Patients with hematological malignancies who undergo treatment with hematopoietic stem cell transplantation (HSCT) are confronted with a life-threatening illness and a stressful treatment. It is known that these patients suffer from elevated levels of anxiety and depressive symptoms, and that the presence of anxiety and depressive symptoms decreases patients' quality of life. Psychological supportive care for this patient group is not systematically pursued, however. The general aim of this thesis is to study outcome of and need for psychological supportive care following treatment with HSCT in patients with hematological malignancies. Specifically, we aim to provide answers to the following questions: would an offer of a specific psychological supportive care intervention to patients undergoing autologous stem cell transplantation (auto-SCT) be effective in reducing psychological distress and improving quality of life? Which problems and care needs do patients have after treatment with HSCT? What are patients' reasons for (not) engaging in help-seeking behavior after HSCT? And finally, which factors predict patients' quality of life after transplantation?

Hematological malignancies and hematopoietic stem cell transplantation
Hematological malignancies collectively refer to cancer in the blood, bone marrow, and/ or lymph nodes, specifically comprising the diagnoses leukemia, lymphoma, and multiple myeloma. Together, these cancer types represent approximately 7% of all new malignant tumors and cancer deaths in Europe [1]. The incidence (the number of new cases) of hematological malignancies in the Netherlands in 2012 was 8.042. The five-year survival rate varies considerably per diagnosis, from 18% for acute myeloid leukemia to 84% for Hodgkin lymphoma (2006-2010) [2].

For patients diagnosed with hematological malignancies, hematopoietic stem cell transplantation (HSCT) is a commonly used first-line or second-line treatment option. HSCT concerns the intravenous infusion of stem cells in a patient, after prior high-dose chemotherapy and/or radiation therapy [1]. Two general types of HSCT can be distinguished: autologous stem cell transplantation (auto-SCT) and allogeneic stem cell transplantation (allo-SCT). Auto-SCT has been developed to facilitate the use of myeloablative doses of chemotherapy; it enables recovery of the normal bone marrow and re-establishment of normal hematopoiesis after these have been damaged by high-dose chemotherapy [3]. In auto-SCT, stem cells are collected from the patient's peripheral blood, then harvested and stored. Then, the patient is treated with conditioning therapy to destroy any remaining cancer cells. This conditioning therapy consists of high-dose chemotherapy, which sometimes is combined with radiation therapy, depending on diagnosis. Subsequently, the collected stem cells are re-infused for recovery of hematopoiesis. The transplant-related mortality of auto-SCT is low (<5%), but relapsed disease occurs in 5% to 50% of patients, depending on their diagnosis [1,3]. For the whole procedure, patients are hospitalized for three to four weeks.

In contrast to using patients' own stem cells in auto-SCT, in allo-SCT stem cells from a matching donor are used. The use of donor cells implies that the infused cells are free of contamination by malignant cells, and that they are capable of mediating an immunological reaction against foreign antigens. This can be a major advantage if this reaction is directed against remaining cancer cells, which is called a 'graft-versus-tumor effect', decreasing the chance of disease relapse. However, the reaction can also be directed against normal cells, leading to the destruction of normal organ tissue: graft-versus-host disease (GVHD) [3]. Approximately 30% to 70% of patients are affected by chronic GVHD after treatment with

allo-SCT [4]. GVHD can cause serious damage to bodily organs, and is a major cause of late death. Compared with auto-SCT, transplant-related mortality after allo-SCT is higher, but relapsed disease occurs less frequently [1]. Whether patients receive treatment with auto- or allo-SCT depends on several factors, such as (inter)national protocols, availability of donors, patients' age, and patients' clinical condition.

The use of HSCT is common, and the number of transplants still increases. Approximately 11.000 and 17.715 auto-SCT's were provided in the U.S. in 2011 and Europe in 2012, respectively, to patients with leukemia, lymphoma, or multiple myeloma. For allo-SCT, these numbers were approximately 5.500 in the U.S. in 2011, and 12.262 in Europe in 2012 [5,6].

Consequences of disease and treatment
Treatment including HSCT generally leads to improved survival. At the same time, hematological malignancies as well as treatment procedures are associated with impairments in patients' quality of life. According to the World Health Organization, quality of life reflects a subjective concept, defined as "individuals' 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" [7]. *Health-related* quality of life (in this chapter referred to as QOL) refers to those domains of quality of life directly affected by changes in health, and can be defined as the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient [8]. QOL consists of several broad domains, including physical functioning, psychological functioning, social functioning, and occupational functioning. The QOL of patients with hematological malignancies treated with HSCT is well-documented [9-11]. Several studies compared the QOL of patients treated with auto-SCT with population norms. Before and directly after auto-SCT, patients report impairments in physical, emotional, and role functioning. These impairments are caused by the original disease, prior treatment, and the intensive conditioning therapy. In the subsequent months and years after auto-SCT, these QOL domains reach or surpass pre-transplant levels, but continuing long-term impairments are observed for physical functioning, role functioning, and global QOL [9-11]. Also the QOL of patients treated with allo-SCT has been compared with population norms. Before and shortly after allo-SCT, patients report impaired physical, psychological, social, and role functioning. All QOL domains decline rapidly immediately after allo-SCT, but then improve gradually toward pre-transplant levels in the years following allo-SCT. Long-term impairments are observed for all QOL domains [9-11].

Impairments in QOL in patients treated with HSCT often stem from the presence of physical symptoms. Treatment including HSCT is associated with various short-term and long-term side effects. Short-term side-effects may consist of, among others, nausea, mucositis, and fatigue. Further, disease and treatment may lead to the presence of medical complications with a potential long-term impact, such as endocrine dysfunction, cardiovascular disease, pulmonary complications, bone loss, or subsequent malignant neoplasms [12]. Patients may also report longer-lasting fatigue, sexual dysfunction, cognitive problems, sleeping problems, and musculoskeletal problems [13]. Besides, emotional problems such as depression and fear of relapse may occur and affect patients' QOL [9,13]. Emotional problems are frequently referred to as psychological distress, which has been defined as "a multi-determined unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer,

its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common feelings of vulnerability, sadness, and fears to problems that may become disabling, such as depression, anxiety, panic, social isolation, and spiritual crisis" [14]. Consistent with other studies in the psycho-oncology literature, the term psychological distress is used in this thesis to indicate elevated symptoms of depression and/or anxiety. Previous research in HSCT patients showed large variation in the prevalence of depressive and anxiety symptoms. In the period from before transplantation to one year post-transplant, prevalence rates of 5% to 48% have been reported for depressive symptoms, and 5% to 45% for anxiety symptoms [15-19]. The period of initial hospitalization has repeatedly been pointed at as being most stressful [20-22]. In long-term survivors, i.e. persons who have survived five years or longer after HSCT, it has been found that 20% to 45% have at least some psychological distress, and 9% to 20% have clinical depression [23-28]. It is evident that psychological distress is an undesirable outcome in itself. Moreover, it has been shown that psychological distress is a strong predictor of certain QOL domains after HSCT: patients who suffer from elevated depressive or anxiety symptoms in the phase surrounding transplantation have been shown to be more likely to face impaired psychological functioning [15,29-34] and physical limitations [15] after transplantation.

Treatment of psychological distress
The findings on psychological distress being a prognostic determinant of QOL provide a strong basis for an intervention focusing on treatment of psychological distress. In HSCT patients specifically, treatment of psychological distress has not been studied well. However, it has been studied extensively in other groups of cancer patients. Many different forms of psychological treatment have been subject of investigation, among which are relaxation techniques, cognitive behavioral therapy, and problem-solving techniques (for an overview, see e.g. [35]). Also outcome measures differ: some interventions aim at treating depressive symptoms, others at relieving anxiety symptoms or improving general psychological distress. In general, studies evaluating treatment for anxiety or depressive symptoms in cancer patients show small-to-medium effect sizes [35]. In this thesis, we aim to test whether an intervention targeted at improving psychological distress would be effective in HSCT patients.

In delivering treatment for psychological distress, the stepped care approach has been strongly advocated [36-38]. In this approach, patients start with the least intensive treatment that is most likely to work. Only those patients insufficiently helped by the initial treatment receive more intensive and costly interventions. Stepped care aims at an effective and efficient allocation of therapeutic resources. The intervention that we aimed to test in this thesis was a stepped care program consisting of three steps: (I) watchful waiting; (II) internet-based self-help program; (III) face-to-face counseling by a consultant psychiatric nurse, medication, or referral to other services. As psychological distress often improves without active treatment, watchful waiting is a meaningful first step of a stepped care intervention. The second step of the intervention, an internet-based self-help program, was based on Problem Solving Treatment (PST). This has shown to be an effective intervention for reducing psychological distress [39], also in cancer survivors [40,41]. PST does not aim to directly solve patients' problems, but rather to strengthen patients' self-management skills to solve present and future problems. Patients learn to regain control of their problems by (a) prioritizing problems which matter most to them and which in principle can be solved; (b) analyzing the problem and generating alternative solutions; (c) selecting methods for solution and

implementing these; and (d) evaluating the results and preparing for the future. This may help patients cope with the challenges they encounter related to disease and treatment [42]. Patients with hematological malignancies treated with HSCT may therefore profit from improved problem-solving skills. Also the face-to-face counseling in the third step of the intervention was based on PST.

In the field of psycho-oncology, it has been common in intervention studies targeting psychological distress to apply broad eligibility criteria, and include all cancer patients regardless of their current level of psychological distress. However, in recent years it has been argued with increasing emphasis that this results in a too heterogeneous group of patients, in which a large part will not suffer from psychological distress. Other patients will improve without treatment, leaving only a certain part of patients to actually benefit from distress treatment [e.g. 35,43,44]. Since we assumed that all patients undergoing HSCT could benefit from improved problem-solving skills, we offered our stepped care program to all patients, regardless of their level of psychological distress.

Chapter 2 and 3 of this thesis present the design and results of a randomized clinical trial we conducted in patients with hematological malignancies treated with auto-SCT, in which the effectiveness of a stepped care intervention on psychological distress and QOL was tested.

Patients' problems, care needs, and help-seeking behavior after HSCT
During the execution of the abovementioned trial, we noticed that the majority of our study participants were not in need of active interventions to improve psychological distress: most patients chose for watchful waiting, a minority for the internet-based self-help intervention, and no patients entered the step including individual face-to-face counseling, medication, or referral to other services. Clinical experience and previous research indicated, however, that HSCT patients did face many symptoms or problems in the time after transplantation. For which problems patients had a need for help, then, remained unclear. Therefore, we decided to study patients' problems and care needs after HSCT.

As mentioned previously, multiple studies reported on the physical symptoms and psychological problems patients undergoing HSCT may encounter [9-11]. However, a comprehensive problem profile, comprising the wide range of physical, psychological, practical, social, and spiritual problems, was lacking. Such an overview of experienced problems could guide supportive care provision. Another requirement for establishing patient-centered care provision is insight into patients' care needs. For some problems, patients have a need for help (care need), whereas for other problems they do not have this need. In case of a care need, patients may already receive help to fulfill this need (met need) or not (unmet need). A recent review summarized the findings on unmet needs in cancer patients, and concluded that unmet needs most frequently occur in the activities of daily living domain, and then, in succession, in the psychological, information, psychosocial, and physical domains [45]. Prevalence rates of unmet needs differ considerably between studies, however. This is partly because of differences in the classification and measurement of unmet needs, but also as a consequence of differences in disease, treatment, and provision of healthcare services [46,47]. Therefore, it has been argued that assessment of needs should be conducted within homogeneous patient samples [45]. Two earlier studies investigated care needs in patients

with hematological malignancies. The first study, conducted in multiple myeloma patients, reported that a quarter of patients had at least one unmet need. Practical needs, such as hospital parking and obtaining (life) insurance, were most frequently reported [48]. The other study, investigating patients with hematological malignancies at treatment completion, showed the most frequently reported needs to concern managing fear of recurrence, the need for a case manager, and communication with treating doctors [49]. Care needs have not been studied in HSCT patients specifically. Therefore, Chapter 4 contains a description of HSCT patients' problems and corresponding care needs.

In the trial we observed that relatively few patients report a need for additional professional psychological care; this observation is supported by clinical experience and some research [48,50]. Hence, a discrepancy appears to exist between symptoms patients report in the years after transplantation, and their need for additional care: it seems that a substantial number of patients who report emotional problems after auto-SCT do not engage in help-seeking behavior. Indeed, previous research showed that only 50% of HSCT patients with clinically significant distress had sought mental health services; a number comparable to that among other cancer populations [50]. Further examining HSCT patients' help-seeking behavior could shed light on these findings. Help-seeking behavior has been described as intentional action to solve a problem that challenges personal abilities [51], although it often involves a reactive, spontaneous decision [52]. Since our observations concerned patients' need for additional professional care, it is sensible to consider determinants of health care use. Andersen and Newman proposed a framework for individual determinants of health care use, in which they suggest that people's health care use is a function of (a) their predisposition to use services, referring to background variables such as demographic factors; (b) factors that enable or impede use, such as social structure; and (c) their need for care [53,54]. In HSCT patients, reasons for (not) seeking care have hardly been investigated, but from previous research in other cancer patients we know that a low perceived need for care seems a major reason for not seeking care. Motives for lung cancer patients not seeking care were patients' current ability to manage, sufficient help from their own support networks, and viewing other patients as more needy than themselves [55]. Distressed cancer patients who had completed curative treatment mentioned receiving adequate social support as a reason for their absent need for psychological services. Other motives were wishing to improve by themselves and considering help at a later point in time [56]. Impeding factors seem another relevant explanation for not seeking help. Earlier studies mentioned physical impairments [56], lack of knowledge, emotional barriers [50], not thinking that talking would help, not willing to talk about problems [56], and patients' confidence that their doctor would have recommended treatment if available [55]. Although these findings provide important insights, there is a need to further clarify the discrepancy between facing a life-threatening disease and stressful treatment, and the low need for and seeking of additional care after HSCT. Therefore, in Chapter 5, we present a qualitative interview study in which we aimed to gain more insight into the factors underlying this discrepancy, by exploring auto-SCT patients' needs and help-seeking behavior in relation to their experienced problems.

Factors predicting patients' QOL after HSCT
As mentioned before, impairments in QOL occur during the entire post-transplantation period, and may concern physical as well as psychological functioning [9-11]. While general statements about patients' QOL after HSCT can be made, QOL differs substantially between

patients. Most patients adapt well to the consequences of their disease and treatment, while others experience more difficulties. These individual differences may depend on various factors; demographic, somatic, psychological, or social. In order to provide supportive care tailored to the needs of the individual patient, the identification of factors that predict QOL following HSCT would be useful. This would help clinicians estimate their patients' functioning after HSCT, and may also be helpful in providing tailored education about expected post-transplant functioning. As the studies that have been published on prognostic factors were scattered, we systematically reviewed the prognostic factors for health-related QOL after HSCT in hematological malignancies. The results of this study are presented in Chapter 6.

After obtaining a comprehensive overview of the evidence for prognostic factors of QOL after HSCT, a logical next step is to build a prediction model to estimate patient functioning after HSCT. Such a model would help clinicians estimate patients' physical and psychological functioning, identify those patients at risk, and focus resources on added supportive care for those most in need. In Chapter 7, we examined which risk prediction model could best predict physical and psychological functioning in HSCT survivors. It has been recommended that the variables to be selected for a predictive model should be widely available [57]. We therefore focused on demographic and medical-somatic factors as potential predictors of physical functioning and psychological functioning.

Aims and outline of this thesis
The overall objective of this thesis is to study outcome of and need for psychological supportive care following treatment with HSCT in patients with hematological malignancies. In particular, the first aim of this thesis is to examine whether a stepped care intervention would be effective in reducing psychological distress and improving QOL in patients treated with auto-SCT. Second, we aim to increase our understanding of the problem profile and care needs of HSCT patients, and gain more insight into the discrepancy between facing a life-threatening illness and stressful treatment, and the relatively low need for and seeking of additional care after HSCT. Our third aim is to identify predictive factors for patients' functioning after transplantation.

In line with our aims, Chapter 2 and 3 describe the design and results of a randomized clinical trial which we conducted to test the effectiveness of a stepped care intervention in reducing psychological distress and improving QOL in patients treated with auto-SCT for hematological malignancies. Chapter 4 contains a description of patients' distress, problems, and corresponding care needs in the five years after auto-SCT and allo-SCT; additionally, this chapter explored the risk factors for distress, problems, and care needs. Chapter 5 provides the results of an interview study by means of which more insight was gained into auto-SCT patients' help-seeking behavior. Chapter 6 contains a systematic review of the literature on prognostic factors for health-related QOL after HSCT in hematological malignancies. Chapter 7 explores which risk prediction model could best predict physical and psychological functioning of HSCT survivors. Finally, Chapter 8 summarizes and discusses the main findings of the studies included in this thesis.

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