Chapter 8

Summary & General Discussion
The general aim of this thesis was to study outcome of and need for psychological supportive care following treatment with hematopoietic stem cell transplantation (HSCT) in patients with hematological malignancies. More specifically, our first aim was to investigate whether offering a psychological supportive care intervention to patients undergoing autologous stem cell transplantation (auto-SCT) would be effective in reducing psychological distress and improving health-related quality of life (QOL). Second, we aimed to increase our understanding of the problem profile and care needs of HSCT patients, and gain more insight into patients’ help-seeking behavior. Third, we aimed to identify prognostic factors for post-transplant QOL.

In this final chapter, the main findings of Chapters 2 through 7 will be summarized. Subsequently, the main findings will be discussed in relation to other research studies, and an overview of lessons learned will be given. Further, clinical implications of our findings and methodological considerations will be addressed. Finally, recommendations for future research will be presented.

Summary of the main findings

Chapter 2 described the study protocol of a randomized clinical trial by means of which we examined the effectiveness of a stepped care intervention program on psychological distress and QOL in hematological cancer patients treated with auto-SCT.

In Chapter 3, the results of our randomized clinical trial were presented. The stepped care program as examined in this study was not effective in treating psychological distress in hematological cancer patients treated with auto-SCT. This could mainly be explained by the low uptake of the intervention, probably because of the low baseline levels of psychological distress. In addition, 10.3% of the patients in the study received psychological or psychiatric care outside of our intervention program at some point during the study period.

In Chapter 4, we aimed to elucidate the problem profile and care needs of patients treated with auto-SCT or allogeneic stem cell transplantation (allo-SCT). We also determined risk factors for reporting distress and/or problems after HSCT. The results showed that up to five years after auto-SCT or allo-SCT, patients continue to experience problems, mainly in the physical domain. Cognitive-emotional and practical problems were also reported, but less frequently. A minority of HSCT patients reported care needs. A risk factor for reporting distress as well as problems after auto-SCT was presence of comorbid diseases. Risk factors for reporting distress and problems after allo-SCT included younger age, shorter time after transplantation, and presence of graft-versus-host disease (GVHD).

Chapter 5 concerned an interview study with the purpose to elucidate patients’ help-seeking behavior after treatment with auto-SCT. We aimed to gain more insight into the observed discrepancy that patients with auto-SCT face a life-threatening disease and stressful treatment, yet report a relatively low need for additional supportive care. The results of the study showed that patients’ personal goals, future perspective, and phase of recovery determined whether patients experienced a symptom as a problem. Patients preferred to deal with problems themselves or with support from (close) relatives rather than bring in professional help. Finally, patients’ appeal for professional help depended on their coping strategies, social network, and knowledge of available care.
Chapter 6 consisted of a systematic literature review on prognostic factors for QOL after HSCT. Evidence from 35 studies was reviewed. Strong evidence suggested that presence of graft-versus-host disease (GVHD) predicted worse global QOL, and that chronic GVHD predicted diminished physical well-being. Strong evidence suggested that conditioning regimen predicted neuropsychological functioning in allo-SCT patients: patients receiving myeloablative conditioning (compared with reduced intensity conditioning) showed more impairments on various neuropsychological tasks. Being female (strong evidence, mixed patient group) and receiving less social support (moderate evidence, allo-SCT patients) predicted depression; pre-transplant distress (strong evidence, mixed patient group) predicted post-transplant psychological distress. Female patients returned to work less often and later compared with male patients (mixed patient samples). Finally, in auto-SCT patients, strong evidence was found for older age predicting better social functioning.

In Chapter 7, we aimed to develop and test a prediction model to estimate patients’ functioning after HSCT. Specifically, we examined which models could best predict physical functioning and psychological functioning in HSCT survivors, 3-10 years after transplantation. We concluded that it is possible to predict physical and psychological functioning with readily accessible predictors. However, the accuracy of the prediction models as developed in this study needs improvement before they can be recommended for use in clinical practice. We identified younger age, higher BMI, employment status (part-time work, or no part-time or full-time work, as opposed to full-time work), more comorbid diseases, autologous transplantation, and extensive chronic GVHD were identified as predictors of physical functioning. Female gender, younger age, higher BMI, having no partner, autologous transplantation, and extensive chronic GVHD predicted psychological functioning.

Discussion of the main findings
At the start of the studies resulting in this thesis, it was known that patients with hematological malignancies who undergo treatment with HSCT suffer from elevated levels of psychological distress [1-14]. The presence of psychological distress had been proven to decrease patients’ QOL [1,15-20]. Further, psychological follow-up care for this patient group was not systematically pursued. These findings provided strong ground for an intervention aimed at decreasing psychological distress, and thereby improving QOL in this patient group. The randomized clinical trial as described in Chapter 2 and Chapter 3, in which we tested this intervention, showed that the intervention was not effective in treating psychological distress in patients treated with auto-SCT. The uptake of the intervention program was very limited, for which various explanations could be offered. Our study sample had a relatively low prevalence rate of psychological distress. The nature of the intervention did not seem to match the needs of the majority of patients, as they appeared to be resilient enough to cope with the disease and treatment by themselves. Finally, current health care provision seemed to match the needs of most patients quite well, as 10.3% of the patients received mental health care outside of our intervention program, at some point during the study. Reflecting on the trial during as well as after completing the study, provided us with a few lessons learned.

The first lesson concerns targeted selection of patients for an intervention. When designing the trial, we assumed that all patients diagnosed with a life-threatening illness and undergoing a stressful treatment such as auto-SCT, could benefit from improved
problem-solving skills. We expected this to lead to a decrease in psychological distress and improvement of QOL. Our stepped care intervention was therefore offered to all patients treated with auto-SCT. Eventually, on average only 7% of the patients in our trial suffered from psychological distress at the first assessment (at hospitalization for auto-SCT). This prevalence rate was lower than expected from both clinical experience and previous literature: rates from 5 to 48% had been reported for elevated depressive symptoms, and 5 to 45% for anxiety symptoms [1-5]. Our patient sample was on the lowest side of this range. Because of that, a floor effect probably took place, precluding demonstration of an intervention effect. This has been common in intervention studies targeting distress in cancer populations. There has been much discussion on whether or not to preselect patients for psycho-oncology trials [e.g. 21-23]. On the one hand, it has been argued that it is not logical to expect effectiveness of an intervention with patient samples that as a whole are lacking in clinically significant distress [21]. On the other hand, it has been proposed that certain interventions could be broadly applicable, and might also be effective in preventing or minimizing future distress in currently non-distressed individuals [22]. Under the impression that all patients could benefit from certain interventions, many researchers did not preselect patients on characteristics like psychological distress or specific care needs. In recent years it has become clear that trials which apply pre-selection of patients, for example patients with high levels of distress, tend to result in larger effect sizes [24,25,26]. Consequently, it might be best to target supportive care interventions only at patients with predefined characteristics, such as elevated psychological distress or presence of unmet care needs.

The second lesson is related to patients’ need for care. An interesting observation in our trial was that presence of psychological distress was not equal to presence of care needs. Some patients with psychological distress did not have a need for help, whereas some patients without distress were interested in and completed our self-help intervention. In addition, the patients who had received mental health care outside of our trial (10.3% of the sample) were not necessarily those with the highest levels of distress. Other studies also reported that not all cancer patients with psychological distress express a need for help, nor do all accept help when a referral is offered [27,28]. In HSCT patients it has been shown that approximately 50% of patients with clinically significant distress had sought mental health services [27]. In a group of patients with various cancer types, 48-60% of distressed patients did not have an unmet need for psychological services, whereas 9-20% of patients without distress had an unmet need [28].

The majority of the patients in our trial seemed to have a low need for additional psychological care after auto-SCT. However, the actual care needs of this patient group had never been investigated. These observations led us to study patients’ problems and related care needs after treatment with HSCT, as described in Chapter 4. We showed that patients experience many problems after transplantation, mainly physical, but also cognitive-emotional and practical. Despite a substantial amount of problems, only 0-10.6% of patients with problems reported unmet care needs, depending on the problem category. This was partly due to patients’ needs already being met, but this could not explain the large discrepancy. We proposed a couple of explanations, including patients being able to cope by themselves and thereby not needing professional care, or unawareness of treatment options. Some of these explanations were supported by previous research, also in other cancer patient populations [27-29]: a major reason for not seeking care was a low perceived need for care, but also impeding factors like physical impairments, lack of knowledge and
emotional barriers appeared to explain why patients do not seek help. To further explore the observed discrepancy between patients’ problems and low need for care, we examined patients’ help-seeking behavior after auto-SCT in Chapter 5. This study led to a few new insights. First, we found that physical symptoms or emotional concerns were not always perceived as problems. Whether patients perceived symptoms as problems was determined by their personal goals, future perspective, and phase of recovery. Thus, to assume that patients see each impairment as burdensome is overly simplified. Further, most patients preferred to deal with problems themselves or with support from (close) relatives rather than bring in professional help, as was also shown in previous research studies [28,29]. This appeared to be a rather strong principle for the majority of patients, which hugely influences help-seeking behavior. At the same time, it emphasizes the ability of cancer survivors to cope resiliently with the consequences of their disease and treatment [30], and it points at the importance of having a social support network, for both emotional and practical support [1,31]. Besides patients’ coping strategies and social support network, patients’ actual appeal for additional professional care depended on their knowledge of available care. Patients’ emotional well-being was not always discussed between patients and their doctor or nurse, and some patients indicated they had a lack of knowledge regarding psychological care options.

Concluding, we learned that in providing supportive care, it cannot be assumed that all patients with psychological distress are in need for care to solve their distress. This need for care depends on a lot of factors, among which are the explicit preference of patients to deal with their problems themselves or with help from close relatives, other coping strategies, and knowledge of available care.

The third lesson concerns cancer patients’ resilience, a subject which has been touched upon in the previous paragraphs. As mentioned before, on average only 7% of the patients in our trial suffered from psychological distress at hospitalization for auto-SCT; this prevalence rate was lower than expected. Also the need for additional psychological support appeared to be low; most patients appeared to be capable of coping well with the demands of their disease and treatment. Not only in our trial, but also in the studies as described in Chapter 4 and Chapter 5, it is notable that many patients seem resilient, even if their disease is life-threatening and treatment is intensive with known short-term and long-term consequences. We were positively surprised by this observation, which contains a positive message, and realized that the resilience of cancer patients should be taken into account when organizing supportive care.

A vast amount of studies investigated resilience in cancer patients. The definition of the concept is not unambiguous, however: in some studies, resilience is defined by characteristics or traits, already present in individuals before a potentially traumatic event might happen [32-34], for example demographic variables, personal resources such as optimism or sense of coherence, or pre-existing social support. In other studies, resilience simply reflects absence of anxiety or depression. However, in the majority of studies, also in cancer patients, resilience represents a particular trajectory or mechanism of positive adaptation, changing over time, protecting against psychological distress or even leading to personal growth [35-37]. In these studies, resilience has been defined as “the ability of adults in otherwise normal circumstances who are exposed to an isolated and potentially highly disruptive event (…) to maintain relatively stable, healthy levels of psychological and physical functioning” [38].
Four trajectories are generally identified: (a) chronic disruption of normal functioning; (b) recovery after a short-lived disruption of functioning; (c) delayed disruption of functioning; and (d) resilience, with little or no disruption of functioning [36,38]. In the year(s) following diagnosis, 65-67% of cancer patients show resilience, 12-16% recovery, 7-13% a delayed response, and 7-9% chronic levels of dysfunction [36,37]. Thus, the majority of persons are resilient in the face of potentially traumatic events, such as a cancer diagnosis. Patients might even get to report positive outcomes after the cancer experience, like personal growth or posttraumatic growth [14,39]. It suggests that supporting this resilience may be sufficient for most survivors.

Our study findings and the three lessons learned state that the majority of cancer patients are able to cope well, with a smaller group of patients reporting psychological distress and/or psychological care needs [40]. A consequence of these findings is that supportive care should be targeted at this smaller group of patients. Subgroups at risk for difficulties adjusting to their disease and/or treatment can be identified by means of prognostic factors of psychological functioning. In Chapter 6 and Chapter 7, we examined prognostic factors of post-transplant functioning. From the systematic review in chapter 6 we concluded that impairments in different QOL domains were predicted by female gender, younger age, pre-transplant psychological distress, receiving less social support, GVHD, and specific conditioning regimens. Interestingly, these identified predictors were similar to predictors of resilience in the face of potentially traumatic experiences in general, including the capacity for positive emotions, resources (i.e. emotional and social support), and demographics (i.e. male gender, older age, and higher educational level) [38]. This provides evidence for use of these predictors in clinical practice. To test whether use of these factors is recommendable, and if so, to ease use of these predictors, we constructed prediction models for physical functioning and psychological functioning in the study as described in chapter 7. In this first step in this field of research, we used readily accessible predictors like demographic and medical factors, which are standardly available in patients’ medical record. From the results of this study, we concluded that using these accessible predictors alone was not yet sufficient to adequately predict post-transplant physical and psychological functioning. Since the results from our systematic review also pointed at pre-transplant functioning to significantly predict post-transplant functioning, extension of the models with pre-transplant functioning could lead to improvement of the prediction models.

In the light of these findings, it should be considered whether the identified predictors are changeable. It has been argued that most of the identified predictors of resilience are not changeable, and as such, intervening on these variables is not possible, nor desirable [38]. This indeed applies to most of the identified predictors (age, gender, educational level), but certainly not all. And if intervening on specific predictors is not possible, knowledge on predictors of post-transplant functioning still is valuable: patients at risk for impairments in post-transplant functioning may be identified and benefit from at least extra monitoring, and an offer of specific interventions when indicated.

**Clinical implications**

The findings from the present thesis can be used to optimize psychological supportive care in HSCT patients. First, in patients undergoing HSCT for treatment of hematological malignancies, and probably in all cancer patients, the option of psychological supportive care
should be standardly available. From our qualitative study, it followed that even patients who did not want to use this care option, emphasized the importance of discussing emotional issues in the doctor-patient relationship. Knowing that such support was available, and how they or their caregivers could get to this help if needed, was seen as an important part of hospital care. The patients who participated in the interviews did not perceive a stigma to discuss emotional issues, but it is known that such barriers to mental health care exist in some patients [27], which makes it even more important to put psychological support on the agenda of clinicians. As recommended in (inter)national guidelines, addressing emotional issues during and after treatment should be part of general follow-up care, just like other complications or long-term effects after cancer treatment, such as fatigue or impaired physical condition [41-44].

Second, our findings suggest that interventions should target specific care needs, and should be offered only to those patients with these specific care needs. As discussed previously, it cannot be assumed that all patients with psychological distress are in need for care to solve their distress. Furthermore, some patients without distress do have a need for additional supportive care. That raises the question whether care needs rather than specific symptoms or distress should be target of intervention. Up to now, a limited but increasing amount of trials investigated interventions that target cancer patients’ care needs. The majority of these trials did not report an intervention effect [45-53]. This may be explained by a couple of reasons, among which are insufficient psychometric rigor of unmet needs measures, small study samples, a lack of effectiveness of the tested interventions, non-adherence to intervention protocols, or (again) floor effects because studies lacked targeted selection of patients with high unmet needs [45]. Further research is certainly needed to explore these issues, because directly intervening on patients’ care needs seems a logical approach. On the other hand, specific care needs might stem from, for example, underlying psychological distress or cognitive problems. It makes sense that targeting specific care needs while ignoring those problems leading to care needs, might eventually not be effective. Nonetheless, at this point in time, it seems sensible to be aware of the discrepancy between psychological distress and need for psychological care, when considering psychological supportive care interventions.

Timing of offering treatment may also be a relevant issue. The results from the study described in Chapter 4 indicated that many patients who report problems, but not report a current care need, would consider asking for help at a later moment in time. Further, in the interview study we found indications that the type of care needs varies over time: patients were only able to think about emotional issues when they had left the acute physical recovery stage. The findings from these studies supported an earlier hypothesis, which stated that during and shortly after HSCT, the primary focus is on physical effects of disease and treatment. When moving through the disease and recovery process and returning to daily activities, the impact on social and role function becomes clearer [54]. In addition, some patients perceived the time after diagnosis as being the most arduous, and the time after treatment completion as a period for rebuilding and recovery. Others reported that the emotional processing only started after treatment completion. As each patient has his/her own individual recovery process, timing of offering additional supportive care seems essential. Emotional issues and the possibility for psychological supportive care may need to be repeatedly discussed during the disease and treatment process, also after treatment completion.
In Chapter 5, we identified a few factors on which actual need for psychological care depends. Among these factors were the explicit preference of patients to deal with their problems themselves or with help from close relatives, other coping strategies, the availability of social support, and knowledge of available care. It is important to take these factors into account when organizing supportive care. Our findings emphasize the importance of a good balance between support of patients' self-reliance and their need for professional care. Further, the urgency of a social support network which provides emotional as well as practical support was highlighted by our findings. Certainly in patients undergoing allo-SCT, social support is standardly evaluated. However, also after treatment with auto-SCT, social support is of substantial importance.

As psychological functioning and physical functioning are strongly related, and as psychological functioning can vary substantially during the disease and treatment process, doctors and nurses are in a good position to signal and address emotional concerns during treatment or follow-up appointments. A close collaboration between hemato-oncologists and nurse practitioners is essential: with limited time for follow-up appointments and often urgent medical issues to discuss, psychological aspects cannot be expected to be thoroughly discussed during each session. The nurse practitioner seems to be in a good position to further address emotional concerns, and to fulfill a coordinating role in organizing additional supportive care (physical, emotional, and social) [55]. If patients are in need for more intensive help, further steps could be taken in close collaboration with the patient, like offering a self-help program or referral to a psychologist or psychiatrist. It seems important to embed psychological supportive care in patients' self-management of their disease and treatment.

Methodological considerations
In this thesis, various study designs were used to answer our study questions. Each chapter contains a discussion of the methodological issues related to the specific study design in that particular chapter. Here, we will discuss the general methodological concerns of this thesis.

To study whether our stepped care intervention would be effective in treating psychological distress and thereby improving QOL, we conducted a randomized clinical trial in which stepped care was compared with care as usual. This pragmatic randomized clinical trial was the most rigorous way to test effectiveness of our intervention in 'real world' conditions. However, the study had some methodological limitations. Although statistically powered to show a main intervention effect, the amount of patients who adhered to the intervention protocol eventually was too small to detect an effect. Also the number of patients with distress was low, which hampered evaluation of the effectiveness of the intervention for distressed patients only. In testing the effectiveness of interventions aimed at decreasing psychological distress, which are offered to all cancer patients, the relatively low number of patients with psychological distress should be taken into account. This requires much larger sample sizes in order to obtain enough statistical power to evaluate the effectiveness of the intervention [56].

The study as described in Chapter 4, investigating HSCT patients' problems and care needs, had a cross-sectional design. Questionnaires were sent to all eligible patients who had been transplanted in the past 5.5 years at the Hematology department of our hospital. By using this design, we were able to show differences between groups of patients: we compared patients at 0-1, 1-2.5, and 2.5-5.5 years after transplantation. We were not able,
however, to investigate if and how patients’ problems and care needs change over time. For this, a longitudinal design would be more appropriate.

The qualitative research design of the study described in chapter 5 was adopted for gaining more insight into the observed discrepancy between patients’ substantial amount of problems and low need for care. A qualitative study design provides the opportunity to conduct an in-depth exploration of the subject of investigation. A commonly named pitfall in qualitative research is the subjectivity of the researchers. Because the same researcher was involved in the design of the study, approaching the patients, executing the interviews, and analyzing the data, we adapted several quality indicators to ensure the validity and reliability of the research process. Thick description (a rich and thorough description of the research setting and the participants) was used to improve generalizability of the results. Peer review was used to enhance credibility. Finally, in a member check, a short summary of the interview and a description of the researchers’ interpretations were sent to the study participants, who were in turn asked to provide written feedback on the accuracy of the emerging interpretations and theoretical constructs [57]. The findings in this study have provided us with insight into the help-seeking behavior of patients in the year after auto-SCT, and with explanatory hypotheses. These hypotheses should be tested in future (quantitative) studies.

Finally, in chapter 7, we used data from a study conducted at the Fred Hutchinson Cancer Research Center in Seattle, WA, USA [58]. With these data, we were able to construct prediction models for physical and psychological functioning 3-10 years after transplantation. A limitation of this study was that the prediction models contained two post-transplant variables: comorbidity and cGVHD. Comorbidity did not exactly represent pre-transplant comorbidity, as some conditions likely developed after transplantation. Therefore, we tested whether the other predictors in the model would be influenced by leaving the post-transplant variables out of the model. This was not the case. However, in future research it would be worthwhile to evaluate the value of adding pre-transplant comorbidities to the model. This would allow the model to be entirely calculated prior to transplant.

Recommendations for future research

This thesis was aimed at providing knowledge on how to optimize psychological supportive care in hematological cancer patients. Building on the knowledge as provided in this thesis, a couple of recommendations for future research can be made.

We made a start with studying the care needs of patients treated with HSCT. Future research could further look into HSCT patients’ care needs in the years following transplantation. Longitudinal studies could examine the change of individual patient’s needs over time, to identify which needs are most prominent at which points in time. To do that, there is a need for a Dutch instrument with good psychometric qualities to measure care needs [59,60]. Also the development of interventions aimed at targeting care needs could be considered, but caution is warranted, considering the trials examining interventions aimed at care needs thus far [45].

Patients’ resilience seems another promising research subject. As the majority of cancer patients seems to be able to resiliently cope with the demands of a cancer diagnosis and treatment, supporting this resilience may be sufficient for most survivors. Besides supporting
resilience in patients who generally do well, improving resilience in more vulnerable patients could be helpful. An intervention aiming at stress management and teaching resilience showed promising results in breast cancer survivors [61].

To identify those patients have difficulties in adjusting to the consequences of their disease and treatment, further research is needed into the predictors of psychological functioning. Further, it should be investigated whether closely monitoring those patients at risk, and offering treatment at critical moments in time, is a successful approach.

**Conclusion**

Psychological support is an important aspect of care in patients with hematological malignancies who undergo treatment with HSCT. This thesis provides several directions to optimize this type of care. First, providing all patients with psychological supportive care is not effective: supportive care interventions should be targeted only at patients with predefined characteristics, such as elevated psychological distress or presence of unmet care needs. Second, the presence of psychological problems or distress does not necessarily mean that patients are in need for care to solve their problems. In organizing psychological supportive care, it is important to balance patients’ resilience and their preference to deal with their problems within their own support network, and their potential need for professional support. Nonetheless, it is important to discuss care options for psychological problems at various moments during the disease and treatment process. When these issues are being taken into account, it is expected that patients will more optimally profit from psychological supportive care in the demanding time during and after treatment with HSCT.
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