Allogeneic Stem Cell Transplantation for Elderly Patients with Myelodysplastic Syndrome

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Running title: Allogeneic SCT in Elderly MDS

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Abstract

Allogeneic hematopoietic stem cell transplantation is well accepted as a curative treatment approach for younger patients with myelodysplastic syndrome (MDS) and has become one of the most frequent indications for allogeneic stem cell transplantation as reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). However, MDS patients are usually elderly with a median age of about 75 years at diagnosis. Large register studies have confirmed the feasibility of the procedure in elderly MDS patients and in the register of the European Group for Blood and Marrow Transplantation (EBMT) 1/3 of the allogeneic transplant procedures for MDS were performed in 2010 in patients aged > 60 years. Despite its curative potential, its role in the treatment of elderly MDS patients is less defined. Because of the inherent complications of the transplantation leading to treatment-related mortality and the risk of relapse, a careful calculation of the benefit for each patient is mandatory, taking into account comorbidities, disease status, donor selection, and effective non-transplant therapies. Prospective multicenter studies are needed to define optimal intensity of the conditioning regimen, timing of transplantation within a treatment algorithm including drug-based therapies and post-transplant strategies to reduce the risk of relapse.

Introduction

Myelodysplastic syndrome (MDS) summarises a heterogenous group of hematological diseases which are characterised by a clonal abnormality of hematopoietic stem cells resulting in cytopenias, abnormal blasts, and risk of transformation into AML. The clinical course of the disease varies from an indolent course over several years to a more rapid progression within months [1, 2]. MDS is predominantly a malignant disease of an elderly person with a median age at diagnosis of around 75 years [3], and more than 80% are reported to be older than 60 years of age [4]. Allogeneic stem cell transplantation is considered to be a curative treatment option in MDS patients, and its role in treatment of “younger” patients with MDS is well established [5, 6, 7, 8, 9, 10, 11, 12], even if the data relating outcomes are obtained mainly from retrospective studies. For many years because of therapy-related morbidity and mortality, allogeneic stem cell transplantation has been performed only in younger patients with MDS, while elderly patients who represent the majority of MDS patients have been excluded. It has to be pointed out that in the transplant setting, patients older than 50 years of
age are considered to be “elderly patients.” Furthermore, even when transplantation is performed on patients up to the age of 75 years of age, the majority of transplanted patients are still younger than the median age of MDS patients at diagnosis (about 75 years).

The introduction of toxicity-reduced, reduced-intensity or non-myeloablative conditioning regimens has resulted in a drastic reduction of transplant-related toxicity and mortality leading to a rapidly growing number of transplantations in elderly patients with hematological diseases [13, 14, 15]. In the register of the EBMT the numbers of allogeneic stem cell transplantation for MDS/sAML have increased from 737 in 2001 to 1636 in 2010 (see also figure 1). In parallel the percentage of transplantation in MDS patients aged >50 years, >60 years or >65 years increased from 47%, 10% and 2% in 2001 to 64%, 33% and 14% in 2010 (see figure 1). Despite the increase of literature reporting the feasibility of this approach in elderly MDS patients, prospective comparing trials are lacking, and despite the curative potential even in elderly patients, there is great need to define the population of elderly MDS patients who will benefit with a high probability of long-term freedom from disease versus the inherent complications of the transplant procedure. It is also important to develop the timing of treatment sequence of allogeneic transplantation in the context of novel drugs, such as hypomethylating agents or immunomodulating drugs.

**Does recipient age influence transplant outcome?**

The majority of the large retrospective trials consider a patient’s age as a major prognostic factor for therapy-related mortality [7, 8, 16]. In one of these studies, patient’s age is also associated with a high risk of relapse [16]. These results were obtained mainly after standard myeloablative conditioning. Two recent large register trials address the specific issue of elderly MDS patients and allogeneic stem cell transplantation (see Table 1).

The retrospective study of the of the European Group for Blood and Marrow Transplantation (EBMT) reported on 1333 patients aged over 50 years with MDS [17]. Interestingly, despite advanced age, 38% of the patients received a standard myeloablative conditioning regimen. The patients were divided into age categories of 50-60 years and >60 years. The cumulative incidence of non-relapse mortality (NRM) at 4 years was 36% for the 50-60 years group and 39% for the group 60 years and older (p=0.39). The cumulative incidence of relapse at 4 years
was 32% for the 50-60 years group and 41% for the >60 group (p=0.02), while overall survival at 4 years did not differ between the groups (34% vs. 27%, p=0.2). In a multivariate analysis for overall survival, only advanced stage of the disease at time of transplantation (HR 1.55) was associated with inferior survival.

The Center for International Blood and Marrow Transplantation (CIBMTR) performed a similar study in 1080 elderly patients with MDS or AML in 1. CR who received a reduced-intensity (RIC) or non-myeloablative (NMA) conditioning regimen followed by allogeneic stem cell transplantation. The patients were divided into 4 age categories: 40-54 years, 55-69 years, 60-65 years, and ≥65 years. There was a trend for a higher incidence of relapse and non-relapse mortality in the group 60-65 years and ≥65 years in comparison to the two <60 years groups (see Table 1), but none of these differences reached statistical significance. However, a selection bias for the older transplant cohort has to be taken into account while interpreting the data. Disease-free and overall survival did not differ between the age categories. In a multivariate analysis, age had no significant effect on OS, while low performance status, mismatched unrelated donors, and unfavourable cytogenetic were associated with inferior overall survival [18]. It is controversial whether elderly MDS patients who undergo allogeneic stem cell transplantation have a higher risk of graft-versus-host disease (GvHD). While in some HLA-identical sibling transplantation studies recipient age was associated with an increased risk of graft versus host disease [19], in unrelated transplantation the National Marrow and Donor Program reported that only increased donor age was associated with a higher risk of severe acute GvHD [20]. In sibling transplantation, donor age is closely linked to recipient age, and so it has been difficult to demonstrate an effect of age on GvHD incidence in matched sibling transplant. A more recent trial including more than 1000 patients did not show significant impact of age on occurrence of GvHD [18]. However if GvHD occurs, steroids are often less tolerated in older than in younger patients.

These two large retrospectives studies suggest that recipient age alone can not be considered as contraindication for allogeneic stem cell transplantation.
**Impact of comorbidities**

Since patient’s age per se is not a major risk factor, other factors, such as comorbidities that by nature increase with increasing age, are taken into account. Comorbidity has a major impact on outcome of MDS patients in the non-transplant setting [21], and several scores have been developed for allogeneic stem cell transplantation. The Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI), developed by Sorror et al., has been demonstrated to be useful in patients with MDS or AML who underwent allogeneic stem cell transplantation after reduced-intensity or standard conditioning regimen [22]. If patients were stratified according to HCT-CI score and disease status, the risk of NRM increased with higher HCT-CI score and high-risk disease status. Patients with the highest HCT-CI score and also high-risk disease had the worst survival rate (OS at 2years: 29%) independent of the intensity of the conditioning regimen because the lower NRM in the RIC treated patients was offset by a higher risk of relapse [22]. Other reports confirmed inferior survival in MDS patients with higher comorbidity scores after allogeneic stem cell transplantation independent of the chronological age of the patients [23, 24].

**Role of iron overload**

Iron overload, which is not part of most comorbidity scores, may also influence toxicity and survival after transplantation and should be considered as comorbidity. Iron overload in MDS patients is caused by red blood cell transfusion and also by an increased gastrointestinal absorption of iron due to ineffective erythropoiesis [25]. This iron is accumulated in macrophages in tissues, such as liver, spleen, and bone marrow.

Once the capacity of plasma transferrin to bind iron is exhausted, non-transferrin-bound iron (NTBI) appears in blood and labile plasma iron (LPI) as redox-active component of NTBI and is considered the most likely mediation of tissue damage and higher risk of infectious complications [26].

Iron overload is usually determined by serum ferritin in patients who undergo allogeneic stem cell transplantation. An elevated serum ferritin of $\geq 1000 \mu g/l$ has been associated with a higher NRM and increased risk of infection after allogeneic stem cell transplantation and
myeloablative conditioning [27, 28]. The retrospective study by the Guppo Italiano Trapianto Midollo Osseo (GITMO) confirmed the impact of elevated serum ferritin on outcome of allogeneic transplantation but only after myeloablative conditioning and not after reduced-intensity conditioning [29]. More appropriate methods for iron overload, such as liver or cardiac magnetic resonance imaging (MRI), transfusion frequencies, and measurement of non-transferrin bound iron, and/or labile plasma iron, are needed to determine the impact of iron overload on outcome after stem cell transplantation [30]. Most of the transplant-related mortality due to elevated serum ferritin occurs within the first 3 months after stem cell transplantation [27]. It is very likely that the complications of iron overload, such as infections and organ toxicity, are due to the release of non-transferrin-bound iron (NTBI) and labile plasma iron (LPI) induced by the cytotoxic conditioning regimen catalysing reactive oxygen species. In our own study we could show that in patients who underwent allogeneic stem cell transplantation after myeloablative conditioning regimen NTBI and transferring, saturation peaked early after starting conditioning therapy and remained elevated up to 2 weeks after initiation of the conditioning regimen [31]. First attempts to use chelation, such as deferasirox, during conditioning regimen have shown dramatic reduction of LPI [32]. Alternatively, administration of plasma apotransferrin has been shown to lower NTBI during stem cell transplantation and restored the inhibitory effect on growth of staphylococcus epidermidis in vitro [33].

The available data suggest a major impact of comorbidity on outcome after transplantation, but the most valuable comorbidity score needs to be determined and validated in larger cohorts of patients. Iron overload can be considered as comorbidity and is associated with a higher NRM. Prospective allogeneic stem cell transplantation trials in MDS should include measurement of overload and determination of comorbidity indices. However, it is currently unclear how to treat iron overload in patients who undergo allogeneic stem cell transplantation.

**Should all elderly patients receive only reduced-intensity conditioning?**

The exploration of reduced-intensity conditioning regimens (RIC) resulted in less toxicity and has broadened the application of allogeneic stem cell transplantation especially in the cohort of elderly patients with haematological malignancies [13, 14]. The rationale for reduced-
intensity conditioning is to promote graft-versus-leukemia effect without excessive toxicity of the conditioning regimen, therefore resulting in less treatment-related mortality. The EBMT performed a retrospective comparing RIC with standard myeloablative conditioning (MAC) in 836 patients with MDS who received stem cell grafts from HLA-identical siblings. The EBMT found a lower risk for TRM (p=0.015) but a significantly higher risk for relapse (p=0.001) for the RIC transplanted patients, resulting in similar survival rates in both groups [34]. The CIBMTR compared transplant outcome in more than 3000 patients with AML or MDS who received allogeneic stem cell transplantation either after RIC or non-myeloablative conditioning or after standard myeloablative conditioning. Those patients who received a reduced-intensity conditioning regimen had a higher risk of relapse and less probability of disease control in comparison to those who received a conventional ablative regimen [35]. Other single center retrospective studies have shown that a lower intensity of the conditioning regimen results in higher relapse rate and inferior outcome, especially in patients with more advanced disease [36, 37]. A more recent retrospective analysis from EBMT also suggests that the very low-intensity approach (2Gy TBI) has the highest risk of relapse in MDS and AML patients, and the treatment-related mortality after reduced-intensity conditioning transplantation has not reached a plateau after 1 year and differs only slightly at 5 years in comparison to myeloablative conditioning [Rodrigo Martino personal communication, manuscript in preparation]. All these studies have been performed retrospectively, and the inherent bias in selecting patients for a specific intensity of conditioning regimen should be considered because patient assignment to either reduced intensity or myeloablative conditioning was based on physician or patient preference. An ongoing prospective randomised trial comparing RIC versus MAC from the MDS Subcommittee of the EBMT is addressing this issue (NCT 00682396).

However, in discussing intensity of conditioning regimen, it has to be pointed out that there is no clear cut-off between reduced-intensity conditioning and the myeloablative conditioning regimen. The major achievement of the new conditioning regimens is the reduced organ toxicity that broadens the application of allogeneic stem cell transplantation to elderly patients. However, reducing organ toxicity does not exclude myeloablation or reduced anti-leukemic activity. For instance, targeting drug level or using intravenous formulation as part of the conditioning regimen has substantially reduced toxicity of busulfan; both have been shown to reduce transplant-related complications and improve outcome for MDS patients [38,
allowing the use of this drug at myeloablative doses safely. Furthermore, cyclophosphamide as a toxic drug with only limited anti-leukemic activity can be substituted by fludarabine, inducing less organ toxicity without obvious loss of anti-leukemic activity [40]. Other alkylating drugs, such as treosulfan, can also be used safely as part of a myeloablative conditioning regimen with low toxicity and NRM in MDS patients [41, 42].

Even if results from prospective randomised trials are lacking, available literature suggests that patients up to 70 years of age can tolerate myeloablative conditioning regimen and that age per se should not be a criterion for selecting the intensity of the conditioning regimen rather than performance status/comorbidity and the status of the disease at time of transplant. The current data also support that there is no “one-size-fits-all” conditioning regimen in elderly MDS patients, and the selection of regimen intensity has to become more individualized.

**Role of cytogenetics and molecular genetics on outcome**

Cytogenetic abnormalities have an important impact on prognosis of patients undergoing allogeneic stem cell transplantation for myelodysplastic syndrome. The established risk groups regarding cytogenetic abnormalities within the International Prognostic Scoring System (IPSS) have also major impact on outcome after allogeneic stem cell transplantation [43, 44].

The EBMT reported 692 patients with an overall survival of 47% for good risk, 40% for intermediate risk, and 31% for high-risk cytogenetic IPSS [44]. The failure to transplant was mainly attributed to a higher risk of relapse, which was 34% for good risk, 35% for intermediate risk, and 57% for high-risk patients [44]. Once patients with IPSS high-risk cytogenetics were analysed in detail, more recent data from EBMT suggest that single abnormalities on chromosome 7 had significantly better survival than complex or monosomal karyotype[45]. If outcome of transplantation was analysed according to the new 5 cytogenetic risk groups proposed for MDS, a significant difference for the risk of relapse could be observed between the very good risk (8%), good risk (17%), intermediate risk (19%), poor risk (26%), and the very poor-risk cytogenetics (48%) groups [46]. Improvement in outcome might be achieved by using pre-transplant novel drugs, such as lenalidomide or
hypomethylating agents, which have been shown to induce cytogenetic remission in patients with 5q- or monosomy 7 abnormalities [47, 48].

Besides cytogenetic abnormalities, modern genomic technology, such as next generation sequencing and mass spectrometry-based genotyping, allow the detection of molecular abnormalities – even in cytogenetically normal patients – such as mutations in TP53, EHZ2, ETV6, RUNX1, TET2, ASXL1, which influence survival in a non-transplant setting [49]. Furthermore, newly discovered mutations of the splicing machinery have become the most frequent detectable mutations in MDS patients, which might also have an impact on outcome in a non-transplant setting [50, 51].

Reducing the number of blasts prior transplant – the issue of cytoreductive pre-transplant therapy

The EBMT study of allogeneic stem cell transplantation in elderly MDS patients suggests that in advanced stage, relapse is the most frequent cause of treatment failure [17]. The number of blasts and not being in complete remission at time of transplantation are the most significant factors for inferior outcome especially after RIC transplantation in MDS patients [7, 16, 34, 37, 52]. Therefore, the issue of performing induction chemotherapy before transplantation has been a matter of debate since starting allogeneic transplantation in MDS patients. Unfortunately, the only randomized study from the EBMT had to be stopped due to slow recruitment, and as a result, no valid data are available. Smaller retrospective single center studies showed no conclusive results [52, 53, 54], and it is very likely that obtained results are biased by the selection of patients who received intensive chemotherapy before transplantation and those who did not achieve CR and never received a transplantation. Especially in the older populations, the intensive induction chemotherapy carries the risk of long-lasting myelosuppression and organ toxicities. To overcome the limitation of long-lasting myelosuppression but gain the anti-leukemic effect of pre-transplant induction chemotherapy, some centers have evaluated AML-like induction chemotherapies, such as anthracycline/cytosine arabinoside/fludarabine, or clofarabine/cytosine arabinoside-based chemotherapy, followed by only 3 days’ rest before performing a reduced-intensity conditioning and subsequent allogeneic stem cell transplantation[55, 56, 57]. With those
conditioning regimens and matched related or unrelated donors, 2-year overall survival rates of 69% and 56% can be achieved [56, 57].

Newer agents, such as 5-azacytidine or decitabine which have been shown to be active in MDS [58, 59], may also be used as pre-transplant cytoreductive therapy. However, the CR rate of about 10% is much lower than after conventional induction chemotherapy, and the reported trials confirmed the feasibility without significant survival benefit [60, 61]. Larger studies from EBMT and CIBMTR are currently under investigation regarding this issue.

**Timing of transplantation**

The clinical course of MDS patients varies from several years to only a few months. Prognostic score systems, such as the IPSS [1] which includes number of blasts, cytopenia and cytogenetic, or the WHO prognostic scoring system (WPSS) which includes also the transfusion dependency, [62] may help to determine the prognosis of MDS patients at diagnosis or during the course of the disease [63]. While these scoring systems have been validated in a non-transplant MDS cohort, both scoring systems have also been shown to be useful as a predictive model for outcome after allogeneic stem cell transplantation [64, 65]. The arguments for early transplantation are based on low incidence of relapse. The Seattle group reported on outcome of unrelated stem cell transplantation in MDS patients according to IPSS pre-transplant. No relapse was seen in the IPSS low-risk group; while in IPSS high risk, the relapse rate increases to 42%, resulting in an relapse-free survival of 80% in the low risk group and only 29% among patients with an IPSS score higher than 2 [66]. A similar study was performed from EBMT in 374 patients with early disease defined as refractory anaemia or refractory anaemia with ringsideroblasts, since IPSS scores were only available in half of the patients. The predictive factors for survival were recipient age, year of transplantation and interval between diagnosis and transplantation. Earlier transplantation after diagnosis was associated with a 10% increase of survival rate at 4 years (57% vs. 47%) [67].

Whether these data support early transplantation in elderly MDS patients is questionable since no comparisons with non-transplant approaches were made, and IPSS low-risk patients often do not require treatment. Furthermore, the risk of non-relapse mortality (NRM) should be carefully balanced, and even if NRM has decreased in recent years, the NRM is still
considerably high and should be carefully balanced with a non-transplant approach [67]. Despite its curative potential, in the face of treatment-related mortality and the risk of relapse, one might ask whether elderly patients should be offered allogeneic stem cell transplantation at all, and whether conservative, less toxic approaches would be more suitable.

So far no prospective trial has compared allogeneic stem cell transplantation with non-transplant approaches. In the past the non-transplant options were supportive without obvious prolongation of life. Hypomethylating agents such as 5-azacytidine have shown prolongation of survival in MDS patients in comparison to other non-transplant therapies [58, 59]. If younger patients with MDS who received an HLA-identical sibling transplantation after standard myeloablative conditioning were compared with a non-transplant cohort within a multi-state model (Markov-model), the obtained results suggest that IPSS high and intermediate II patients benefit from immediate transplantation, while intermediate I or low-risk patients benefit more from a delayed (in case of progression) transplantation [68].

The EBMT also recently used a multi-state model to compare elderly (>55 years) advanced MDS patients (RAEB or RAEB-t) who received allogeneic stem cell transplantation and were reported to EBMT with a non-transplant cohort from the Düsseldorf MDS-registry. Here no benefit for allogeneic stem cell transplantation could be found, but the analysis also showed the limitation of even sophisticated statistical analysis if patients from two different registries are compared and the selection of patients for transplant or non-transplant is not clear [69]. To address this important issue, the German MDS study group has started a prospective study in elderly (55-69 years) IPSS intermediate II or high-risk patients, comparing 5-azacytidine with a reduced-intensity allograft (NCT 01404741). Those studies should also include quality of life evaluation because any potential survival benefit should also be balanced with the gain or loss in quality of life.

From the clinical point of view it is important to define optimal timing of allogeneic stem cell transplantation in treatment algorithms including hypomethylating and other effective drug-based agents such as lenalidomide. For clinicians it is reasonable to start with hypomethylating agents in elderly patients with intermediate II or high-risk IPSS while searching for a donor. But it remains unclear at which point of time the transplantation should be performed in responding patients: at time of best response or after progression? After failure to hypomethylating agents, the median survival is only 5.6 months. Long term survival

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can then be achieved only by allogeneic stem cell transplantation as salvage therapy (median survival 19.5 months) [70].

**Donor selection**

Stem cell transplantations from unrelated donors have been increasingly used in recent years. In the EBMT registry unrelated stem cell transplantations accounted for 59% of all allogeneic transplants for MDS in 2009. While early studies on unrelated SCT in MDS reported a NRM of more than 40% [71], the incidence of NRM has been considerably and steadily improved in recent years and is comparable to HLA-identical sibling transplantation after adjusting for other risk factors (EBMT unpublished results). In addition, the National Marrow Donor Program (NMDP) reported a relative risk for DFS of 1.43 (p=0.03) for unrelated stem cell transplants for MDS performed between 1988 and 1993 versus more recent transplantations [72].

In elderly patients with MDS, the available HLA-identical sibling is likely to have similar age as the recipient. Since in unrelated stem cell transplantation increasing donor age is associated with inferior survival [20], the MDS subcommittee of EBMT investigated the influence of donor age in elderly MDS patients (>50 years) who underwent allogeneic stem cell transplantation. The question of the study was whether in elderly MDS patients a young unrelated donor would result in better outcome after allogeneic stem cell transplantation than an HLA-identical sibling. 719 patients with MDS and a median age of 58 years (r: 50-73) were included. The median age of the HLA-identical sibling donors was 56 years, and of the unrelated donors, 34 years. While there was no influence of donor age in the HLA-identical sibling cohort, age of matched unrelated donor had significant influence on survival (HR: 1.03, p=0.02), resulting in significantly improved survival in elderly MDS patients if the age of the unrelated donor was less than 30 years, in comparison to HLA-identical sibling donors and to matched unrelated donors>30 years: 40% vs. 33% vs. 24% (p=0.04).

This retrospective study suggests that for elderly MDS patients, a young unrelated donor (< 30 years) is a more preferable donor than an HLA-identical sibling, but an HLA-identical donor should be preferred to an older matched unrelated donor [73].
Preventing relapse

Relapse has become the main reason for treatment failure after allogeneic stem cell transplantation in MDS patients. While the cumulative incidence of non-relapse mortality has substantially decreased in the recent years, no major advancement in reducing the risk of relapse has been made [74].

In the EBMT trial [17] the risk of relapse was significantly higher in patients ≥60 years in comparison to the age category 50-59 years (41% vs. 32%, p=0.02). This could be due to the fact that those patients received more reduced-intensity conditioning regimen than the younger group but also to biological factors. Prevention of relapse after allogeneic stem cell transplantation in MDS patients is therefore of even greater need in elderly patients. Since the treatment of relapse resulted in disappointing results, more effort has to be put into prevention of relapse. Limited experience of donor lymphocyte infusions for relapse treatment or relapse prevention exists: in 2 studies 14-22% achieved a complete remission which lasted in 2 patients more than 5 years [75, 76]; and prophylactic DLI improved relapse-free survival, but this has not been investigated in a randomized fashion and the results might be biased by patient selection [77].

5-azacytidine in combination with DLI has shown activity with 23% CR after allogenic SCT in relapsed AML/MDS patients [78]. The MD Anderson Cancer Center investigated 5-azacytidine in a dose-finding study as maintenance therapy after transplantation in high-risk AML and MDS patients. They observed no severe side effects and no impact of azacytidine on GvHD and chimerism. The recommended dose is 24 mg/m² x 5 and has currently been tested in a randomized trial [79, 80]. Potential effects of hypomethylating agents post transplant are the increase expression on cancer-testis antigen, which may become the target for donor cells to induce a tumor-specific immune response [81, 82]. However, other in vitro studies show immunosuppressive properties of 5-azacytidine which in contrast may abrogate effective immune response by increasing T-regulatory cells [83].

To avoid overtreatment by prophylactic post-transplant strategies such as DLI or hypomethylating agents, a more optimized way would be therapeutic intervention based on detectable minimal molecular residual disease after transplantation as it has been shown for CML, MPN or AML [84].
Monitoring CD34+ lineage-specific chimerism might be able to detect residual disease or early relapse and might allow successful intervention with 5-azacitidine [85]. The more recent discovery of mutation in MDS patients [49, 86] by modern sequencing techniques allow for screening patients prior to transplantation for specific mutations and can be used after transplantation as a marker for residual disease and as a guide for adoptive immunotherapies to prevent clinical relapse.

**Conclusions**

Allogeneic stem cell transplantation is well accepted as curative treatment approach in patients with myelodysplastic syndrome (MDS) and has become the third most frequent indication for allogeneic stem cell transplantation as reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) [87]. The majority of MDS patients are elderly with a median age of 65-70 years at diagnosis. However, the role of stem cell transplantation in elderly patients with MDS is not well defined. Large retrospective studies confirmed the feasibility of allogeneic SCT in elderly MDS patients, as well as curative potential; but benefit in terms of survival has not been demonstrated yet in randomized trials. Chronological age, which has been used for a long time as exclusion criteria for allogeneic stem cell transplantation, is probably only a poor predictor for survival due to the lack of data on organ dysfunction and performance status. Beside chronological age, physical function and organ comorbidities should be taken into account for selecting patients for transplantation. The intensity of the conditioning regimen is not well established but retrospective studies suggest that there is no “one-size-fits-all” conditioning regimen for elderly MDS patients, and comorbidities and risk of relapse are the main determinants for selecting the intensity of the conditioning regimen in a more “individualized” fashion. Allogeneic stem cell transplantation should early be included in the treatment plan for MDS patients, which includes novel agents such as hypomethylating agents or immunomodulatory drugs to achieve cytogenetic response or reduction of the number of blasts prior transplantation. Molecular marker detectable with new sequencing methods should be investigated at time of diagnosis and used as residual disease marker after transplantation to guide either drug based or immunological based therapies such as donor lymphocyte infusion, alloreactive NK cells, or vaccination strategies to lower the risk of relapse and improve overall survival.
Contribution: NK wrote the article and has nothing to disclose.

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Table 1 Allogeneic stem cell transplantation in elderly MDS patients
(* this study includes also AML patients)

<table>
<thead>
<tr>
<th>Author</th>
<th>Numbers</th>
<th>Median age (range)</th>
<th>conditioning</th>
<th>NRM</th>
<th>relapse</th>
<th>DFS</th>
<th>OS</th>
</tr>
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<tbody>
<tr>
<td>Lim et al. (2010)</td>
<td>1333</td>
<td>56 y (50-74)</td>
<td>RIC: 833 (62%) MA: 500 (38%)</td>
<td>36% (median: 44)</td>
<td>50-60 y: 36% &gt;60 y: 39%</td>
<td>36% (median: 44)</td>
<td>50-60 y: 32%, p: 0.02 &gt;60 y: 41%, p: 0.02</td>
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<tr>
<td>McClune et al. * CIBMTR (2010)</td>
<td>1080</td>
<td>(MDS: n=535) (AML 1.CR: n=545)</td>
<td>MDS: 40-78 y (&gt;65 y: 10%) AML: 40-79 y (&gt;65 y: 12%)</td>
<td>only RIC or NMA (2 Gy TBI)</td>
<td>40-54 y: 25% (median: 2 y) 55-59 y: 22% (median: 2 y) 60-64 y: 32% (median: 2 y) ≥65 y: 34% (median: 2 y)</td>
<td>33% (median: 2 y) 34% (median: 2 y) 37% (median: 2 y) 33% (median: 2 y)</td>
<td>42% (median: 2 y) 43% (median: 2 y) 31% (median: 2 y) 34% (median: 2 y)</td>
</tr>
</tbody>
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Abbreviations: NMA: non myeloablative; RIC: reduced-intensity conditioning; MA: myeloablative; NRM: non-relapse mortality; DFS: disease-free survival; OS: overall survival
Figure 1: Development of allogeneic stem cell transplantation for MDS/sAML in EBMT register according age categories
The issue of stem cell transplantation in elderly MDS patients:

- If?
  - Determination of survival benefit in comparison to non-transplant approaches including QoL in prospective trials

- Who?
  - Prospective validation of comorbidity indices to balance individual life expectancy with or without transplant

- When?
  - Determine timing of allogeneic SCT according to IPSS to gain maximum survival benefit and QoL within prospective trials

- How?
  - Optimize transplant outcome by:
    1. "individualization" of the conditioning regimen according to risk of NRM and relapse (no "one-size-fits-all")
    2. Lower iron overload-induced morbidity / mortality
    3. Developing efficient pre-and post-transplant therapies to reduce the risk of relapse
    4. Detect molecular marker for detection of MRD
    5. Improving donor selection
Allogeneic stem cell transplantation for elderly patients with myelodysplastic syndrome

Nicolaus Kröger