting/Partner	72 (77)
Single	22 (23)
Stem cell source (n, %)	
Peripheral blood haematopoietic cells	85 (90)
Bone marrow	7 (8)
Cord blood	2 (2)
Donor: RD/URD (n, %)	42/52 (45/55)
Conditioning regimens (n, %)	
MAC*/RIC†	16/78 (17/83)
Serotherapy (n, %)	
Alemtuzumab/Antithymoglobulin (n)	71/17 (76/18)
Inpatient period, mean (range)	
Days of hospitalisation	32 (18–162)
MAC/RIC	39 (23–69)/31(18–162)
Days with neutrophil counts <0.5	16 (10–54)
MAC/RIC 20 (10–54)/16(11–31)	
Diagnosis (baseline/at 3 years) N	
Acute leukaemia 51/22	
Myelodysplastic syndrome 8/1	
Chronic myeloid leukaemia 7/4	
Chronic lymphocytic leukaemia 4/3	
Myeloproliferative disease 4/1	
Multiple myeloma 10/2	
Lymphoma 5/2	
Prolymphocytic leukaemia 1/0	
Other‡ 4/3	
Acute GvHD (n)	
Grade 1 and 2/Grade 3 and 4 37/17	
Chronic GVHD (n)	
Limited/Extensive 19/31	

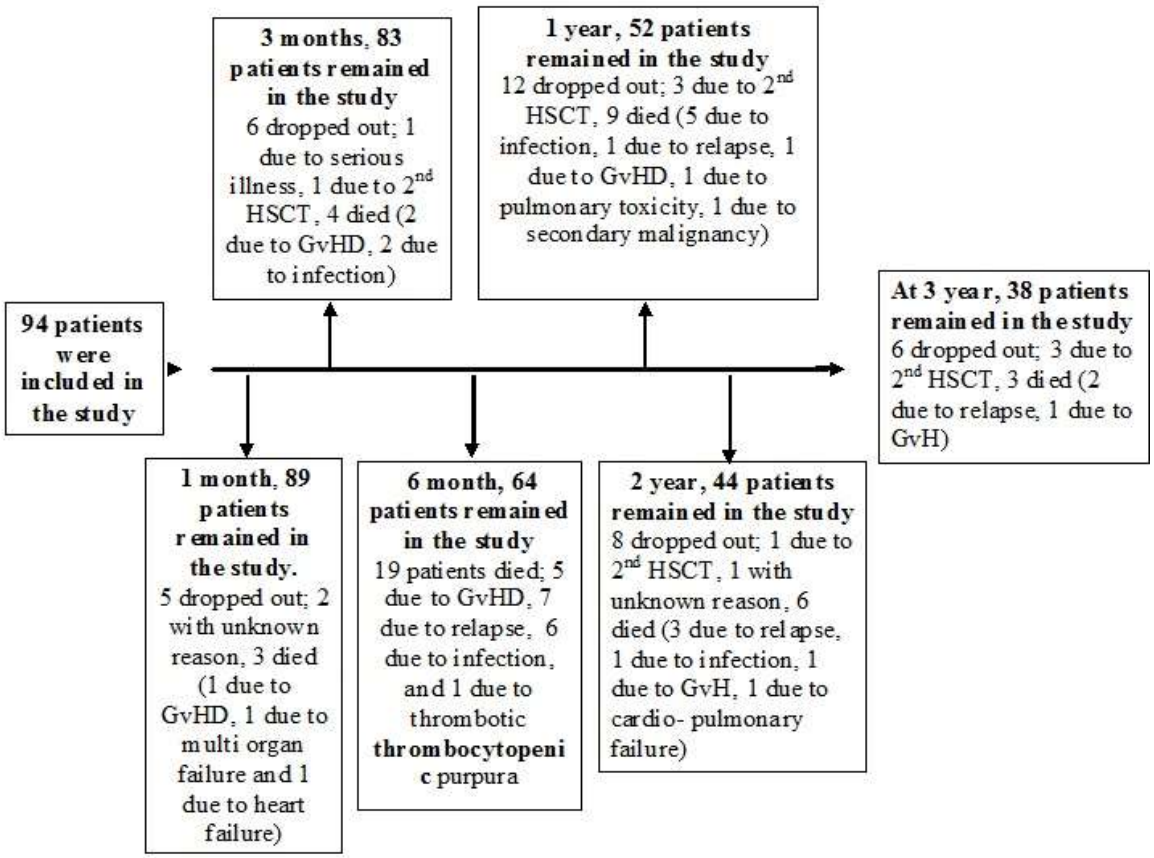
94 patients were included in the study
3 months, 83 patients remained in the study
6 dropped out; 1 due to serious illness, 1 due to 2nd HSCT, 4 died (2 due to GvHD, 2 due to infection)
1 year, 52 patients remained in the study
12 dropped out; 3 due to 2nd HSCT, 9 died (5 due to infection, 1 due to relapse, 1 due to GvHD, 1 due to pulmonary toxicity, 1 due to secondary malignancy)
At 3 year, 38 patients remained in the study
6 dropped out; 3 due to 2nd HSCT, 3 died (2 due to relapse, 1 due to GvH)
1 month, 89 patients remained in the study.
5 dropped out; 2 with unknown reason, 3 died (1 due to GvHD, 1 due to multi organ failure and 1 due to heart failure)
6 month, 64 patients remained in the study
19 patients died; 5 due to GvHD, 7 due to relapse, 6 due to infection, and 1 due to thrombotic thrombocytopenic purpura
2 year, 44 patients remained in the study
8 dropped out; 1 due to 2nd HSCT, 1 with unknown reason, 6 died (3 due to relapse, 1 due to infection, 1 due to GvH, 1 due to cardio- pulmonary failure)

Fig. 1.

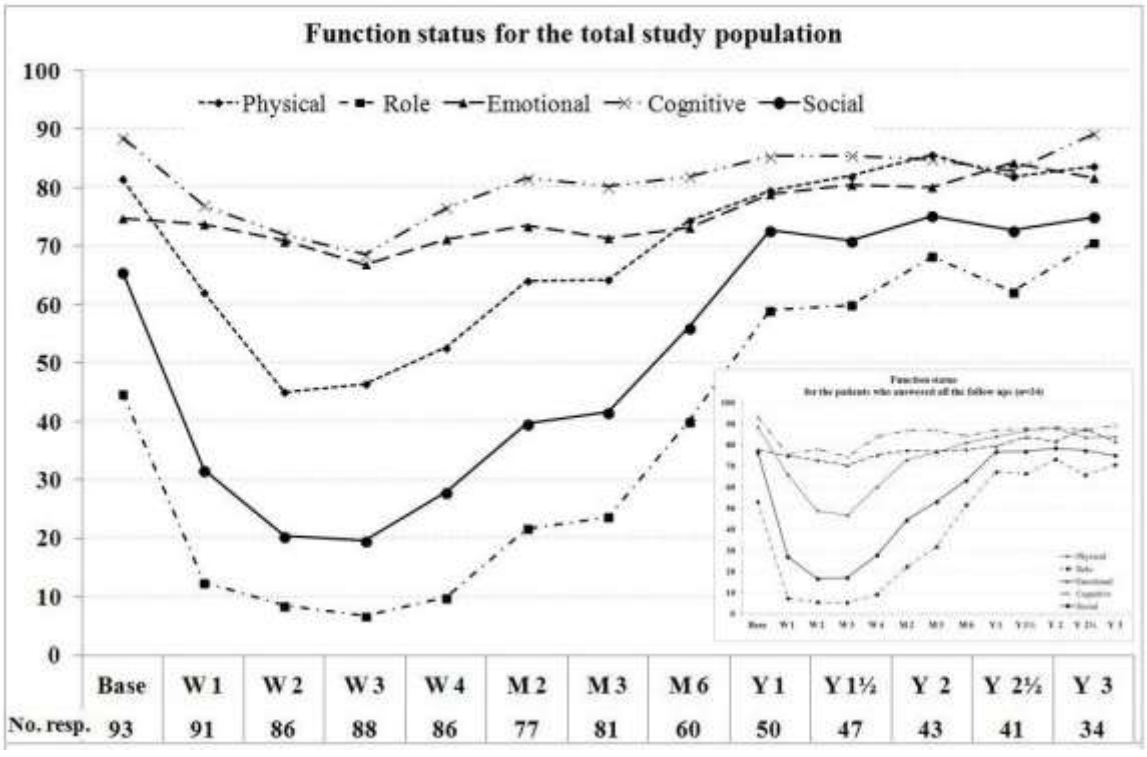
Function status for the total study population
Physical
Role
Emotional
Cognitive
Social
100
90
80
70
60
50
40
30
20
10
0
Base W1 W2 W3 W4 M2 M3 M6 Y1 Y1½ Y2 Y2½ Y3
No. resp. 93 91 86 88 86 77 81 60 50 47 43 41 34

Fig. 2

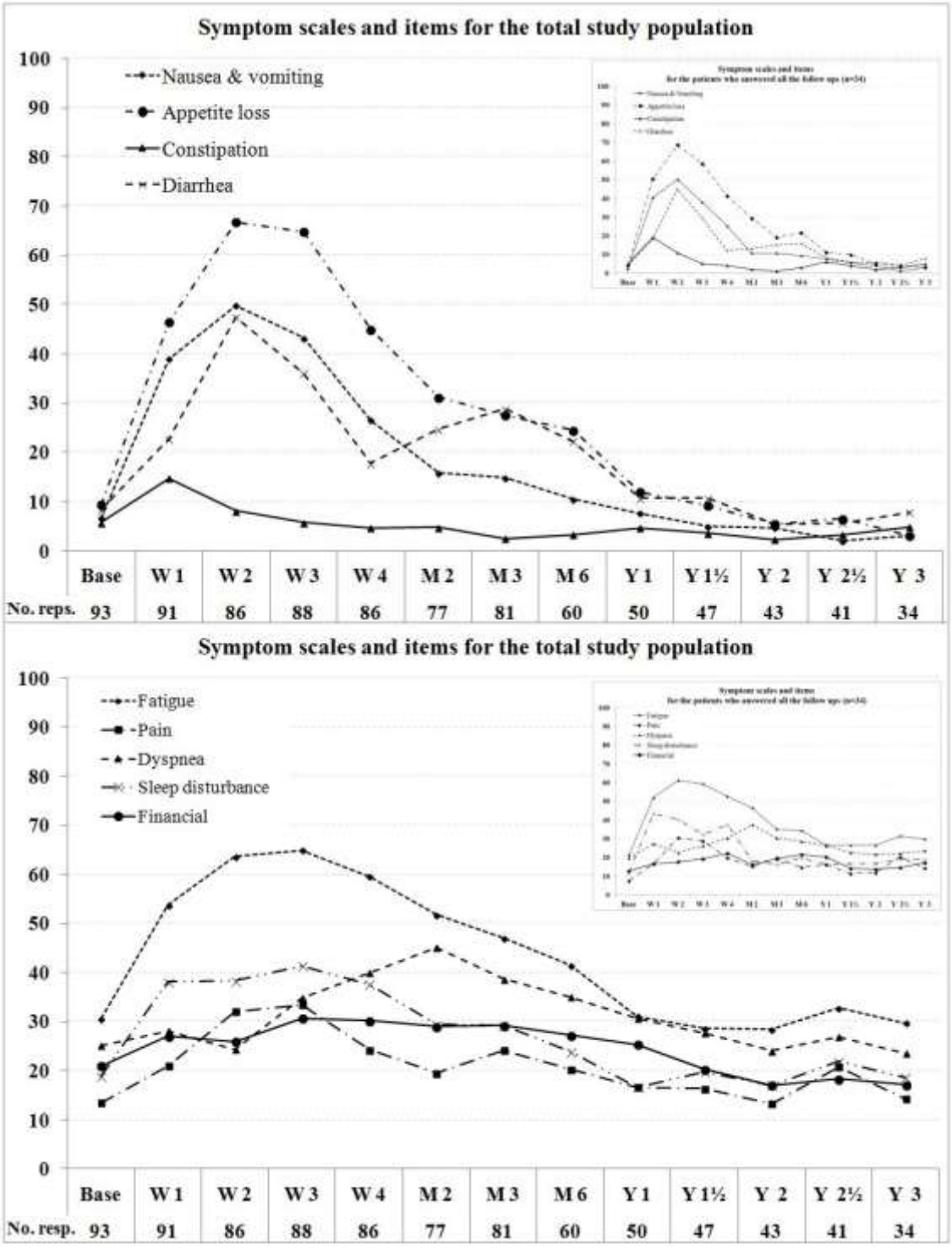
Symptom scales and items for the total study population
Nausea & vomiting
Appetite loss
Constipation
Diarrhea
100
90
80
70
60
50
40
30
20
10
0
Base W 1 W 2 W 3 W 4 M 2 M 3 M 6 Y 1 Y 1½ Y 2 Y 2½ Y 3
No. reps. 93 91 86 88 86 77 81 60 50 47 43 41 34
Symptom scales and items for the total study population
Fatigue
Pain
Dyspnea
Sleep disturbance
Financial
100
90
80
70
60
50
40
30
20
10
0
Base W 1 W 2 W 3 W 4 M 2 M 3 M 6 Y 1 Y 1½ Y 2 Y 2½ Y 3
No. resp. 93 91 86 88 86 77 81 60 50 47 43 41 34

Fig. 3.

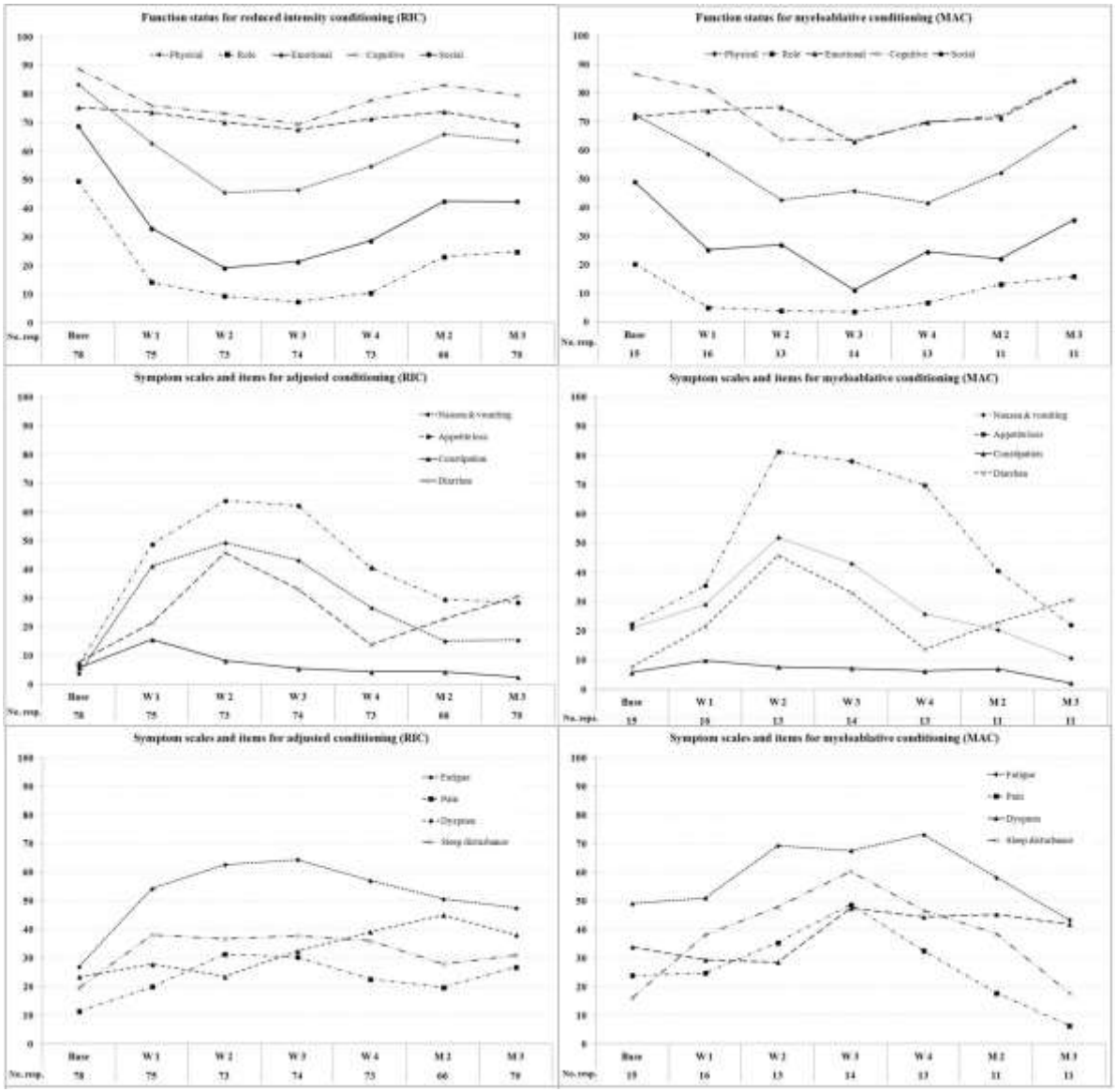
Function status for reduced intensity conditioning (RIC)
Physical
Role
Emotional
Cognitive
Social
Function status for myeloablative conditioning (MAC)
Symptom scales and items for adjusted conditioning (RIC)
Nausea & vomiting
Appetite loss
Constipation
Diarrhea
Symptom scales and items for myeloablative conditioning (MAC)
Symptom scales and items for adjusted conditioning (RIC)
Fatigue
Pain
Dyspnea
Sleep disturbance
Symptom scales and items for myeloablative conditioning (MAC)
Base
W 1
W 2
W 3
W 4
M 2
M 3
No. resp.

Fig. 4.

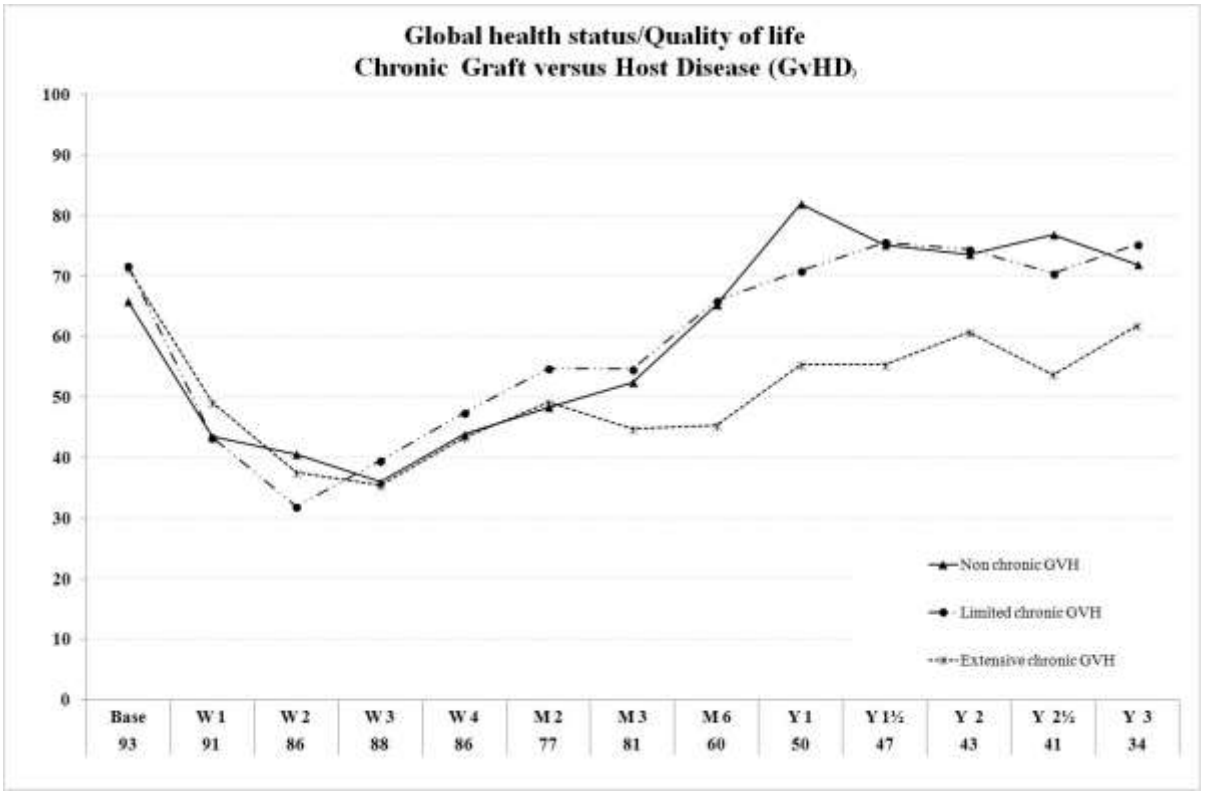
Global health status/Quality of life
Chronic Graft versus Host Disease (GvHD)
100
90
80
70
60
50
40
30
20
10
0
Non chronic GVH
Limited chronic GVH
Extensive chronic GVH
Base 93
W 1 91
W 2 86
W 3 88
W 4 86
M 2 77
M 3 81
M 6 60
Y 1 50
Y 1½ 47
Y 2 43
Y 2½ 41
Y 3 34

Fig. 5.

Table 1. Patient characteristics

Number of patients (n)	94
Men/Women (n) (%)	47/47 (50/50)
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Single	22 (23)
Stem cell source (n) (%)	
Peripheral blood hematopoietic cells	85 (90)
Bone Marrow	7 (8)
Cord blood	2 (2)
Donor: RD[1]/URD[2] (n) (%)	42/52 (45/55)
Conditioning regimens (n) (%)	
MAC[3]/RIC[4]	16/78 (17/83)
Serotherapy (n) (%)	
Alemtuzumab/Antithymoglobulin (n)	71/17 (76/18)
Inpatient period, mean (range)	
Days of hospitalization,	32 (18-162)
MAC/RIC	39 (23-69)/ 31(18-162)
Days with neutrophil counts < 0,5	16 (10-54)
MAC/RIC	20(10-54)/16(11-31)
Diagnosis (baseline / at 3 years)	Number
Acute leukemia	51 / 22
Myelodysplastic syndrome	8 / 1
Chronic myeloid leukemia	7 / 4
Chronic lymphocytic leukemia	4 /3
Myeloproliferative disease	4 / 1
Multiple myeloma	10 / 2
Lymphoma	5 / 2
Prolymphocytic leukemia	1 / 0
Other[5]	4 / 3
Acute GvHD[12](n)	
Grade 1 & 2/Grade 3 & 4	37/17
Chronic GVHD (n)	
Limited/Extensive	19/31

[1]**RD**: Related donor, [2]**URD**: Unrelated donor

[3]**Myeloablative conditioning (MAC)**: TBI+FAM (Total body irradiation: 12 Gy, Fludarabine 50 mg/day, and Ara-C 1 g/m^2 for three days; Melphalan 140mg/m^2 on day -1), BEAM (Becenun 300 mg/m^2, and Etoposide 200 mg/ m^2, and Ara-C: 400 mg/ m^2 for four days; Melphalan: 140 mg/m^2 on day -1), BuCy (Busulphan 4 mg/kg for four days, Cyclophosphamide 60 mg/kg for two days), FLAMSA-Cy-TBI (Fludarabine 30 mg/m^2, and Ara-C 2 g/m^2, and Amsacrin 100 mg/m^2 for four days; Cyclophosphamide 40 mg/kg for two days; TBI 4Gy on day -4).

[4]**Reduced intensity conditioning (RIC)**: FCM (Fludarabine 80mg/day, and Cyclophosphamide 300mg/day, both orally for five days; Melphalan 140 mg/m^2 intravenously on day -1), FC + ATG (Fludarabine 50 mg/day, and Cyclophosphamide 500mg/ m^2 for five days; antithymoglobulin: 4-8 mg/kg in 4 days), FAM (Fludarabine 50 mg/day, and Ara-C 1 g/m^2 for five days; Melphalan 140mg/m^2 on day -1), IFAM, MFAM (I=Idarubicin 20 mg, M= Mitoxantrone 12mg/m^2), FluBu (Fludarabine 30 mg/m^2 for six days, Busulphan 4 mg/kg for two days).

[5] **Other**: 2 aplastic anaemia and 2 paroxysmal nocturnal hemoglobinuria, [6]**GVHD**: Graft versus host disease,

Table 2. Difference in health-related quality of life between baseline and follow -ups at week 3, year 1 and 3 over a 3-year period measured with EORTC QLQ C-30 (0 - 100 points)

	Mean	**Diff with mean at baseline (n)α**			
	Baseline	*Week 3*	*Month 3*	*Year 1*	*Year 3*
Quality of life	69	-34 (87) *	-19 (80) *	-3 (50)	-8 (34)
Physical	81	-36 (79) *	-20 (80) *	-8 (50)	-5 (34)
Role	45	-39 (84) *	-24 (79) *	9 (50)	18 (34) *
Emotional	75	-8 (87) *	-2 (80)	3 (50)	4 (34)
Cognitive	89	-20 (87) *	-7 (80) *	-5 (50)	-4 (34)
Social	66	-46 (86) *	-23 (80) *	7 (50)	-1 (34)
Fatigue	31	36 (87) *	18 (80) *	6 (50)	8 (34)
Pain	13	21 (87) *	12 (80) *	6 (50)	7 (34)
Dyspnea	25	11 (86) *	14 (80) *	8 (50)	4 (34)
Sleep disturbance	19	23 (86) *	11 (80) *	3 (50)	7 (34)
Nausea & Vomiting	7	38 (87) *	11 (80) *	5 (50) *	1 (34)
Appetite loss	9	58 (87) *	21 (80) *	9 (50) *	-1 (33)
Constipation	6	0 (86)	-3 (80)	0 (50)	0 (34)
Diarrhea	8	29 (85) *	22 (79) *	5 (49)	3 (33)

α The difference is calculated with the mean at baseline for the same group of patients who answered the follow- up
*p<0.05 (Pairwise comparison between baseline and week 3, month 3, year 1 and 3)