Allogeneic hematopoietic stem cell transplantation in the elderly


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Abstract

The development of reduced intensity or non-myeloablative conditioning (NST) in preparation for allogeneic stem cell transplantation (SCT) revolutionized the field and led to reconsideration of the dogma of upper age limit that was set up by the transplant centers as an

Abbreviations: aGVHD, acute GVHD; AIDS, acquired immunodeficiency syndrome; AML, acute myelogenous leukaemia; ATG, anti-thymocyte globulin; AUC, area under the curve; CCI, Charlson CI; CI, comorbidity indices; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; cGVHD, chronic GVHD; CR, complete remission; Css, concentration at steady-state; CVA, cerebrovascular accident; DFS, disease free survival; DLI, donor lymphocyte infusion; EBMT, European blood and marrow transplantation; EFS, event free survival; G-CSF, granulocyte colony stimulating factor; GVHD, graft-versus-host disease; GVT, graft versus tumor effect; HLA, human leukocyte antigens; IBMTR, International Bone Marrow Transplantation Registry; IL, interleukine; IPS, international prognostic scoring system; JSHCT, Japan Society for Hematopoietic Stem Cell Transplantation; LFS, leukemia free survival; MDR, multi drug resistance; MDS, myelodysplastic syndromes; MIC, minimal-intensive conditioning; MM, multiple myeloma; MMF, mycophenolate mofetil; MOC, moderately intensive conditioning; MPS, myeloproliferative syndromes; MUD, matched unrelated donor; NHL, Non-Hodgkin’s lymphomas; NRM, non-relapse mortality; NST, non-myeloablative SCT; OS, overall survival; PBSC, peripheral blood stem cells; PFS, progression free survival; PS, Performance status; RIC, reduced intensity conditioning; RRT, regimen-related toxicity; SCT, Stem cell transplantation; SOT, solid organ transplantation; TRM, transplant related mortality; WHO, World Health Organization

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1. Introduction

Allogeneic hematopoietic stem cell transplantation (SCT) is a potentially curative procedure for patients with chemotherapy resistant or recurrent hematological malignancies. However, SCT has been preferentially used for younger patients without significant comorbidities primarily due to concern about the high incidence of treatment-related morbidity and mortality. Due to age limitation, currently most transplant centers restrict the application of conventional myeloablative conditioning regimens to patients below the age of 55, although significant differences among the eligibility criteria still exist. Since HLA-identical siblings are available to only 30% of the patients in need, an important limitation of SCT except age is the availability of a matched donor [1]. An extended family search identifies a suitable donor for less than 5% of the patients of Caucasian origin [1]. Moreover, the possibility of finding a matched family donor is even lower in older patients, because the number of potential family donors decreases with the aging of the family [2]. For patients lacking a suitable family donor, matched unrelated donor provides an alternative option. A matched unrelated donor can be found in almost 50–60% of patients of north European or North America origin [3]. However, SCT from an unrelated donor, especially in older individuals, is associated with an increased risk of morbidity and mortality in comparison with transplants from matched siblings, mostly due to increase in the incidence of severe acute graft versus host disease (GVHD) [4]. Consequently, currently most transplant centers limit the application of SCT from matched unrelated donor (MUD) to patients younger than 50 years old [5]. The following review will focus on clinical application of SCT for elderly recipients with particular attention on the increasing indication for SCT in the aged using reduced intensity conditioning (RIC) and NST.

2. Hematological malignancies in the elderly

The incidence of most of the hematological malignancies increases proportionally with age. For most of these diseases such as, chronic myelogenous leukemia (CML), acute myelogenous leukemia (AML), myeloproliferative syndromes (MPS), myelodysplastic syndromes (MDS), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), Non-Hodgkin’s lymphomas (NHL), the median ages at diagnosis are 55–70 years [6]. Moreover, for some of these diseases such as AML and NHL, advanced age represents a significant adverse prognostic factor. AML in the elderly is usually associated with unfavorable cytogenetic abnormalities, prior myelodysplastic phase, high expression of multi drug resistance (MDR) genes, microsatellite instability, etc., resulting in poor survival outcomes when these patients are treated conventionally [7–9]. Age above 60 years is considered as an adverse prognostic factor for the outcome of patients with high grade NHL, and is incorporated in the international prognostic scoring system (IPS) [10].

3. Ageing of the population in developed countries

The population in the developed countries is getting older with time as life expectancy increases primarily due to improvements in medical care. Presently, the life expectancy of a 60-years old healthy woman is estimated to be above 83 years. People above 65 years, who at the present account for about 12% of the western population, are anticipated to represent more than 20% of the whole population by the year 2030 [11]. Therefore, it is obvious that the vast majority of patients in need of SCT, are currently ineligible by conventional criteria acceptable by most transplant centers, only due to age limitations. Moreover, as the population of developed countries is getting older, for a growing number of patients in need at an advanced age may remain an exclusion criterion.

4. Advancements in solid organ transplantation in the elderly

The need to extend the age barrier for patients in need of an allograft is not unique for candidates of stem cell transplantation. Advanced recipient age is no longer considered as a contra-indication for solid organ transplantation (SOT). Patients older than 65, are undergoing transplantation with increasing frequency. The percentage of renal allografts performed in patients older than 65 years increased from 2.9% in 1983 to 12.5% in 1999 [12]. Reports from several transplant centers document that overall short-term survival of older patients undergoing SOT are comparable to survival rates of younger adults. Paradoxically, in this regards, older patients
may benefit from a senescent immune system, which results in decreased requirements for immunosuppressive drugs, and possibly a lower rate of acute allograft rejection. Despite good overall short-term survival in the elderly, long-term survival may be worse because of an increased risk resulting from poor response to infections and increased rate of late complications, such as malignancy and heart disease [13]. However, although advanced age is a negative risk factor, advanced age alone should not exclude a patient from solid organ transplantation. In a recent study, Macrae et al. examined the outcomes of geriatric patients (>75 years) with dialysis-dependent renal failure selected for kidney transplantation. Outcome of patients above the age of 75 years who received a kidney transplant from 1994 to 2000 was compared with the outcome of patients remaining on dialysis or on a transplant waiting list. Superior 5 year survival after kidney transplantation was attained by the geriatric cohort given a kidney transplant (40–55%), compared with dialysis patients waiting for transplant (29%), or those who were not selected for kidney transplantation remaining on dialysis (12.5%). Taken together, even 75-year-old patients can benefit from kidney transplantation with excellent graft survival [14].

5. Factors predictive of transplant related mortality

Age is perhaps the most commonly used eligibility criterion for patient enrolment in SCT clinical trials. However, chronological age by itself does not necessarily parallel with biological age and the ability of the recipient to tolerate the highly intensive regimens used for preparation of conventional stem cell allografts. Many other parameters have been tested for their efficacy to predict the transplant outcome of the individual patient, and will be briefly summarized below: (1) Performance status (PS) as defined by Karnofsky, Zubrod, or WHO scales represents a simplified tool for functional assessment, and has been extensively explored as a prognostic factor for the transplant outcome. Analysis of data from large studies of both autologous and allogeneic SCT has reliably shown the significant association of PS score with transplant related mortality (TRM) and overall survival (OS) [15–17]. However the utility of PS in clinical decision-making is limited because only few of the patients that are actually transplanted have poor PS scores, and because PS does not account for the presence or absence of other specific comorbidities that may affect the outcome of patients with good PS scores. (2) Single organ comorbidities prior to transplant have been studied extensively as predictors of transplant outcome. Cardio-pulmonary, hepatic, and renal function testing has been included in the pre-transplant evaluation since many years. Results from studies exploring the prognostic significance of single organ dysfunction have been conflicting [15,18–22]. Although the prognosis of patients with severe organ dysfunction is poor, the prognostic significance of borderline dysfunction seems to be less clear. Furthermore, many patients may have more than one comorbid factor. Because of the above limitations, the presence or absence of single organ comorbidities is not sufficiently predictive of transplant outcome to allow for clinical decision-making. (3) Comorbidity scoring systems, or comorbidity indices (CI) has been developed in an effort for more accurate prediction of the treatment outcome in various disease states. CI represents the sum of a wide variety of different medical morbidity conditions that may influence the outcome of certain diseases [23]. Within the field of oncology, such indices have been used to assess the outcome of prostate, breast, and colon cancer patients respectively [24–26]. One of the most common CI in use, is the Charlson CI (CCI) that evaluates the presence or absence of 19 different medical conditions such as, hypertension, diabetes, liver, renal, pulmonary disease, previous CVA, metastases from solid tumor, AIDS, etc. [27]. Recently, the clinical utility of CCI has been explored in the setting of SCT. Shahjahan et al. [28] retrospectively analyzed a cohort of AML, and MDS patients in order to examine the impact of CCI on the transplant outcome. After analysis of their data, they showed that the higher the CCI score, the higher the TRM, and the lower the OS. Diaconescu et al. [29] and Sorror et al. [30] reported similar results in the setting of non-myeloablative SCT (NST). In conclusion, CI seems to be a valuable tool for predicting TRM. However, its clinical utility in decision-making should be further evaluated with prospective randomized trials. (4) Previous high dose therapy followed by autologous or SCT is another prognostic factor associated with increased TRM [31,32]. Second SCT in patients with leukemia is associated with very high TRM, especially in cases with a short time interval between the two transplants [33].

6. Myeloablative allogeneic stem cell transplantation

6.1. Theoretical considerations

Common experience suggests that advanced age is associated with inferior outcome after myeloablative allogeneic SCT. Most of the transplant centers usually set up eligibility criteria, including an upper age limit for enrollment of otherwise eligible candidates into therapeutic protocols. However, in recent years an increase in the upper age limit has been noticed, mostly due to the improvements in the medical care of transplant recipients, yet transplant physicians are reluctant to treat older patients primarily due to concerns about the high risk of regimen-related toxicity and the increase in the incidence of acute (aGVHD) and chronic GVHD (cGVHD) resulting in increased TRM.

From the theoretical point of view, the poor transplant outcome with increasing age may be related to many factors: (1) higher incidence of comorbid conditions such as, heart, lung, renal, obesity, metabolic disorders that make such patients prone to increased transplant related mortality and morbidity; (2) differences in drug pharmacokinetics between young and older patients: It has been proven by different studies that
the regimen-related toxicity of certain drugs such as busulfan is related to area under the plasma concentration–time curve (AUC) and average steady-state concentrations ($C_{ss}$) [34]. Excessively high busulfan AUC or $C_{ss}$ have been associated with increased incidence of veno-occlusive disease of the liver, while low levels have been related to higher rates of relapse and graft rejection [35,36]. Also older individuals are more prone to the development of severe cerebellar toxicity after administration of high dose cytarabine [37]; (3) Finally, common experience suggests that older patients not only suffer from more GVHD, but also they are more prone to GVHD related mortality and morbidity, because they are less tolerant to the side effects of the immunosuppressive regimens given for the treatment of GVHD. In support of these theoretical concerns are the observations of the increased treatment mortality that has been observed in older patients treated with conventional chemotherapy AML-induction protocols, or with autologous bone marrow transplantation [38,39]. Analysis of the existing literature related to the influence of age on the transplant outcome is briefly summarized in the following paragraphs.

6.2. Is older age associated with increased incidence of acute and chronic GVHD?

Data from 2036 recipients of HLA-identical sibling transplants reported by the International Bone Marrow Transplantation Registry (IBMTR) showed in univariate analysis that older age among others was associated with increased incidence of aGVHD. However, older patients were more often transplanted from a female donor, and when female to male transplants were excluded age was no longer a significant risk factor [40]. Nash et al. analyzed the factors associated with the incidence of aGVHD in a group of 446 patients after HLA-identical sibling transplantation [41]. Recipient age above 40 years was a significant risk factor for the development of aGVHD grade III–IV. Weisdorf et al. reported the incidence of aGVHD in 469 patients following HLA-identical sibling transplantation [42]. Age above 18 years old was significantly associated with increased incidence of aGVHD. However, increasing age did not confer any incremental risk of GVHD in older individuals. In another study of 192 patients, Doney et al. reported that an increased risk of aGVHD was associated with an increasing recipient age [43]. Similar results were reported by Ringden and Nilsson [44], and Bross et al. [45]. In contrast a study of 291 patients performed by Hagglund et al. did not reveal any correlation between age and the incidence of aGVHD [46]. Analysis of the reported data is also suggestive of an increased incidence of cGVHD in older individuals. IBMTR has reported data from 2534 transplant recipients to identify risk factors for cGVHD. In this study, recipient age above 20 years, prior aGVHD, and female donors were identified as the most significant factors predictive for the development of cGVHD [47]. In contrast, a study performed by Aschan et al. in 182 patients after allogeneic stem cell transplantation revealed that aGVHD rates were similar in patients above 30 versus under 30 years [48]. Similar results showing a correlation between age and risk of cGVHD have been reported by studies performed by Storb et al. [49], Ochs et al. [50], and Carlens et al. [51]. The results of the above studies should be interpreted with caution. In most of these studies a significant number of pediatric patients were included resulting in a patient population with a median age of 20–25 years. Hence, the results of one of these studies may simply reflect differences between children or adolescents and adult patients. Moreover, analysis of the published data does not give an answer to the question if there is an upper age limit beyond which the incidence of GVHD may be prohibitive. Taken together, analysis of the above data shows that although increasing recipient age increases the risk of acute and chronic GVHD, recipient age may not represent contra indication for allogeneic SCT.

6.3. Influence of age on the transplant outcome after conventional myeloablative SCT

Table 1 shows a list of studies addressing the influence of age on outcome after conventional myeloablative SCT [52–71]. Although many of the studies listed in Table 1 showed an association between older age and an inferior transplant outcome, these results should be interpreted with caution because of the following reasons: (1) A significant percentage of patients below the age of 20 years were included in most of these studies, raising the concern that the superior outcome in the younger population may in fact be attributed to the inclusion of pediatric patients. In fact when studies have a median population age of 20–25 years, then the issue of age becomes one of comparing the outcomes between pediatric and young adult patients. (2) If there is any difference in the transplant outcome between cohorts of 25–35 and 35–45 years of age, such difference seems to be modest. (3) None of these studies provides an answer to the critical question, if there is an upper age limit above which, allogeneic SCT should be better avoided. (4) Most important, in these studies the percentage of patients above the fifth decade was very small and therefore, the relative risk of allogeneic SCT in patients above the age of 50–55 cannot be addressed.

6.4. Myeloablative SCT for patients above the age of 50

Reports on the influence of age above 50 on the outcome after conventional myeloablative transplantation are relatively limited. Published studies are shown in Table 2 [72–80,36]. Some of these reports will be briefly discussed below. Early studies performed by Klingeman et al. [72], showed that advanced age is associated with worse outcome after syngeneic and HLA-identical sibling transplantation. A large retrospective analysis of outcome after HLA-identical sibling bone marrow transplants for leukemia including 1993 patients was reported by the IBMTR [73]. A total of 2180 recipients were divided into four cohorts according to age: 30–39 years ($n = 1282$), 40–44 years ($n = 527$), 45–49 years
Table 1
Influence of recipient age in the transplant outcome

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Year</th>
<th>Donor</th>
<th>Diseases</th>
<th>No of patients</th>
<th>Results-Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortin et al. [52]</td>
<td>1983</td>
<td>MSD</td>
<td>AML</td>
<td>156</td>
<td>Age had no influence on transplant outcome</td>
</tr>
<tr>
<td>Thomas et al. [53]</td>
<td>1986</td>
<td>MSD</td>
<td>CML</td>
<td>198</td>
<td>Age above 30 years is associated with inferior outcome</td>
</tr>
<tr>
<td>Beelen et al. [54]</td>
<td>1987</td>
<td>MSD</td>
<td>MUD AL CML</td>
<td>52</td>
<td>Patients aged 30–39 years had similar outcome with patients aged 40–49 years</td>
</tr>
<tr>
<td>Goldman et al. [55]</td>
<td>1988</td>
<td>MSD</td>
<td>CML</td>
<td>405</td>
<td>Age above 20 years is associated with inferior outcome</td>
</tr>
<tr>
<td>Barrett et al. [56]</td>
<td>1989</td>
<td>MSD</td>
<td>ALL</td>
<td>690</td>
<td>Age above 16 years is associated with inferior transplant outcome (only in CR2 patients)</td>
</tr>
<tr>
<td>Copelan et al. [57]</td>
<td>1991</td>
<td>Siblings</td>
<td>AML</td>
<td>127</td>
<td>Age had no influence on transplant outcome</td>
</tr>
<tr>
<td>Bacigalupo et al. [58]</td>
<td>1993</td>
<td>MSD</td>
<td>CML</td>
<td>100</td>
<td>Age had no influence on transplant outcome</td>
</tr>
<tr>
<td>Sutton et al. [59]</td>
<td>1993</td>
<td>MSD</td>
<td>ALL</td>
<td>184</td>
<td>Age had no influence on transplant outcome</td>
</tr>
<tr>
<td>Valls et al. [60]</td>
<td>1993</td>
<td>MSD MUD</td>
<td>AML ALL</td>
<td>174</td>
<td>Age above 26 years is associated with increased risk of early TRM</td>
</tr>
<tr>
<td>Snyder et al. [61]</td>
<td>1993</td>
<td>MSD</td>
<td>AML ALL</td>
<td>99</td>
<td>Increasing age is associated with inferior transplant outcome</td>
</tr>
<tr>
<td>Gratwohl et al. [62]</td>
<td>1993</td>
<td>MSD</td>
<td>CML</td>
<td>947</td>
<td>Increasing age is associated with increased TRM, and decreased LFS</td>
</tr>
<tr>
<td>Rapoport et al. [63]</td>
<td>1995</td>
<td>MSD</td>
<td>Different diseases</td>
<td>92</td>
<td>Age below or above 40 years did not have any influence on the outcome</td>
</tr>
<tr>
<td>Davies et al. [64]</td>
<td>1995</td>
<td>MUD</td>
<td>Different diseases</td>
<td>211</td>
<td>Increasing age is associated with increased TRM, and decreased OS</td>
</tr>
<tr>
<td>Sutton et al. [65]</td>
<td>1996</td>
<td>MSD</td>
<td>MDS</td>
<td>71</td>
<td>Age above 37 years is associated with decreased OS, and DFS, and with a trend for increased TRM</td>
</tr>
<tr>
<td>Keating et al. [66]</td>
<td>1996</td>
<td>MSD</td>
<td>AML</td>
<td>270</td>
<td>Increasing age is associated with increased TRM</td>
</tr>
<tr>
<td>Frassoni et al. [67]</td>
<td>1996</td>
<td>MSD</td>
<td>AML ALL</td>
<td>2195</td>
<td>Increasing age is associated with increased TRM, and decreased DFS</td>
</tr>
<tr>
<td>Cahn et al. [68]</td>
<td>1997</td>
<td>MSD</td>
<td>AML ALL</td>
<td>1311</td>
<td>Age below or above 40 years did not have any influence on the outcome</td>
</tr>
<tr>
<td>Appelbaum et al. [69]</td>
<td>1998</td>
<td>MSD MUD</td>
<td>MDS</td>
<td>251</td>
<td>Increasing age is associated with increased OS, and DFS</td>
</tr>
<tr>
<td>Zikos et al. [70]</td>
<td>1998</td>
<td>MSD</td>
<td>AML</td>
<td>60</td>
<td>Age above 29 years is associated with increased TRM</td>
</tr>
<tr>
<td>Novitzky et al. [71]</td>
<td>2005</td>
<td>MSD</td>
<td>Different diseases</td>
<td>62</td>
<td>Age had no influence on transplant outcome</td>
</tr>
</tbody>
</table>

(n = 291), and 50 years and older (n = 80). This study showed that the incidence of leukemia-free survival, GVHD and relapse were comparable among the four age cohorts. Patients with advanced leukemia aged 45 years or older had a slightly higher risk of TRM, and the 45–49-year-old cohort had a higher risk of interstitial pneumonia. In a study done in a single institution, Du et al. [74] compared the outcome of 59 patients above the age of 50 years with 124 patients aged 40–50, and 253 patients aged 18–39 years, treated with HLA-identical sibling, and matched unrelated donor (MUD) allograft for various hematological malignancies. Except for an initial higher TRM, overall survival and GVHD were not

Table 2
Myeloablative allo-SCT for patients above 50 years

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Year</th>
<th>Donor</th>
<th>Patients &gt;50 years</th>
<th>Total no of patients</th>
<th>Comments–results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klingemann et al. [72]</td>
<td>1986</td>
<td>MSD syngeneic</td>
<td>13</td>
<td>63</td>
<td>Age &gt;50 is associated with increased GVHD, TRM, and decreased OS, DFS</td>
</tr>
<tr>
<td>Ringden et al. [73]</td>
<td>1993</td>
<td>MSD</td>
<td>80</td>
<td>2180</td>
<td>Same incidence of OS, DFS, GVHD in all age groups. Patients &gt;45 with advanced leukaemia, increased TRM</td>
</tr>
<tr>
<td>Clift et al. [79]</td>
<td>1993</td>
<td>MSD</td>
<td>33</td>
<td>33</td>
<td>Patients with CML &gt;50 have comparable outcome with younger patients</td>
</tr>
<tr>
<td>Du et al. [74]</td>
<td>1998</td>
<td>MSD MUD</td>
<td>59</td>
<td>436</td>
<td>Same incidence of OS and GVHD. Older age is associated with increased TRM</td>
</tr>
<tr>
<td>Hansen et al. [77]</td>
<td>1998</td>
<td>MUD</td>
<td>13</td>
<td>196</td>
<td>Age &gt;50 is associated with decreased OS</td>
</tr>
<tr>
<td>DeGe et al. [36]</td>
<td>2000</td>
<td>MSD MUD</td>
<td>50</td>
<td>50</td>
<td>Allo-SCT is feasible for MDS patients &gt;55, with OS = 30%</td>
</tr>
<tr>
<td>De la Camara et al. [75]</td>
<td>2002</td>
<td>MSD</td>
<td>32</td>
<td>129</td>
<td>Same incidence of OS, DFS, TRM, RRT, and TRM</td>
</tr>
<tr>
<td>Farag et al. [76]</td>
<td>2003</td>
<td>MSD</td>
<td>51</td>
<td>262</td>
<td>Age &gt;50 is associated with increased TRM. On multivariate analysis age &gt;50 was an adverse factor only for high risk patients</td>
</tr>
<tr>
<td>Yanada et al. [78]</td>
<td>2004</td>
<td>MSD MUD</td>
<td>398</td>
<td>5147</td>
<td>Age &gt;50 is associated with decreased OS, and increased TRM. Allo-SCT is feasible in selected patients &gt;60, with OS = 35%</td>
</tr>
<tr>
<td>Wallen et al. [80]</td>
<td>2005</td>
<td>MSD</td>
<td>52</td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>
different among the 3 age groups. Similar to the previous studies, De la Camara et al. compared the outcome of 59 patients above the age of 50 years with 97 patients aged 20–40, after HLA-identical sibling stem cell transplantation [75]. Overall survival, disease free survival (DFS), relapse rate, GVHD, and TRM were not different among the 2 age groups. Farag et al. [76], retrospectively analyzed the outcome after SCT from matched sibling donors of 313 patients with various hematological malignancies treated in the same institution. Fifty-one patients were above the age of 50-years, while 262 patients were below this age-limit, and both groups received the same conventional non-total body irradiation (TBI) containing myeloablative conditioning regimen. The incidence of aGVHD was similar between the 2 groups, while there was a trend for more cGVHD and interstitial pneumonitis in the group of older patients. Despite the use of radiation-free regimen, TRM was increased in patients above the age of 50 years. In patients with low-risk disease, age had no influence on OS, while the opposite was true for patients with high-risk disease states. Multivariate analysis indicated that age above 50 years was an adverse factor for transplant outcome only when high-risk patients were considered. Hansen et al. [77], analyzed the outcome of 196 CML patients after matched unrelated donor bone marrow transplantation, and showed that recipient age above 50 years was associated with inferior overall survival [77].

The data from the aforementioned studies should be interpreted with caution, since it is well known that patients undergoing SCT represent a highly selected population. It is reasonable to assume that this selection bias is even stronger among the older recipients. Thus, the similar transplant outcome among the different age groups may be related to the fact that only a small subset of well fit older patients were actually included in these studies. The largest retrospective multicenter study addressing the influence of age above 50 years on the transplant outcome was reported recently by the Japan Society for Hematopoietic Stem Cell Transplantation (JSHCT) [78]. In this study 5147 patients treated with HLA-identical and MUD transplantation for various hematological disorders were analyzed, and among them 389 patients above the age of 50 years were identified. Despite the fact that the authors recognized that these patients represent a selected population, age above 50-years was found to be associated with increased GVHD, TRM, and decreased overall survival.

6.5. Conclusions

Although it is clear that pediatric patients have superior transplant outcomes in comparison with adults because of reduced incidence of GVHD and TRM, the influence of age in the transplant outcome in adult population (older then 20 years) is less clear. Analysis of the literature data suggests that the effect, if any, of increasing age, from 25 to 45–50 years, on the outcome after conventional myeloablative allo-SCT, seems to be modest. Although there is not solid data supporting an age cut-off above which a sharp increase in the TRM is observed, analysis of the existing data suggests that recipient age above the age of 50–55 years is associated with an inferior outcome after myeloablative allo-SCT.

7. Non-myeloablative or reduced intensity conditioning in preparation for allogeneic stem cell transplantation

7.1. History–definitions

The development of the so-called RIC or truly non-myeloablative regimens during the last years led to reconsideration of the dogma of upper age limit that was set up by the transplant centers as an eligibility parameter. Several protocols were designed based on minimizing the intensity of the conditioning regimen down to the range of non-myeloablative levels, followed by infusion of donor stem cells, preferably G-CSF-mobilized blood stem cells enriched with circulating T lymphocytes, collected by apheresis. The main new component of most of the new regimen was based on the use of intensive immunosuppression with fludarabine pre-grafting. For reasons of simplicity, in this review, any SCT transplantation with regimen less intense than the standard myeloablative preparative regimens is named non-myeloablative stem cell transplantation (NST). Fludarabine-based protocols initially introduced in MD Anderson in Houston and Hadassah Hospital in Jerusalem [81,82] were found to constitute the safest conditioning regimens for recipients of HLA matched sibling or MUD allografts, a finding that has since been confirmed by many transplant centers worldwide [83–85]. A different approach was adopted later by the Seattle group. Their initial preparative regimen consisted of low dose TBI, followed by post transplant administration of cyclosporine and mycophenolate mofetil (MMF) in an effort to reduce the graft rejection and incidence of GVHD [86]. The various NST regimens differ in the degree of the myeloablation and immunosuppression used during the conditioning. A subset of NST uses minimal-intensive conditioning (MIC). Examples of MIC regimens are regimens consisting of fludarabine and cyclophosphamide, or TBI 2Gy with or without fludarabine. Another larger subset of NST is based on the use of moderately intensity conditioning (MOC) regimens. Examples of MOC regimens are regimens consisting of fludarabine in combination with busulfan ≤8 mg/kg or melphalan ≤100 mg/m² with or without anti-thymocyte globulin (ATG), or anti-CD52 (Mab-Campath or Alemtuzumab). Fast recovery of autologous hematopoiesis always occurs after MI regimens even if donor cells are not accepted, whereas this not the case after MO regimens. Although MIC regimens are minimally toxic, persistent mixed chimerism is very common and withdrawal of post-transplant immunosuppression, administration of donor lymphocyte infusion (DLI) or both, is sometimes necessary for conversion of mixed to
complete donor chimerism or to eliminate minimal residual disease. In contrast, clinical experience from the use of MOC regimens showed that conversion to complete donor chimerism occurs spontaneous in most cases without any post-transplant immune manipulation.

7.2. Did non-myeloablative preparative regimens reduce transplant-related mortality?

The influence of the intensity of the conditioning on the transplant outcome in the elderly is not easy to be directly evaluated due to the following reasons: (1) no well designed prospective randomized trial or carefully matched observational study has been conducted so far, (2) in all these studies mentioned below, a significant number of patients below the age of 50 years were included. However we should take in consideration that the aging process is not simply a chronological issue. Instead, it is rather clear that biological aging and the associated comorbidities are the main parameters with a significant impact on the transplant outcome. Also we should bear in mind, that young patients transplanted using a NST regimen were in fact ineligible for a conventional allografting because of significant comorbidities or a previous transplant. On the contrary, patients above the age of 50–55 years who underwent myeloablative conditioning represent a highly selected population, since most physicians are reluctant to propose this option to patients above this age limit. Having

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Donors</th>
<th>Diseases</th>
<th>No. of NST patients</th>
<th>No. of ablative patients</th>
<th>Results–comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alyea et al. [87]</td>
<td>MSD MUD</td>
<td>Different malignancies</td>
<td>71</td>
<td>81</td>
<td>Decreased TRM, similar GVHD, improved OS in the NST group</td>
</tr>
<tr>
<td>Diaconescu et al. [29]</td>
<td>MSD</td>
<td>Different malignancies</td>
<td>73</td>
<td>73</td>
<td>Decreased RRT and NRM in the NST group. CCI scores predict RRT and NRM</td>
</tr>
<tr>
<td>Sorror ML., et al. [30]</td>
<td>MUD</td>
<td>Different malignancies</td>
<td>60</td>
<td>74</td>
<td>Decreased RRT, GVHD, and NRM in the NST group. CCI scores predict RRT and NRM. Decreased TRM, and improved OS in the NST group</td>
</tr>
<tr>
<td>Valcarcel et al. [88]</td>
<td>MSD</td>
<td>Different malignancies</td>
<td>57</td>
<td>100</td>
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<td>Canals et al. [89]</td>
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<td>Different malignancies</td>
<td>27</td>
<td>23</td>
<td>Decreased TRM and improved PFS in the NST group</td>
</tr>
<tr>
<td>Perez-Simon et al. [90]</td>
<td>MSD</td>
<td>Different malignancies</td>
<td>150</td>
<td>88</td>
<td>Decreased incidence of aGVHD, similar incidence of extensive cGVHD, shorter duration of immunosuppression in the NST group. Decreased incidence of aGVHD in the NST group. Similar incidence of Cvhd between the 2 groups</td>
</tr>
<tr>
<td>Mielcarel et al. [91]</td>
<td>MSD MUD</td>
<td>Different malignancies</td>
<td>44</td>
<td>52</td>
<td>Increased incidence of GVHD with more intensive regimens. Similar incidence of GVHD, and relapse. Lower NRM in the NST group. OS was superior for high risk patients treated with NST</td>
</tr>
<tr>
<td>Couriel et al. [92]</td>
<td>MSD</td>
<td>Different malignancies</td>
<td>92</td>
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<td>Kojima et al. [100]</td>
<td>MSD</td>
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<tr>
<td>Massenkeil et al. [94]</td>
<td>MSD MUD</td>
<td>AML, ALL</td>
<td>25</td>
<td>50</td>
<td>Decreased NRM in the NST group, but similar OS in both groups</td>
</tr>
<tr>
<td>Aoudjhane et al. [97]</td>
<td>MSD</td>
<td>AML</td>
<td>315</td>
<td>407</td>
<td>Decreased incidence of GVHD and TRM, but increased relapse rate in the NST group. Similar OS and DFS</td>
</tr>
<tr>
<td>Vela-Ojeda et al. [93]</td>
<td>MSD</td>
<td>AML, CML</td>
<td>34</td>
<td>27</td>
<td>Similar incidence of TRM, GVHD, OS, and DFS in both groups</td>
</tr>
<tr>
<td>Martino et al. [99]</td>
<td>MSD</td>
<td>MDS</td>
<td>215</td>
<td>621</td>
<td>Decreased incidence of NRM, but increased relapse rate in the NST group. Similar OS and DFS</td>
</tr>
<tr>
<td>Shimoni et al. [98]</td>
<td>MSD MUD</td>
<td>AML, MDS</td>
<td>67</td>
<td>45</td>
<td>Decreased incidence of NRM, but increased relapse rate in the RIC group. Similar OS and DFS</td>
</tr>
<tr>
<td>Dreger et al. [95]</td>
<td>MSD MUD</td>
<td>CLL</td>
<td>73</td>
<td>82</td>
<td>Decreased TRM in the NST group, but similar EFS between the 2 groups</td>
</tr>
<tr>
<td>Bertz et al. [96]</td>
<td>MSD MUD</td>
<td>Different lymphoma subtypes</td>
<td>12</td>
<td>13</td>
<td>Decreased NRM and better OS in the NST group</td>
</tr>
</tbody>
</table>
all these in mind, it is reasonable to assume that the published data may in fact underestimate the beneficial influence of NST regimens on transplant-related mortality. Finally it is obvious that definite conclusions should be given only under the context of well-controlled prospective randomized trials. Studies comparing the outcome after SCT following RIC or NST regimen versus conventional ablative conditioning are briefly summarized below (Table 3).

(1) Alyea et al. [87] performed a retrospective analysis on the outcome of 152 patients above the age of 50 years, with hematological malignancies undergoing NST or myeloablative SCT from HLA-identical siblings and MUD. NST patients were at higher risk for TRM than patients receiving myeloablative conditioning. The incidence of moderate to severe aGVHD, was similar in the 2 groups, while TRM was lower in the NST group (32% versus 50%). OS was improved in NST group at 1 year (51% versus 39%), and at 2 years (39% versus 29%).

(2) Diaconescu et al. [29] compared the morbidity and mortality after a non-myeloablative versus myeloablative SCT from HLA-matched related donors in patients with hematological malignancies. In this study, 73 patients with a median age of 54 years received a NST regimen consisted of TBI 2 Gy either alone or with fludarabine, while 73 patients with a median age of 48 years received standard myeloablative conditioning. In theory, NST patients were at greater risk for TRM than patients receiving myeloablative conditioning because of higher age, longer time from diagnosis to transplant, higher pre-transplantation Charlson comorbidity scores, and more often due to a prior transplant. Nevertheless, NST patients experienced significant less regimen-related toxicity (RRT) and lower non-relapse mortality (NRM) at day 100 (3% versus 23%), and at 1 year (16% versus 30%). In multivariate analysis, the strongest factor predicting reduced RRT and NRM was the use of non-myeloablative conditioning, while higher CCI scores predicted of higher NRM.

(3) In a similar study, Sorror et al. [30] compared the morbidity and mortality after non-myeloablative versus myeloablative SCT from matched unrelated donors, in patients with haematological malignancies. NST group consisted of 60 patients with a median age of 54 years, and was compared with a group of 74 consecutive patients of median age of 41 years, who underwent myeloablative SCT during the same time period. Even though NST patients had significantly more comorbidities, were older, and more often had a previous ablative SCT, they experienced less RRT, aGVHD, and lower 1-year NRM. Multivariate analysis showed higher comorbidity scores to result in increased toxicity and mortality.

(4) A recently reported study by Valcarcel et al. [88] compared the outcome after RIC versus myeloablative SCT from HLA-matched related donors in patients with hematological malignancies. One hundred patients with a median age of 39 years, received standard myeloablative conditioning (TBI-containing regimens were used in 80% of the cases), while 57 patients with a median age of 51 years received a reduced-intensity regimen which consisted of fludarabine in association with either busulfan or melphalan. Despite the fact that more patients in the RIC group had adverse risk factors, TRM was lower (22% versus 30%), and OS was increased in comparison with patients who underwent myeloablative SCT (59% versus 52%).

(5) A study performed by Canals et al. [89] compared two different approaches used to reduce TRM after SCT from HLA-matched sibling donors in patients above the age of 45 years with hematological malignancies. Twenty-three patients were treated with conventional myeloablative preparative regimen and were transplanted with CD34 positively selected peripheral blood stem cells (PBSC), while 27 patients were treated with RIC which consisted of fludarabine in combination with either melphalan or busulfan, and were transplanted with unmanipulated PBSC. Patients characteristics were well balanced between the 2 groups. The incidence of aGVHD as well as the relapse rate were similar in both groups. Patients in the RIC group featured significantly less TRM at 6 months (7% versus 30%), and at 1 year (15% versus 39%). RIC patients featured significantly increased OS (69% versus 43%), and progression free survival (PFS) (67% versus 43%) in comparison with patients treated with myeloablative conditioning.

(6) Perez-Simon et al. [90] compared the incidence of GVHD after allo-PBSC transplantation from matched sibling donors in patients prepared with either a RIC or a conventional myeloablative conditioning. One-hundred and fifty patients were treated with a RIC regimen consisting of fludarabine in combination with either melphalan or busulfan, while 88 patients were treated with myeloablative conditioning (TBI-containing regimen was used in 90% of the cases). The cumulative incidence of grade II–IV aGVHD was lower in the RIC group (29% versus 39%). In multivariate analysis intensity of the preparative regimen was the only factor with a significant influence on aGVHD incidence.

(7) Mielcarel et al. [91] compared the incidence of GVHD after SCT from matched related and unrelated donors in 96 patients with hematological malignancies prepared with either NST, or standard myeloablative conditioning. The cumulative incidence of grade II–IV aGVHD was lower in the NST group (64% versus 85%), while the incidence of cGVHD was similar between the 2 groups.

(8) In a similar study Couriel et al. [92] retrospectively analyzed the effect of the conditioning on the incidence of GVHD in 137 patients after SCT from HLA-identical...
siblings donors. Again, they showed that increasing the intensity of the preparative regimen was associated with higher incidences of acute and chronic GVHD.

(9) Vela-Ojeda et al. [93] compared the outcome after SCT using PBSC following either reduced intensity or standard myeloablative conditioning in 61 patients with acute leukemia or chronic myeloid leukemia. Donors were HLA-identical siblings in all the cases. Patients in the RIC group had more adverse prognostic factors. The proportion of patients with aGVHD, cGVHD, and infections, as well as NRM, DFS, and OS were similar between the 2 groups.

(10) Massenkeil et al. [94] compared the outcome of 25 patients with ALL and AML after reduced intensity SCT from matched related and unrelated donors, to a historical group of 50 patients treated with standard myeloablative conditioning. Despite the fact that RIC patients had significant more comorbidities, aGVHD and severe infections were similar in both groups. Patients in the RIC group had decreased TRM (4% versus 24%), while the DFS, and OS were similar between the 2 groups.

(11) A retrospective comparison between a reduced-intensity or a myeloablative conditioning before SCT from matched related and unrelated donors in patients with CLL was performed by Dreger et al. on behalf of the Chronic Leukaemia Working Party of EBMT [95]. Seventy-three patients, median age of 53 years, were treated with different RIC regimens, while 82 patients received standard myeloablative conditioning (TBI-containing regimen was used in 84% of the cases). Patients in the RIC group were older, were transplanted more recently, and more often received PBSC. TRM was lower in the RIC group, while there was a trend for increased relapse rate in the same group. OS and EFS were comparable between the 2 groups.

(12) Bertz et al. [96] compared the outcome of 12 patients with different lymphoma subtypes after reduced intensity SCT to a historical group of 13 patients treated with a myeloablative conditioning in the same institution. TRM was lower while OS was better in the RIC group.

(13) Aoudjhane et al. [97] on behalf of the Acute Leukaemia Working Party of EBMT, performed a retrospective comparison on the outcome after RIC versus myeloablative conditioning in HLA-identical sibling SCT for patients older than 50 years of age with AML. Three hundred and fifteen patients with a median age of 57 years were treated with a RIC regimen consisting of fludarabine in combination with either busulfan, or low-dose TBI, while 407 patients with a median age of 54 years received myeloablative preparative regimen. In multivariate analysis, aGVHD grade II–IV and TRM were significantly decreased in the RIC group, while the relapse rate was increased in the same group. LFS and OS were not different between the 2 groups.

(14) Shimoni et al. [98] compared the outcome of 67 patients with MDS and AML after reduced intensity SCT from matched related and unrelated donors, to a historical group of 45 patients treated with standard myeloablative conditioning. Patients in the RIC group had decreased NRM (8% versus 22%), while the DFS, and OS were similar between the 2 groups. However, increased relapse rates were observed in the group of patients treated with a RIC regimen.

(15) In a multicenter retrospective study conducted by Martino et al. [99], the outcomes of 836 patients MDS who underwent transplantation with HLA-identical sibling donor were analyzed according to 2 types of conditioning: reduced-intensity conditioning in 215 patients, and standard myeloablative in 621 patients. In multivariate analysis, the 3-year relapse rate was significantly increased after RIC, but the 3-year NRM rate was decreased in the RIC group. The 3-year probabilities of PFS and OS were similar in both groups. The authors considered that the lower 3-year NRM after RIC is encouraging, since these patients were older and had more adverse pretransplantation variables.

Taken together, analysis of the above reports leads to the conclusion that reduction of the intensity of preparative regimen is associated with significant decrease in RRT, and TRM, as well as in the incidence of GVHD. However in studies with acute leukemia patients, an increase in relapse rate may be observed in the RIC group, resulting in similar OS and DFS rates between patients treated with reduced-intensity and those treated with myeloablative regimens. In contrast in studies including patients with different hematological malignancies the decreased TRM was translated in improved OS, and DFS in patients treated with reduced-intensity regimens.

### 7.3. Published experience with NST regimens for patients above the age of 55–60 years

In the initial studies that addressed the feasibility and the efficacy of NST regimens, only patients that were considered ineligible for conventional myeloablative SCT were enrolled. Therefore, in these studies young patients with various comorbidities were also included. Most of these studies included patients with a median age between 45 and 55 years old. After the initial encouraging results, some transplant centers tested the feasibility of extending the upper age limit of patients in need of SCT. Studies reporting the results of SCT with a NST regimen in patients with a median age above 55–60 years are relatively limited, and are briefly summarized below.

(1) Wong et al. [2] explored the feasibility of unrelated donor SCT after reduced intensity conditioning in 29 patients above the age of 55 years with myeloid malignancies, most of them in an advanced stage of disease. The median age at transplantation was 59 years (range
Conditioning consisted of the combination of fludarabine with melphalan, either alone or in combination with pre-transplant administration of ATG in 18 of the cases. Grade II–IV aGVHD was observed in 41%, while cGVHD developed in 63% of the patients, respectively. With a median follow up period of 27 months the probability in 1-year of OS, EFS, and NRM were 44%, 37%, and 55%, respectively.

We reported our initial experience using NST with recipients of related and unrelated SCT after reduced intensity conditioning for patients above the age of 60 years [101]. Eighteen patients with a median age of 63 (range 60–67) with various hematological malignancies were included. Only 1 of these patients was in complete remission at the time of transplantation while the rest had active disease most of them refractory to previous salvage chemotherapy. Most of these patients had also other significant comorbidities and 3 of them were transplanted from partially mismatched donors. Patients were treated with different fludarabine-based conditioning regimens. All the patients experienced fast tri-lineage engraftment, and grade III–IV aGVHD was observed in 3 patients, while 6 patients developed cGVHD. With a median follow-up of 13 months the OS, and TRM were 30%, and 33%, respectively.

In a study by Bertz et al. [102] 19 patients above the age of 60 years with acute myeloid leukemia underwent reduced intensity SCT from matched related and unrelated donors. The median age of the patients was 64 years (range 60–70). Only 3 patients had CR at the time of transplantation, 6 were untreated, while the rest had chemorefractory relapse. Conditioning consisted of a combination of fludarabine, melphalan, and carmustine. None of the patients experienced graft rejection, while 13 out of 19 achieved complete remission. Grade II–IV aGVHD and cGVHD developed in 10 and 10 patients, respectively. With a median follow-up period of 825 days (range 595–1028), the overall survival in this group of patients was 68%.

Shimoni et al. [103] recently reported results pooled from 2 different institutions on the outcome of patients above the age of 55 years with various hematological malignancies, after reduced intensity SCT from matched unrelated donors. Their study included 36 patients with a median age of 58 years, (range 55–66). Patients received preparative regimens consisted of fludarabine in combination with either busulfan, treosulfan, or melphalan. Pre-transplant administration of ATG, or Mab-Campath was given to all patients. Acute GVHD grade II–IV, and cGVHD were observed in 31% and 45% of the patients, respectively. With a median follow-up of 10 months, range (1–54), the OS, DFS, and NRM, were 52%, 43%, and 39%, respectively. Multivariate analysis showed that survival rates were higher in patients with pre-transplant chemosensitive disease, and in patients conditioned with intravenous busulfan or treosulfan.

In a recent study in our institution, we reviewed our experience with the use of a single non-myeloablative preparative regimen in SCT from related and unrelated donors in 37 patients aged 55 years with various hematological malignancies. The vast majority of the patients were heavily pretreated pre-transplantation due to advanced disease. With a median follow up period of 12 months, (range 3–112) the 1-year overall survival, and disease free survival, were 55% and 55%, respectively, while the overall NRM was 35%. Patients transplanted from related and unrelated donors had similar outcome [104].

8. Should all patients above the age of 50 years be treated with a NST regimen? What is the preferred NST regimen?

The choice of the preparative regimen should be based on many parameters such as the type of disease, status of the disease at the time of transplantation, previous treatment, characteristics of the recipient, etc.

8.1. Characteristics of the disease

Disease type and status are one of the main factors that affect the outcome of SCT. The efficacy of SCT is dependent on the direct cytoreductive effect provided by the preparative regimen, and on the graft versus tumor (GVT) effect provided by alloreactive donor T-lymphocytes, not excluding NK cells. Different diseases have different sensitivity to the GVT effect depend on the degree and speed of proliferation of donor alloreactive lymphocytes and degree of alloreactivity against host alloantigens and tumor-associated antigens. The efficacy of GVT effects may also depend on the capacity of tumor cells to present tumor specific or tumor-associated antigens by “professional” dendritic cells. Indeed, the extreme efficacy of GVT effects in patients with CML may be partly explained by the fact that bcr/abl translocation exists in stem cells, thus also expressed in antigen presenting cells. Since the GVT effect is usually a slow process, it is reasonable to assume that in case of aggressive malignancies an initial tumor debulking seems mandatory in order to give enough time for the GVT effect to eliminate host malignant cells. In contrast, in cases of slow-growing or less malignant tumors such as low-grade lymphomas or CML, the cytoreductive potential of the conditioning regimen seems to be of less important from a theoretical point of view. In support of this hypothesis are the results of the EBMT retrospective comparison between NST and standard myeloablation in patients above 50 years with AML [97]. In this study, the observed low TRM in the NST group was offset by higher relapse rates, resulting in similar rates of OS and DFS in both groups. De Lima et al. reported the results of a retrospective comparison of a MIC versus a MOC in patients with AML and high risk MDS [105]. Data analysis revealed that increas-
ing the intensity of the preparative regimen resulted in lower relapse rates but at the cost of increased TRM and without difference of the final outcome. Recently, Crawley et al. [106] on behalf of EBMT, retrospectively analyzed the outcome of 186 CML patients treated with SCT with different NST regimens. In this study a moderate intensity regimen consisting of the combination of fludarabine, busulfan and ATG was proved to be superior to all other NST regimens, resulting in improved outcomes, especially in the early but also in advanced disease states. Similar results in CML patients in first chronic phase, were reported by our institution [107]. Another EBMT study by Robinson et al. [108] reporting the outcome of SCT using NST for patients with lymphoma, showed that NST regimens were effective in controlling low-grade lymphomas with low TRM. The 2-years OS for 65 patients (median age 46 years) with low-grade NHL was 65%. In contrast, patients with high-grade lymphomas, especially those with chemorefractory disease prior to transplant, had a poor outcome. Similar to these observations, single institution studies using MIC regimens have shown excellent results in patients with low-grade lymphomas such as follicular NHL and CLL [109,110]. Although not proven yet by randomized prospective studies, it seems probable that NST regimens may be effective in controlling indolent lymphomas while avoiding excess toxicity associated with myeloablative preparative regimens. In agreement with this assumption is an IBMTR study, by Van Besien et al. [111], reporting on the outcome after myeloablative SCT from matched sibling donors of 113 young patients (median age 38 years) with low-grade NHL. This study showed an increased TRM of 40% at 3 years, while the 3-year OS for the same group of patients was 49%.

### 8.2. Characteristics of the recipient

The ability of an individual patient to tolerate the toxicity of a particular conditioning regimen depends on many factors that have been previously mentioned (age, PS, concurrent comorbidities, prior chemotherapy, etc). Having all these in mind, and since the ultimate goal of SCT is to prolong DFS, the choice of the conditioning regimen should be individualized. For example, a 63 years old patient with refractory AML, and low probability of TRM due to good PS and no co-existing morbidity should be better treated with a conventional myeloablative conditioning, whereas a 52 years old patient with AML in first CR, but with high probability of TRM due to poor PS or co-existing morbidity should be better prepared with RIC or NST. In contrast, for a 50 years old patient with relapsed low-grade follicular lymphoma even with a low probability for TRM, a NST regimen might be preferable.

However, it should be remembered that our considerations are based on our own experience and the retrospective analysis of the literature, yet, well controlled prospective randomized studies are needed in order to definitely assess the role of NST at all age groups. Comorbidity indices might be proved as the most important parameters for the choice of the most proper regimen for each patient in need and should be seriously considered in future trials.

### 9. Conclusions and future perspectives (Table 4)

Using innovative conditioning, age and sometimes even poorer PS should no longer be considered a barrier when SCT is indicated. Future developments based on the principles behind RIC and NST, with more effective and better controlled post transplant immunotherapy, are likely to improve the outcome of SCT in all age groups, especially in the elderly. The most important future strategies seem to consist of one or more of the following: (1) Selective in vivo depletion of host cells with anti-donor alloreactivity to improve engraftment while reducing the intensity of non-specific immunosuppression and myeloablation across minor and even major HLA-barriers focusing on RIC [112]. (2) Selective in vitro or in vivo depletion of donor cells with anti-host alloreactivity to prevent the risk of GVHD while avoiding the need for post-transplant anti-GVHD prophylaxis and retaining immunity against the malignant cells and infectious organisms. (3) Amplification of graft versus malignancy effects using selective tumor-reactive and/or specifically immune donor lymphocytes [113–117]. (4) Selective inhibition of alloreactive T cells targeting IL-2 receptor, early activation pathways such as CD69, blocking costimulatory signals or using tumor specific or hematopoietic specific CD8+ cells against minor histocompatibility antigens restricted to hematopoietic lineage [118], or using regulatory T cells (CD4+25+). (5) Using activated NK cells that can target cancer cells but do not cause GVHD, especially following transplantation of haploidentically mismatched donor stem cells [119–121]. (6) Using tumor specific or tumor-associated monoclonal or bispecific antibodies against targets such as CD20 for direct killing of residual tumor cells [122–123]. (7) Using monoclonal or preferably bispecific antibodies to guide T cells and NK cells selectively to residual cancer cells [124], or (8) Elimination of alloreactive T cells following induction of effective GVT effects by suicide mechanism [125] or by an alkylating agent such as cyclophosphamide that is likely to be more effective against activated T cells [113,126].
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Biography

Michael Y. Shapira, M.D. completed his medical schooling in 1990 at the Hadassah-Hebrew, Hebrew University School of medicine, Jerusalem, Israel. He then completed an Internal Medicine residency at the Division of Internal Medicine, Hadassah-Hebrew, Hebrew University Hospital (graduated with honor, 1999). Then, he joined the staff at the Department Of Bone Marrow Transplantation as a senior physician. During this time he had his specialization in the Department of Bone Marrow Transplantation and Immunotherapy, Hadassah-Hebrew, Hebrew University Hospital and also holds a faculty position at the Hadassah-Hebrew, Hebrew University School of medicine. His main focus is clinical and translational research in the area of transplantation in elderly. For this purpose, he designed several innovative treatment protocols to be used for transplantation in elderly patients or other high-risk patients. Additionally, Dr. Shapira investigates the treatment (primarily by local management) of graft-versus-host disease.