

Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndrome: Current Status

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Abstract Hematopoietic cell transplantation (HCT) offers potentially curative therapy for patients with myelodysplastic syndrome (MDS). However, as the majority of patients with MDS is in the 7th or 8th decade of life, only few of these patients were transplanted following high-dose conditioning regimens. The development of reduced-intensity conditioning has allowed to apply HCT also to older patients and those with clinically relevant comorbid conditions. Dependent upon disease status and the type of clonal chromosomal abnormalities present at the time of HCT, some 25–75% of patients will be cured of their disease and survive long term. Recent results with HLA-matched unrelated donors are comparable to those with HLA genotypically identical siblings. The increasing use of cord blood and HLA-haploidentical donors is expected to make HCT available to a growing number of patients. However, post-transplant relapse and graft-versus-host disease remain problems requiring further instigations.

Keywords Transplantation for MDS · Age · Comorbidities · Conditioning intensity · Relapse

Introduction

Over the past decade, considerable research has been conducted, both in the laboratory and in the clinic, on the

genetics, the pathophysiology and therapy of diseases that we refer to as myelodysplastic syndrome (MDS). Before the French–American–British (FAB) Working Group presented the FAB classification in the late 1970s and early 1980s, these diseases were all referred to as “pre-leukemia” or “smouldering leukemia”. We know now that only about one-third of patients will, indeed, progress to acute leukemia, and the term MDS much better covers the spectrum of these diseases, even though the heterogeneity is considerable (Greenberg et al. 1997; Steensma and Bennett 2006).

MDS is primarily a disease of older individuals, at least in Western countries, with a median age at diagnosis of 70–75 years (Hamblin 2002). At that age, the incidence is estimated at about 40–60/100,000/year (De Roos et al. 2010). MDS is more frequent in Caucasians than in non-Caucasians and occurs at an earlier age in Asian populations than in the West. The age at diagnosis is certainly an important consideration when considering aggressive therapy such as hematopoietic cell transplantation (HCT). Risk factors other than chemotherapy or irradiation for other, antecedent medical indications are not well defined, although MDS appears to be more frequent in smokers than in non-smokers.

The most frequent presentation of MDS is anemia (Greenberg et al. 2006), and red blood cell transfusions will add to the disease-related iron overload with the potential of organ complications, particularly in heart, liver and endocrine organs (Gattermann 2009). However, some 15–20% of patients present with neutropenia or thrombocytopenia and the associated risks of infection or bleeding (Malcovati et al. 2007).

Various therapeutic strategies, including chemotherapy, immunosuppression, and anti-apoptotic manipulations, have been pursued, and currently three drugs, azacitidine,

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decitabine and lenalidomide, are approved for the treatment of MDS in the USA (approval differs from country to country). However, only a proportion of patients will respond, and studies suggest that on average patients gain 9–10 months in life expectancy (Fenaux et al. 2009), except for patients with del(5q) in whom the median duration of response, as measured by transfusion independence, has been approximately 2.2 years. However, even in responding patients MDS will eventually progress.

While there is agreement that chemotherapy will cure only a rare patient with MDS (Beran 2000), and HCT is the only therapeutic modality with proven curative potential (de Lima et al. 2004a; de Lima and Giralt 2006; de Witte et al. 2000; Deeg et al. 2002; Deeg 2009a; Nachtkamp et al. 2009; Scott and Deeg 2006; Sierra et al. 2002), the selection of patients for HCT, the timing, in addition to the optimum strategy to be pursued in preparation for HCT, have remained controversial. First, patients with low-risk MDS, defined by classification systems such as FAB, International Prognostic Scoring System (IPSS), WHO Prognostic Scoring System (WPSS; see below) or other criteria, may have a life expectancy of a decade or more without or with minimal therapy. Second, HCT carries the risk of toxicity and mortality due to complications related to the conditioning regimen and consequences of allogeneic HCT, i.e., graft-versus-host disease (GvHD), the immunologic reaction of donor cells against patient tissues, and associated infections. Third, as stated, the median age at the time of diagnosis is in the 8th decade of life when, frequently, other medical conditions are present and the biologic reserve of the human body has declined substantially. Thus, the risks associated with HCT must be carefully weighed against the expected benefits.

General Considerations

MDS originates in hematopoietic stem or precursor cells, and a logical approach is, therefore, to replace the clonal MDS cells by cells from a healthy donor, i.e., to carry out a HCT. Successful allogeneic HCT requires that the infused cells from the healthy donor establish themselves (engraft), and that the clonal (malignant) cells of the patient's disease are eliminated or inactivated. All patients are prepared with a "conditioning" regimen, consisting of chemotherapy with or without total body irradiation (TBI), antibodies, and possibly radioimmunotherapy. The objective is to overcome the immunological barrier, which protects the body against intrusion by foreign cells (Welniak et al. 2007) and to kill the patient's MDS cells. However, many questions arise as to the best strategy: How intensive does the regimen need to be in order to allow for engraftment and prevent relapse? What intensity will the patient

tolerate? Should the conditioning intensity be adjusted to the disease stage (the risk of relapse)? Would it be beneficial to give pre-HCT "debulking" therapy? Is there a place for post-HCT adjuvant or preemptive therapy?

Over the past decade the approach to treating MDS in general and with HCT in particular has undergone major changes, at least in part related to the Food and Drug Administration approval of three drugs for MDS and the development of new concepts for HCT. As indicated above, drug therapy has improved the prognosis of patients with MDS, with 35 to 65% of patients achieving clinically relevant responses which may last from a few months to several years. Concurrently, the emphasis with HCT has shifted from high-dose therapy, aimed at maximum tumor cell kill, to low- or reduced-intensity conditioning (RIC), relying heavily on donor cell mediated immune effects (graft-versus-tumor [GvT] effects) to eradicate the disease (Deeg et al. 2006; Laport et al. 2008; Welniak et al. 2007). This GvT effect, mediated by donor-derived cytotoxic T cells, eliminates residual cells of the patient's disease via recognition of minor histocompatibility antigens or, possibly, cancer-testis antigens. Unfortunately, it has so far not been possible in humans to separate GvHD from the GvT effects.

Even a cursory review of the literature shows that there are not simply high-dose and RIC regimens, but there is basically a continuum of regimens, spanning the range from just low-dose TBI (2 Gy) to regimens that combine one or two chemotherapy agents with high-dose TBI (e.g. 12 Gy) (Deeg et al. 2006), and any categorization must remain artificial, as we have repeatedly emphasized (Deeg et al. 2006; Deeg 2009b; Deeg and Sandmaier 2010). It would be most appropriate to refer to regimens by their components and dose intensity. As expected, the extent of toxicity correlates with intensity, and in general, the probability of relapse is higher with RIC (Baron and Sandmaier 2005). A major advantage of RIC is the possibility of applying those regimens to older patients, and, indeed, patients in the 8th decade of life have been transplanted successfully (Baron and Sandmaier 2005; Samuelson et al. 2011; Valcarcel and Martino 2007). With such a broad menu of regimens, which provide some ability to offer "custom tailored" HCT to subgroups of patients, transplant-related mortality has steadily declined (Castro-Malaspina et al. 2002; de Witte et al. 2009; Gooley et al. 2010).

Despite considerable progress, however, post-HCT relapse remains a problem, especially in patients with advanced MDS (Ramakrishnan and Deeg 2008; Warlick et al. 2009). This observation has led to efforts at pre-HCT debulking in an attempt to carry out HCT in patients with a lower disease burden and, hopefully, an improved probability of relapse-free survival (RFS; see below). Other strategies include post-HCT preemptive therapy with hypomethylating agents (de Lima et al. 2010).

Only about 25% of patients will have siblings or other family members who are matched for HLA (human leukocyte antigens), the major histocompatibility antigens in humans, encoded on chromosome 6. By definition, an individual inherits one HLA haplotype from the father and one from the mother. However, more than 12 million volunteer donors are now registered in donor banks, and an HLA-matched unrelated donor can be identified for about 50–60% of Caucasians; the proportion is lower for African Americans and may be as low as 10% in some ethnic minorities (Petersdorf 2009; Rocha and Locatelli 2008). Importantly, transplant results with unrelated donors who are HLA matched with patients by high resolution typing are comparable to those with HLA genotypically identical siblings, although the incidence of GvHD tends to be somewhat higher. For patients without HLA-matched related or unrelated donors, cord blood cells or cells from HLA-haploidentical related donors may offer alternatives (Aversa 2008; Brunstein et al. 2010; Brunstein and Weisdorf 2009; Luznik et al. 2008). Results to date show that such transplants, be it from parents, children or other family members, matched for one of the HLA haplotypes but mismatched for the second, are remarkably well tolerated, and intensive research is pursuing this strategy. Cord blood has the advantage of “immaturity”, allowing to transplant HLA-mismatched cells without a significant increase in GvHD incidence. The drawback of limited numbers of cells (Koh and Chao 2004) is at least in part overcome by the use of 2 U of cord blood or in vitro “expansion” of one cord blood unit before infusion (Barker et al. 2005; Delaney et al. 2009; Kelly et al. 2009).

Initial results with haploidentical HCT are encouraging. Graft failure presents only a minor problem, and GvHD rates have been surprisingly low, with RFS and non-relapse mortality (NRM) comparing favorably with results of HLA-identical transplants (Aversa 2008). Results have been better in patients with lymphoid than in those with myeloid malignancies (Kasamon et al. 2010; O'Donnell et al. 2010).

Risk Assessment and Scoring

Several classifications for disease risk have been proposed and proven useful in advising patients in regards to therapy. However, the field is currently in flux, and new insights from molecular studies are likely to lead to additional changes in the currently used scoring systems. We will only provide a brief outline.

Multiparameter Prognostic Scoring Systems

The IPSS (Greenberg et al. 1997) is used widely to assess patient prognosis and has also been a reliable prognosticator

for transplant success. The higher the IPSS score, the lower RFS (Lee et al. 2010; Scott and Deeg 2006). The more recently developed WPSS (Malcovati et al. 2007) includes the WHO classification, karyotype, and transfusion dependence. In contrast to the IPSS, it allows for real-time assessment of prognosis. Recent studies have validated its relevance for HCT outcome (Alessandrino et al. 2008).

The Simplified MDS Risk Score (Kantarjian et al. 2008) proposed by investigators at the MD Anderson Cancer Center includes poor performance status, older age, thrombocytopenia, anemia, increased marrow blasts, leukocytosis, chromosome 7 or complex (≥ 3) abnormalities and transfusion need as adverse risk factors. It has been validated in several studies for secondary MDS and de novo MDS (Breccia et al. 2009). Whether this system is truly simpler than others remains to be seen, but its value might lie in the fact that it incorporates performance status, which in turn might reflect comorbidities. Its possible relevance in the context of HCT remains to be determined.

Cytogenetics

The clonal karyotype is the most powerful predictor of RFS after HCT for MDS (Alessandrino et al. 2008; Oliansky et al. 2009) (Fig. 1). A recent re-examination by Armand et al. (2007b), validated in a multi-center analysis, suggests that MDS patients can be separated into two groups, with good/intermediate versus poor-risk cytogenetics, with significantly differing impact on post-HCT course (Armand et al. 2008, 2010).

Flow Cytometry

Further, we and others have shown that flow cytometric immunophenotypic aberrancies of MDS marrow cells pre-HCT impact post-HCT relapse (Diez-Campelo et al. 2009; Scott et al. 2008; Stetler-Stevenson et al. 2001; Wells et al. 2003). Even among patients with less than 5% marrow myeloblasts, those with an aberrant phenotype had a significantly higher relapse probability (Scott et al. 2008). In addition, gene expression profiling has been shown to predict the risk of progression of MDS to acute myeloid leukemia (AML) (Mills et al. 2009).

Transfusion Dependence and Iron Overload

Transfusion dependence, a frequent situation in patients with MDS (reflected in the WPSS), and iron overload also negatively impact outcome after HCT (Armand et al. 2007a; Busca et al. 2010; Cazzola et al. 2008; Kataoka et al. 2009; Lee et al. 2009; Mahindra et al. 2009; Maradei et al. 2009). Liver iron content seems to be a more specific marker of iron overload than ferritin, which may be

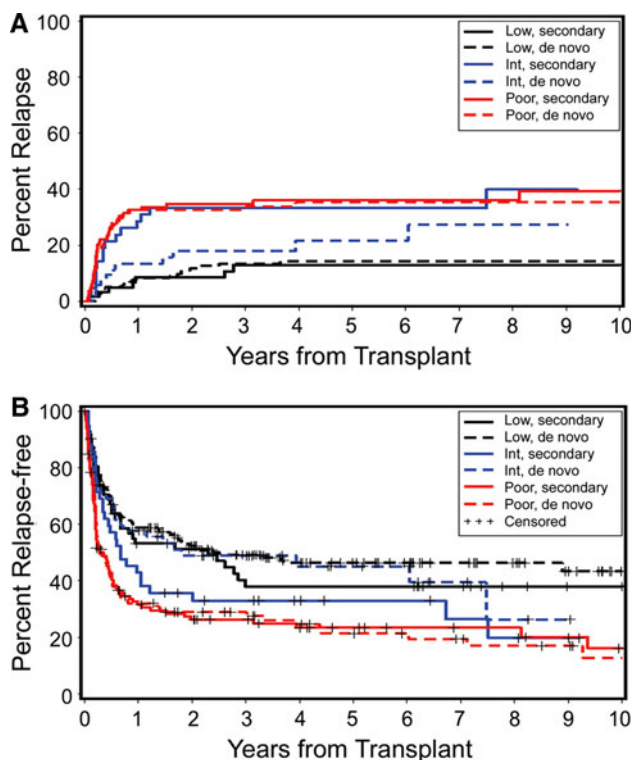


Fig. 1 Impact of cytogenetic risk category on HCT outcome in patients with de novo and with secondary MDS/tAML. **a** Probability of relapse, **b** probability of relapse-free survival, based on cytogenetic risk as defined by IPSS (Greenberg et al. 1997). This research was originally published in *Blood*. Hematopoietic cell transplantation in patients with myelodysplastic syndrome or acute myeloid leukemia (AML) arising from myelodysplastic syndrome: similar outcomes in patients with de novo disease and disease following prior therapy or antecedent hematologic disorders (with permission from the ©American Society of Hematology; Chang et al. 2007)

elevated for several reasons (Busca et al. 2010; Cazzola et al. 2008; Strasser et al. 1998; Sucak et al. 2008). Whether chelation therapy of iron overload improves outcome after HCT (Cazzola et al. 2008; Lee et al. 2009), is controversial.

Transfusion dependence is also linked to marrow fibrosis, long recognized as being associated with more rapid progression of MDS (Cazzola et al. 2008) and recently shown to have a negative impact on post-HCT outcome (Scott et al. 2007).

Age and Comorbidity

Older age was long accepted as a contraindication to allogeneic HSCT (Marcondes and Deeg 2008). However, more recent studies show that co-morbid conditions rather than chronologic age are the major determinants of inferior HCT outcome in older individuals, and the development of RIC regimens along with modern supportive care and complication management has allowed to transplant

successfully patients in their 1960s and even 1970s. Sorror et al. developed a HCT-specific comorbidity index (HCT-CI) (Sorror et al. 2008), and Parimon et al. (2006) generated a primarily pulmonary function-based risk score for pre-HCT risk assessment. While not all studies confirmed the value of those scoring systems (Guilfoyle et al. 2009), the current consensus is that they predict toxicities, NRM and overall survival after RIC HCT better than the Karnofsky Performance Score (Farina et al. 2009; Kataoka et al. 2010).

Timing of Transplantation

Determining the optimal timing of HSCT for MDS has proven difficult although all available data indicate that patients transplanted at an early stage of their disease have superior outcomes. The probability of relapse increases progressively with increased IPSS or WPSS scores (Alessandrino et al. 2008; Deeg et al. 2002). An analysis by Cutler et al. (2004), using a Markov model, showed that patients with high or intermediate-2 risk by IPSS did benefit from early HCT, while patients with low or intermediate-1 risk may have a longer life expectancy if HCT is delayed until evidence of disease progression. It is probably wise to advise patients in the lower risk categories individually, in particular those with severe neutropenia or thrombocytopenia. The analysis by Cutler and colleagues was restricted to patients transplanted from HLA-identical siblings, but results are generally also applied to patients transplanted from unrelated donors (Kindwall-Keller and Isola 2009). Al-Ali et al. (2007) observed that HCT outcome was best if HCT was performed between 6 and 12 months after diagnosis, the negative effect of later HCT being possibly related to frequent blood transfusion, longer duration of pancytopenias, and disease progression while waiting for HCT. If HCT is delayed, for example because of a lengthy search for an unrelated donor, bridging treatment with hypomethylating agents may delay progression to AML (Kindwall-Keller and Isola 2009).

Pretransplant Therapy

In an attempt to improve chances for post-HCT success, patients with a high marrow myeloblast count, say more than 5 or 10%, typically will receive pre-HCT therapy with a hypomethylating agent or with more classical induction type chemotherapy (de Lima et al. 2004b; Kindwall-Keller and Isola 2009; Maris et al. 2004; Nakai et al. 2005; Oliansky et al. 2009; Scott et al. 2005; Warlick et al. 2009; Yakoub-Agha et al. 2000). While no data from controlled prospective trials are available, the clinical impression is

that pre-HCT therapy may select chemosensitive patients since it appears that patients who do respond to such therapy have a superior outcome, and patients who fail to respond a poorer outcome than do untreated patients (Yakoub-Agha et al. 2000). The impact of the depth of response on post-HCT outcome is illustrated in Fig. 2; (de Lima et al. 2004b).

The availability of hypomethylating agents offers an attractive therapy for many patients with MDS. These agents, azacitidine and decitabine, are associated with considerably less toxicity than classic anti-leukemic therapy. A potential disadvantage is that several cycles of therapy are required to result in reduction of DNA methylation and therapeutic efficacy, although it appears that mechanisms of action other than DNA demethylation contribute to the treatment effect. Many patients who currently come to HCT have been exposed to that therapy, and one question currently being debated, is whether patients should be transplanted at the time of best response or, alternatively, when they no longer respond to treatment. Not surprisingly, the former is the preference of transplant physicians, whereas the latter is often the philosophy of physicians who prefer “to buy the maximum time with good quality of life” before exposing the patients to the potential risk of HCT. As stated for pre-HCT above, no controlled studies are available, although the reported data

would suggest that the best HCT outcome can be expected in patients who are “responding” to pre-HCT therapy when they proceed to HCT.

In a recent retrospective study, overall survival, RFS, and cumulative incidence of relapse at 1 year were 47, 41, and 20%, respectively, for patients with MDS and chronic myeloid leukemia receiving 5-azacytidine, compared to 60, 51, and 32% for patients who were not treated (Pidala et al. 2009b). In a small study including 17 patients with MDS, treatment with 2'-deoxy-5-azacytidine (decitabine) did not negatively affect toxicity after HCT, and disease downstaging may improve HCT outcome (De Padua et al. 2009). However, the available data are not conclusive.

Conditioning Regimens

Recent research has been aimed at minimizing toxicity while optimizing efficacy of conditioning regimens. However, there is no one-size-fits-all conditioning regimen (Oliansky et al. 2009). Instead, conditioning should be tailored to diagnosis, disease stage, patient age, prior therapy, comorbidities and the other parameters of HCT, such as donor and stem cell source (Deeg et al. 2006; Ramakrishnan and Deeg 2008; Scott and Deeg 2006).

While high-dose conditioning may be associated with a lower relapse risk than RIC regimens (Warlick et al. 2009), toxicity may render those regimens unsuitable for many older patients and those with comorbidities (Scott and Deeg 2006). Currently, patients age 60 or 65 years and older, and patients even of younger age with comorbidities that result in a score of 3 and higher on the HCT-CI scale, are typically offered HCT using RIC regimens. The potentially higher incidence of relapse is offset by lower treatment-related mortality (TRM) (Alyea et al. 2006; Martino et al. 2006; Oliansky et al. 2009; Scott et al. 2006; Warlick et al. 2009). However, results from retrospective studies must be interpreted with caution, because of likely bias in patient selection (Martino et al. 2006; Sorror et al. 2004, 2005). No prospective randomized study has been conducted; a CTN sponsored phase III trial is currently getting underway in the USA (CTN #0901). We should emphasize, however, that even in that trial only a few different regimens are being studied. Results are expected to provide guidance, but it is likely that further refinements and steps of “individualization” for a given target group of patients will be necessary in order to optimize results.

Donor Selection

Our policy is to search for HLA-identical siblings as a first choice, and try to identify HLA-matched unrelated donors

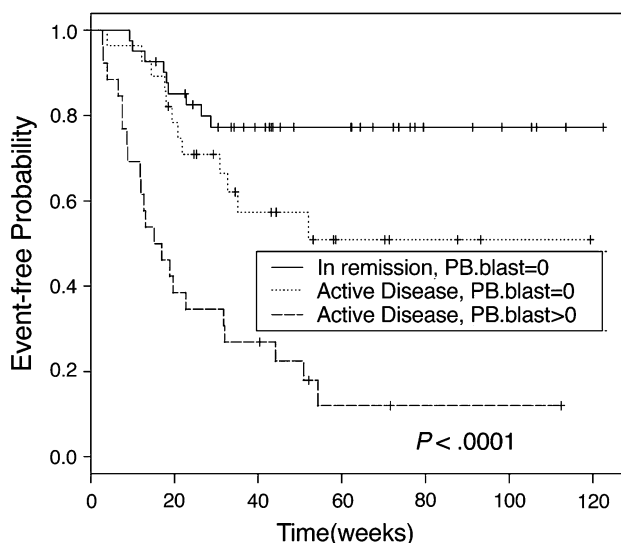


Fig. 2 Relapse-free survival by disease status and circulating blasts. HCT results in 74 patients with AML and 22 patients with MDS. Patients had high-risk disease or were given pre-HCT chemotherapy or both. At HCT patients were either in complete remission without blasts in peripheral blood (PB) or had active disease in the marrow without or with circulating blasts. This research was originally published in *Blood*. Once-daily intravenous busulfan and fludarabine: clinical and pharmacokinetic results of a myeloablative, reduced-toxicity conditioning regimen for allogeneic stem cell transplantation in AML and MDS (with permission from the ©American Society of Hematology; de Lima et al. 2004b)

if no suitably matched siblings are available. Cord blood is a third option, but only limited data in patients with MDS are available (Harrison et al. 2006; Ooi et al. 2003; Sato et al. 2011). Finally, based on initial results reported from Perugia and from Johns Hopkins University, haploidentical transplants (from related donors) represent an area of intensive research with promising early results (Luznik et al. 2008), although only few patients with MDS have so far been given HLA haploidentical transplants (Aversa 2008; O'Donnell et al. 2006).

Stem Cell Source and Manipulation

Hematopoietic stem cells aspirated directly from the marrow (BM), umbilical cord blood cells (UCB), and granulocyte colony-stimulating factor mobilized peripheral blood progenitor cells (PBPC) express different characteristics, in regards to kinetics of engraftment, GvHD and GvT effects (Welniak et al. 2007). While the use of PBPC is associated with an increased risk of GvHD, particularly in its chronic form, basically all studies have also shown a lower relapse rate of the underlying disease (Deeg et al. 2002; Guardiola et al. 2002). In fact, additional data suggest that PBPC use is associated with a better quality of life, despite the presence of chronic GvHD (Pidala et al. 2009a). Results of the prospective trial comparing PBPC with BM in unrelated HCT recipients (BMT Clinical Trials Network protocol 0201) have recently been analyzed; no significant difference between BM and PBPC was apparent (data to be presented at the ASH meeting 2011).

Several groups have reported extensively on the use of UCB cells (Barker et al. 2005; Brunstein and Weisdorf 2009; Koh and Chao 2004; Ooi 2006; Rocha and Gluckman 2009). The data suggest that both the degree of HLA matching and the number of UCB cells infused will determine outcome. Hematopoietic recovery has been improved with “double cord” transplants (Barker et al. 2005; Rocha and Gluckman 2009). Additional data on the efficacy of in vitro expanded UCB are forthcoming (reviewed in Kelly et al. 2009).

What Can Patients with MDS Expect from HCT?

Several comprehensive reviews of current results with HCT in patients with MDS have recently been presented (Bartenstein and Deeg 2010; Harrison et al. 2006; Oliansky et al. 2009). These analyses include data on high dose and RIC from trials conducted between 1990 and 2008 (Kindwall-Keller and Isola 2009; Oliansky et al. 2009).

An analysis by Warlick et al. (2009) showed a 1 year overall survival of 48%, a cumulative relapse incidence of

23%, and a RFS of 38%. At 5 years the corresponding figures were 31, 25 and 29%, respectively. Acute GvHD grades II–IV occurred in 43%, and chronic GvHD in 15% of patients. Neither stem cell source nor conditioning affected outcome in a differential way. For patients with $\geq 5\%$ myeloblasts the incidence of relapse was 35%. Among patients with $< 5\%$ blasts, high-dose conditioning resulted in a lower incidence of relapse than observed with RIC (9 vs. 31%); however, among patients with higher myeloblast counts no difference was observed. The reason may lie in the treatment patients received pre-HCT with the objective of “debulking” the tumor burden.

The EBMT registry analyzed results in a cohort of 374 patients with $< 5\%$ myeloblasts who received HCT from HLA-matched donors after various conditioning regimens (de Witte et al. 2009). At 4 years, RFS was 48%, the relapse incidence 15%, and deaths not related to relapse 37%. The risk of relapse was increased after RIC compared to high-dose conditioning (hazard ratio [HR] 2.8), but overall survival did not differ significantly. Patients transplanted from unrelated donors had a lower relapse risk (HR 0.6), but a higher risk of NRM (HR 1.4), and overall survival did not differ significantly between related and unrelated HCT. T-cell depletion of the transplanted cells resulted in higher NRM. Younger patients and patients transplanted within 12 months of diagnosis had superior outcome.

We analyzed results in 257 patients with secondary MDS who were transplanted at our Center. The cohort included 103 patients in whom MDS had progressed to AML, showing a 5-year incidence of relapse of 33%, which was not different from patients with refractory anemia with excess blasts (RAEB; 36%), but significantly higher than in patients with refractory anemia/refractory anemia with ringed sideroblasts (RA/RARS; 12%). At 5 years, 19% of patients with tAML were surviving in remission, compared to 25% of patients with RAEB, and 41% of patients with RA/RARS. Two-thirds of patients developed acute GvHD grades II–IV and 57% developed chronic GvHD. After adjusting for karyotype, there were no significant differences in outcome between this cohort with secondary MDS and a cohort of 339 patients with de novo MDS. The probability of relapse and RFS correlated significantly with disease stage ($p < 0.001$) and cytogenetics ($p < 0.001$). As in other studies (see above) patients transplanted from unrelated donors ($n = 122$) had a lower risk of relapse ($p = 0.003$) and superior RFS ($p = 0.02$) compared to patients transplanted from related donors. The use of targeted busulfan in combination with cyclophosphamide ($n = 93$) resulted in the highest RFS (43%) and lowest NRM (28%) among all conditioning regimens that had been used. These results were confirmed in principle in a more recent analysis of CIBMTR data (Litzow et al.

2010). Taken together, these studies emphasize the central importance of cytogenetics for HCT outcome.

Martino et al. (2006) analyzed HCT results in an EBMT cohort comparing results in 215 patients with MDS conditioned with RIC and 621 patients who received high-dose conditioning and were transplanted from HLA-identical siblings. For the high-dose and RIC cohorts, NRM at 3 years was 32 versus 22%, overall survival 45 versus 41%, and RFS 41 versus 33%. The incidence of acute GvHD was 58 and 43%, respectively. The corresponding numbers for chronic GvHD were 52 and 45%, respectively. Lack of remission before HCT ($p = 0.001$), poor-risk cytogenetics ($p = 0.03$), transformation to AML and older age were risk factors for inferior RFS.

A British trial (Lim et al. 2006) evaluated results in 75 patients conditioned with an alemtuzumab-based RIC regimen and transplanted from unrelated donors. At 3 years TRM, RFS and overall survival for patients with refractory cytopenia with multilineage dysplasia were 24, 55 and 59%, respectively; the corresponding numbers for patients with RAEB (1 and 2) were 44, 18 and 18%, respectively. HLA mismatch negatively affected all endpoints as did disease status at HCT and patient comorbidity.

We showed recently that a conditioning regimen that included fludarabine and treosulfan resulted in a NRM of <10% (Nemecek et al. 2011), and among patients with AML or MDS without high-risk cytogenetics, a 2-year RFS of >80% (Fig. 3). These data are in agreement with other reports by European investigators (Beelen et al. 2005; Casper et al. 2010). This treosulfan-containing regimen is

by some considered to be of intermediate intensity and may point to new strategies for successful HCT in patients with MDS.

Managing Relapse after HSCT

There has been progress in HCT for MDS, but post-HCT relapse has remained a challenging problem, particularly in patients prepared for HCT with RIC. BM cyto- and histomorphology, cytogenetic monitoring, PCR-assessment of molecular markers, assessment of donor-host chimerism and immunophenotyping (Bacher et al. 2008) may serve as guides to institute prophylactic or preemptive therapy (see below).

Multiparameter flow cytometry has been used effectively to show that aberrancy of marrow blasts pre-HCT significantly influenced outcome after HCT (Diez-Campelo et al. 2009; Scott et al. 2008; Wells et al. 2003). However, since most patients with MDS have aberrant marrow cell phenotypes by flow cytometry and may not be in remission as classically defined for patients with AML, the definition of minimal residual disease in patients with MDS is a matter of debate and requires further work.

The infusion of donor lymphocytes in patients with relapse has shown only limited efficacy, as has withdrawal of immunosuppressive therapy (Campregher et al. 2007; Depil et al. 2004; Kang et al. 2008; Lim et al. 2007; Rizzieri et al. 2007; Spitzer 2005; Warlick et al. 2008). The early administration of hypomethylating agents may be more effective (de Lima et al. 2010; Vaughn et al. 2010). The prophylactic use of drugs such as hypomethylating agents or “small molecule” inhibitors that are coming into use in patients with high-risk disease may be even more effective. Intensive chemotherapy has generally been disappointing, and second HCT in adults have yielded low-success rates (Shaw et al. 2008).

Summary and Conclusions

HCT is the only treatment modality with proven curative potential in MDS. With RIC regimens even patients in their 1970s have been transplanted successfully. The availability of unrelated donors (and the ability to select suitable individuals on the basis of DNA sequencing of HLA), the establishment of cord blood as a source of stem cells, and the recent efforts with HLA-haploidentical donors will allow to offer HCT basically to all patients. Dependent upon disease stage and characteristics, some 25–75% of transplanted patients will be cured. While 20–30% of patients experience chronic medical problems after HCT, 70% report a “good to excellent” quality of life. However,

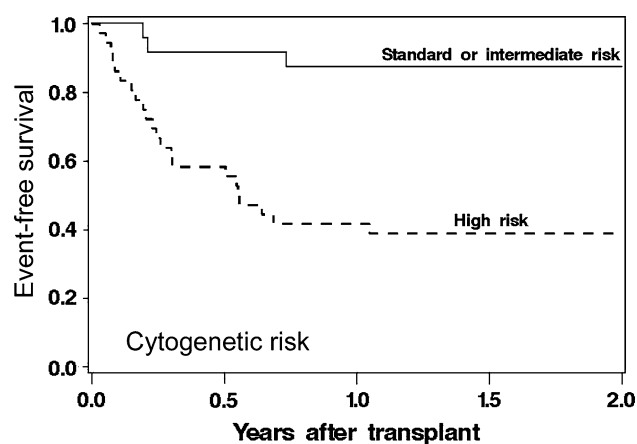


Fig. 3 Relapse-free survival in patients with MDS or AML conditioned with fludarabine plus treosulfan and transplanted from HLA-matched related or unrelated donors. Shown are the results based on cytogenetic risk (per IPSS criteria for MDS, and per cooperative group criteria for AML). Reprinted from *Biology of Blood and Marrow Transplantation*. Conditioning with treosulfan and fludarabine followed by allogeneic HCT for high-risk hematologic malignancies (with permission from ©Elsevier; Nemecek et al. 2011)

disease recurrence and GvHD remain major hurdles. While recent research suggests that it may be possible to separate experimentally a GvT effect from the reactions that cause GvHD (Kawase et al. 2009; Michalek et al. 2003), clinically this remains to be shown. Immunotherapy after HCT is promising, but progress has been slow. Ongoing studies are exploring the incorporation of novel agents used in “non-transplant” therapy into the overall transplant approach, and it will be important to follow the impact of pre-HCT therapy and post-transplant adjuvant treatment on long-term HCT success.

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