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Allogeneic hematopoietic cell transplantation for MDS: For whom, when and how?

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Abstract

Hematopoietic cell transplantation (HCT) is currently the only treatment with curative potential for patients with myelodysplastic syndrome (MDS). However, treatment-related mortality and relapse have remained major barriers to uniform success. Therefore, important questions remain to be answered, such as whom to transplant, when and how. With reduced intensity conditioning (RIC) regimens, patients in their 70s and patients with comorbid conditions have been transplanted successfully, although the relapse incidence with this approach tends to be increased in comparison to high intensity regimens. Success rates are higher in patients transplanted at an early stage of their disease. Encouraging is the fact, that results with unrelated donors who are HLA-matched by high resolution typing are comparable to those achieved with HLA genotypically identical siblings. The establishment of cord blood as a source of stem cells, and the recent success with HLA-haploidentical related donors will allow to offer HCT to virtually all patients. Dependent upon disease stage and characteristics, some 25% to 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. New studies must focus on further reducing GVHD for all patients and on overcoming high relapse rates in patients with high risk disease.

Keywords

Transplantation for MDS; disease stage; age; comorbidities; conditioning intensity; relapse

1. Introduction

Myelodysplastic syndrome (MDS) is primarily a disease of older individuals with a median age of 70–75 years at diagnosis.^{1–3} In that age range, the incidence is estimated at 40–60/100,000/year.³ MDS is more frequent in Caucasians than in non-Caucasians and occurs at an earlier age in Asian populations. Risk factors other than chemotherapy or irradiation for antecedent medical indications are not well defined, although MDS appears to be more frequent in smokers than in non-smokers.¹ The most frequent presentation of MDS is anemia,⁴ and red blood cell transfusions will add to the disease-related iron overload with

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the potential of organ complications.⁵ However, 15%-20% of patients present with neutropenia or thrombocytopenia and are at risk of infection or bleeding.⁶

While MDS had long been a neglected hematologic disorder, over the past decade it has moved centerstage, driven by a veritable explosion of research into the pathogenesis of the disease and, in part, related to the approval of three drugs specifically for the treatment of MDS. About two-thirds of patients with a del(5q) karyotype become transfusion-independent on treatment with lenalidomide for an average of 2 to 2.5 years.⁷ About 40%-60% of patients have clinically relevant responses to the hypomethylating agents 5-azacitidine (5AC) or 5-aza-2-deoxy-cytidine (DAC), and 5AC has been shown to extend the life expectancy of patients by 9 to 10 months.⁸

With the increasing use of mutation analysis and other molecular tools,^{9,10} we expect that we will soon categorize patients on the basis of parameters other than those used currently (cytogenetics, myeloblast count, peripheral blood cells counts/transfusion need) in regards to both their prognosis and their likelihood of responding to a given treatment. It has been suggested, for example, that patients with a mutation in the TET2 gene may have a better chance of responding to 5AC, whereas patients with a mutation in the DNMT3A gene may be more likely to respond to DAC.¹¹ However, there is no evidence that any of the currently approved drugs will cure MDS, and while prolonged responses of several years are observed, they are rare.^{8,12} A recent meta analysis suggested that patients in whom 5AC is discontinued because of a lack of response or because of disease progression, have a median survival of about 5 months.¹³ Data from the same analysis suggested that the most encouraging subsequent results in those patients were achieved with allogeneic hematopoietic cell transplantation (HCT).

2. General Considerations

High dose chemotherapy cures only a rare patient with MDS,¹⁴ and allogeneic HCT is currently the only therapeutic modality with proven curative potential.¹⁵⁻²⁰ Why, then, do we not transplant *all patients* with MDS? Firstly, patients with low-risk MDS, defined by the FAB, IPSS, WPSS (see below) or other criteria, may have life expectancies of a decade or more with minimal support or even without therapy. Therefore, selection based on disease and patient characteristics, including patient age, is essential. Since the median age at diagnosis is in the 8th decade of life, other medical conditions are frequent, and the biologic reserve of the human body has declined substantially.

Secondly, HCT is associated with several risks including treatment-related toxicity, relapse of MDS, and graft-versus-host disease (GVHD), and it is difficult to separate those aspects completely since conditioning intensity is associated with GVHD severity, and both affect the probability of relapse. Intensive research has led to progressive changes of conditioning regimens, such that day-100 mortality (a widely used landmark in HCT) is now less than 10% and in many reports less than 5%.^{21,22} The reduction in conditioning intensity combined with pre- and post-transplant administration of various chemotherapeutic agents has markedly reduced the toxic effects that were so characteristic of “classical”, high-dose HCT protocols. Post-HCT relapse, most significantly impacted by cytogenetic abnormalities, appears to be more frequent with low/reduced intensity conditioning (RIC) regimens, and tends to be lower in patients with GVHD, primarily in its chronic form.²³ However, high risk cytogenetic abnormalities have remained a barrier to long-term disease control, even after high intensity conditioning regimens.

Although the field of allogeneic HCT is rapidly evolving, several questions remain to be answered: How intensive does a conditioning 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 (i.e. the risk of relapse)? Is it beneficial to give pre-HCT “debulking” therapy? Is there a place for post-HCT adjuvant or preemptive therapy?

In general, the emphasis in allogeneic HCT has shifted from high-dose therapy, aimed at maximum tumor cell kill, to low or RIC, relying heavily on donor cell-mediated immune effects (graft versus tumor [GVT] effects) to eradicate the disease.²⁴⁻²⁶ This GVT effect, mediated by donor-derived cytotoxic T-cells and NK cells, eliminates residual cells of the patient’s disease via recognition of minor histocompatibility antigens or tumor-associated antigens. Separation of GVHD from GVT effects in human patients has been the focus of research for decades, but remains a challenge.

3. For Whom? Disease- and patient-associated risk factors

Many classification schemes assessing MDS disease stage and prognosis have been proposed. The field is in flux, and new insights from molecular studies are expected to lead to major changes in scoring systems used for risk stratification.

At present, the *International Prognostic Scoring System (IPSS)*,²⁷ is used widely to assess patient prognosis and has also been a reliable prognosticator to predict the success of allogeneic HCT. The higher the initial IPSS score (based on marrow blast percentage, karyotype, and the number of blood cytopenias at presentation), the lower the relapse-free survival (RFS).^{28,29,29} The more recently developed *WHO Prognostic Scoring System (WPSS)*³⁰ includes the WHO classification, karyotype, and transfusion dependence (which is to be replaced by hemoglobin levels). In contrast to the IPSS, it allows for real-time assessment of prognosis. Recent studies have validated its relevance for outcomes after allogeneic HCT.³¹ The median life expectancy (in non-transplanted patients) ranges from 11–12 years for the WPSS very low risk group to about half a year for the very high risk group.³² When categorizing patients in the new *5-group cytogenetic classification*, median survival ranges from about 5 years for the very good risk group to about 5 months for the very poor risk group.³³ This 5-group cytogenetic classification will be an integral part of the revised IPSS (IPSS-R), which will also generate new categories based on more narrowly defined blast proportions, and a lower critical neutrophil value of $< 0.8 \times 10^9/L$.³⁴ Patients with lower risk MDS tend to have a more indolent, yet still progressive course. In fact, the presence of severe neutropenia or thrombocytopenia may be an indication for HCT, particularly in younger individuals even with a low IPSS score since none of the non-HCT therapies have been shown to be curative (see above). Red blood cell transfusion dependence should also be considered in this context. Since iron overload is thought to negatively impact HCT outcome,³⁵⁻³⁹ it might be preferable to transplant transfusion-dependent patients, who by other criteria are considered good risk, earlier. Transfusion dependence is also linked to marrow fibrosis, which is associated with more rapid progression of MDS,⁴⁰ and we showed recently that MDS patients with marrow fibrosis who are transplanted at a more advanced disease stage have an inferior outcome compared to patients without fibrosis.⁴¹ Whether chelation therapy of iron overload improves outcome after HCT,^{40,42} has yet to be determined.

The presence of immunophenotypic aberrancies of MDS marrow cells as determined by flow cytometry has also been shown to have prognostic relevance^{43,44} and will negatively impact post-HCT RFS.⁴³⁻⁴⁶ Even among patients with less than 5% marrow myeloblasts, those with an aberrant phenotype had a significantly higher relapse probability,⁴⁵ an interesting observation in view of the fact that the IPSS-R also proposes a subdivision of patients with less than 5% myeloblasts.³⁴ In addition, gene expression profiling appears to predict the risk of progression of MDS to AML.⁴⁷

A Simplified MDS Risk Score⁴⁸ 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 de novo MDS and secondary MDS.^{49,50} The value of this system lies in the fact that it incorporates performance status, which, in turn, is likely to reflect patient comorbid conditions. Its possible relevance in the context of HCT remains to be determined.

The decision to proceed to HCT is easier in patients with advanced/high risk disease who “have little or nothing to lose”. Therefore, patients with RAEB-1 or RAEB-2 (i.e. more than 4% or 9% of marrow myeloblasts), patients in WPSS categories intermediate, high and very high risk, and patients in the intermediate, poor or very poor cytogenetic risk categories (by 5-group classification) should definitely be considered for HCT, always assuming they are “fit” candidates,⁵¹ and a suitable donor is available. Patients with therapy-related MDS should also be offered transplantation as it has been shown that, once adjusted for the patient’s karyotype, the probability of transplant success is similar to that in patients with de novo MDS.^{52,53}

The development of various indices to evaluate pre-existing comorbid conditions, such as the HCT-specific comorbidity index (HCT-CI)⁵⁴ and the index generated by Parimon et al. which is based primarily on pulmonary function,⁵⁵ allow for pre-HCT risk assessment and should be part of the evaluation. Patients with HCT-CI scores of 3 or higher (e.g. having had a prior solid tumor, with diabetes or cardiac problems) may have a probability of 30%-40% of dying from treatment-related complications. Co-morbidities become more prevalent with age, which has long been considered a contraindication to allogeneic HCT.⁵⁶ It is important, therefore, to emphasize that co-morbid conditions rather than chronologic age are the major determinants of inferior HCT outcome in older individuals, and the development of low/RIC regimens along with modern supportive care has allowed patients in their 60s and even 70s to undergo successful allogeneic HCT. The current consensus is that the HCT-CI predicts toxicities, NRM and overall survival after RIC HCT better than does the Karnofsky Performance Score (KPS).^{57,58}

4. When? Timing of transplantation

Determining the optimal time of HCT for MDS has proven difficult, even though 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, the major determining parameters being karyotype and myeloblast count.^{19,31} For patients with HLA-identical sibling donors who were prepared for HCT with high intensity conditioning regimens, the results of a Markov analysis 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.⁵⁹ Figure 1 summarizes results on the impact of pre-HCT IPSS risk on post-HCT outcome in patients transplanted from HLA-matched related or unrelated donors. Similar results have been reported for the impact of WPSS.³¹

A similar analysis involving older patients conditioned with RIC regimens is currently ongoing. Preliminary data suggest that older patients with low or intermediate-1 risk are unlikely to derive benefit from HCT, while patients in the intermediate-2 and high risk groups do, although the benefit became significant only years after HCT.⁶⁰ Nevertheless, it is appropriate to advise patients, particularly those in the lower risk categories, with severe thrombocytopenia or neutropenia that they may be at considerable risk of fatal complications, even though their disease may carry a low score (see above :“For Whom?”).

An additional challenge has arisen with the availability of hypomethylating agents and lenalidomide. A proportion of patients with MDS will respond to such therapy, even achieve complete remissions, and, as discussed above, may gain 9 to 10 months in life expectancy through these non-transplant therapies. Typically, patients who respond and are doing well on such therapy are reluctant to change treatment and engage in more aggressive therapy such as HCT, which, even under the best of circumstances, offers RFS in only about 75% of cases. However, Prebet et al recently showed that patients with high risk MDS in whom treatment with 5AC was discontinued for various reasons had a median survival of only 5.6 months; and while allogeneic HCT was the only strategy which held promise, even with HCT the median survival was only 17 months among patients in whom 5AC was discontinued because of progressive disease. On the other hand, it was encouraging, that the median survival was not reached in patients transplanted with stable disease at the time when 5AC was stopped.¹³ These data strongly suggest that patients who are transplant candidates should consider HCT while still responding to hypomethylating therapy. Treatment with hypomethylating agents may be useful as “bridging” to HCT, for example for patients with a protracted donor search.⁶¹

Whether pre-HCT “debulking” therapy will improve HCT outcome has never been addressed in a prospective trial. In a recent retrospective analysis, overall survival, RFS, and cumulative incidence of relapse at 1 year were 47%, 41%, and 20% , respectively, for patients with MDS receiving 5AC, compared to 60%, 51%, and 32% for patients who were not treated;⁶² however, the decision whether to treat with 5AC was likely biased towards higher-risk patients. In a small study including 17 patients with MDS, treatment with DAC did not negatively affect toxicity after HCT and suggested that disease downstaging might improve HCT outcomes.⁶³ However, the currently available data are not conclusive.

Obviously, several questions await answers: Can we identify early after diagnosis patients with MDS who are likely to progress rapidly? Among patients with high risk disease, can we improve the probability of HCT success by downstaging them into lower risk categories by pre-HCT “debulking” therapy ? If pre-HCT therapy is given, what should it be? Should pre-HCT therapy be the same for all patients? Can we develop HCT strategies such that risk factors recognized in the non-transplant setting do not carry over into HCT and post-HCT success?

5. How? The strategy to optimal outcome

5.1. Conditioning regimens

The ideal regimen would have no associated toxicity and prevent relapse in all patients. This goal has fueled considerable research into the optimization of conditioning regimens. A broad spectrum of regimens has been developed, ranging from low-dose TBI (2 Gy) to regimens that combine one or two chemotherapy agents with high-dose TBI (e.g. 12 Gy).^{24,51,64,65} As anticipated, the extent of toxicity correlates with conditioning intensity, and while RIC regimens are associated with minimal toxicity, they carry a higher risk of relapse than high-intensity regimens.⁶⁶ A major advantage of RIC is the possibility of applying HCT to older patients, who are unlikely to tolerate high dose therapy, and, indeed, patients in the 8th decade of life have been transplanted successfully.^{66,66-68} The availability of a broad range of regimens, approaching “custom tailored” HCT , has been instrumental in reducing transplantation-related mortality.^{16,69,70}

Currently, patients more than 60 or 65 years of age and patients of younger age with significant comorbid conditions are typically offered allogeneic HCT using RIC regimens. The potentially higher incidence of relapse is counterbalanced by lower regimen-related toxicity and non-relapse mortality (NRM).⁷¹⁻⁷⁴ However, caution is advised when analyzing

retrospective studies since selection of patients is subject to considerable bias.^{72,75-77} The current Clinical Trials Network-sponsored phase III trial comparing toxicity and efficacy of high intensity and reduced intensity regimens, currently underway in the USA [CTN # 0901], is the first randomized prospective trial to directly compare regimens of different intensity. While only a few regimens are being studied in this protocol, results should provide guidance for the design of additional trials.

As stated earlier, post-HCT relapse has remained a challenge, particularly in patients with high risk disease, especially those with poor risk cytogenetics and increased myeloblast counts.^{74,78,79} Intensification of the conditioning regimens has shown some effect on decreasing post-HCT relapse, but has also been associated with increased toxicity and NRM.^{80,81} Laport et al. observed little, if any, toxicity with a regimen composed of Flu ($3 \times 30 \text{ mg/m}^2$) and 2 Gy of TBI, but reported a cumulative incidence of relapse of more than 50% at 3 years.²⁵ De Lima et al. used a regimen of Flu + melphalan and noted a relapse incidence of less than 25% at 3 years, but a NRM of 40%.^{15,81}

Encouraging results have been reported recently with regimens including treosulfan.^{82,83} In a trial conducted at our Center we prepared 60 patients (primarily with MDS or AML) with a regimen consisting of Fludarabine ($30 \text{ mg/m}^2 \times 5$) and treosulfan (12 g or $14 \text{ g/m}^2 \times 3$) for HCT from HLA-matched related or unrelated donors.²² NRM by 1 year was less than 10%, and survival for patients with standard or intermediate risk karyotypes was 80%. Patients with high risk karyotype, in contrast, showed long-term relapse-free survival of 35%-40%, the difference being due primarily to a higher relapse incidence. In a successor protocol we added 2 Gy of TBI to Flu and treosulfan in an attempt to improve survival for patients with high risk cytogenetics. This trial is still ongoing, but results to date suggest that, indeed, the relapse rate will be lower than observed without TBI. However, in comparison to the Flu plus treosulfan regimen, the frequency of toxicity was increased (primarily skin rashes and mucositis), although manifestations were not severe (B.Gyurkocza et al., unpublished).

5.2. Pre-HCT therapy

One strategy to improve outcome by reducing the incidence of relapse has been pre-HCT “debulking”, generally in patients with high marrow myeloblast counts, i.e. more than 5%–10%.^{62,73,74,84-88} 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 have poorer outcome than do untreated patients. (see also “When?”, above) The depth of response to pre-HCT therapy may well impact post-HCT outcome,⁸⁹ but no controlled studies are available.

The availability of the hypomethylating agents 5AC and decitabine, offers an attractive alternative to classical induction chemotherapy.⁸⁸ Many patients who come to HCT in 2012 have been exposed to such therapy. As discussed already, clinical information suggests that patients receiving hypomethylating therapy who are candidates for HCT can expect the best results from HCT when transplanted at the time of best response.

5.3. Donor Selection and stem cell source

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. Donor availability has been a limiting factor in the past. The development of unrelated donor registries, cord blood banks and, most recently, the use of related HLA-haploidentical donors, allows to identify donors for almost every patient.

More than 14 million volunteer donors are now listed in the various registries (“World Book”), and HLA-matched unrelated donors can be identified for about 50–60% of Caucasians. This proportion is lower for other ethnic groups.^{90,90,91} HCT from unrelated donors HLA-matched with patients by high resolution typing yield comparable results to those with HLA genotypically identical siblings, although the incidence of GVHD tends to be somewhat higher. Cord blood cells or cells from HLA-haploidentical related donors offer alternatives.^{92,92-95} In fact, transplants from parents, children, or other family members who are matched for one of the patient’s two HLA haplotypes (inherited from mother and father, respectively) are remarkably well tolerated.^{96,97}

Cord blood-derived hematopoietic cells have the advantage of “immaturity” allowing for transplantation of HLA-mismatched cells without a substantial increase in GVHD incidence. While a major drawback is the limited number of cells,⁹⁸ this limitation can at least in part be overcome by the use of two cord blood units or in vitro “expansion” of one cord blood unit before infusion.⁹⁹⁻¹⁰² Cord blood cells may have the benefit of a more potent GVL effect.

Our preferred donor for allogeneic HCT remains an HLA-identical sibling. If no suitably matched siblings are available, we search for HLA-matched unrelated donors. Results with unrelated donors who are HLA-matched by high resolution typing are comparable to those obtained with HLA genotypically identical siblings.¹⁹ The use of cord blood represents an additional option, although only limited data in patients with MDS are available.¹⁰³⁻¹⁰⁵ Finally, based on initial results reported from Perugia and from Johns Hopkins University, HLA-haploidentical transplants can be carried out successfully in many patients.¹⁰⁶ Since, in general, RIC regimens are used for conditioning in this setting, intensive pre-HCT therapy is desirable, not only because of concerns about disease eradication, but also to minimize the risk of graft rejection.^{92,94,96,97}

Hematopoietic stem cells aspirated directly from the marrow and granulocyte colony stimulating factor (G-CSF) mobilized peripheral blood progenitor cells (PBPC) are currently being used side by side. The two cell populations show different characteristics, in regards to kinetics of engraftment, GVHD, and GVT effects.²⁶ PBPC provide a more potent GVT effect and are therefore used preferentially in patients with advanced/high risk disease; however, they also carry a higher risk of GVHD, particularly in its chronic form.¹⁰⁷⁻¹¹⁰ Nevertheless, it has been¹⁹ suggested that PBPC use is associated with a better quality of life, despite the presence of chronic GVHD.¹¹¹ A recently concluded prospective trial comparing PBPC with BM in unrelated HCT recipients (BMT Clinical Trials Network protocol 0201) showed no significant difference in overall survival when marrow vs. PBPC was used as graft source, but PBPC were associated with a higher incidence of chronic GVHD.¹⁰⁸ Despite these findings, patients conditioned with RIC regimens almost always receive PBPC because of higher rates of graft failure with marrow.

6. What can patients expect from HCT?

Currently achievable results with RIC and high dose conditioning regimens have been summarized in several recent reviews.^{73,85,112-114}

Warlick et al. analyzed outcome in 84 patients, 18–69 years of age, at any stage of MDS, conditioned with various regimens and transplanted over an interval of 12 years,⁷⁴ showed a 1 (5)-year overall survival of 48% (31%), a relapse incidence of 23% (25%), and RFS of 38% (29%). The cumulative incidences of acute (grades II-IV) and chronic GVHD were 43%, and 15%, respectively. Neither stem cell source, nor conditioning regimen had a significant impact on outcome. For patients with 5% myeloblasts the incidence of relapse

was 35% . Among patients with < 5% myeloblasts the relapse incidence was 9% with high intensity, and 31% with RIC regimens. However, no significant difference was observed among patients with higher myeloblast counts, the reason possibly being treatment administered before HCT with the objective of “debulking” the tumor burden.

Data on 374 patients with < 5% myeloblasts who were transplanted from HLA-matched donors after various conditioning regimens were reported by the European Bone Marrow Transplant group.¹⁶ The probabilities of 4 year RFS, relapse incidence and deaths unrelated to relapse were 48%, 15% and 37%, respectively. The hazard ratio (HR) of relapse after RIC was 2.8 relative to high intensity conditioning, but survival did not differ significantly. The relapse risk was lower (HR 0.6), while NRM was higher (HR 1.4) among patients transplanted from unrelated donors, resulting in similar overall survival. T-cell depletion of the transplanted cells resulted in higher NRM. Younger patients and patients transplanted within 12 months of diagnosis had superior outcome.

Martino et al.⁷² compared results in 215 patients with MDS conditioned with RIC and 621 patients conditioned with high intensity conditioning regimens and transplanted from HLA-identical siblings. The 3-year NRM was 32% vs. 22%, overall survival 45% vs. 41%, and RFS 41% vs. 33% for the high intensity and the RIC cohorts, respectively. Acute (chronic) GVHD developed in 58% and 43% (52% and 45%) of patients, respectively. Not being in remission before HCT ($p=0.001$), having poor-risk cytogenetics ($p=0.03$), as well as transformation to AML and older age were risk factors for inferior RFS.

A report by Lim et al.¹¹⁵ presented data on 1,330 patients with MDS, older than 50 years, including 449 patients who were older than 60 years, transplanted from HLA-matched siblings or from unrelated donors. RIC conditioning was used in 833 (62%) and high intensity regimens in 500 patients (38%). The 4-year overall survival was 31%. Advanced disease stage ($p<0.05$) and RIC conditioning ($p<0.01$) were associated with increased relapse risk. Advanced disease stage ($p=0.01$) and the use of unrelated donors ($p=0.03$) were associated with increased non-relapse mortality. Patient age and conditioning did not significantly affect overall outcome.

Several investigators have presented encouraging results with conditioning regimens that incorporated treosulfan.^{82,83} We showed that a combination of fludarabine and treosulfan resulted in NRM of less than 10% at 1 year,²² and among patients with AML or MDS without high risk cytogenetics, the 2 year RFS was greater than 80% (Figure 2). Preliminary data from an ongoing trial suggest that the addition of 2Gy of TBI may reduce the risk of relapse even in patients with high risk cytogenetics.

We recently analyzed results in patients with MDS who underwent allogeneic HCT at our Center to determine the impact of the recently established 5-group cytogenetic classification of MDS as well as monosomal karyotype on outcome after HCT.⁷⁸ The study included data on 1007 patients, 1–75 (median 45) years of age, transplanted from related ($n=547$) or unrelated ($n=460$) donors. Various intensity conditioning regimens were used, and marrow, peripheral blood or cord blood served as sources of stem cells. Both IPSS and 5-group cytogenetic risk classifications were significantly associated with post-HCT relapse and mortality, but the 5-group classification discriminated more clearly among the lowest and highest risk patients. While at 5 years RFS was 40%–45% in patients with good/very good risk cytogenetics, it was less than 10% in patients with very poor risk karyotype. The corresponding figures for relapse were 15%–20% and greater than 50%, respectively. In addition, the pathologic disease category (by FAB or WHO criteria) correlated with both relapse and mortality. Mortality increased with increasing patient age and with HLA non-

identical donors, and showed some dependence upon the conditioning regimen. Mortality declined significantly in recent years.

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PRACTICE POINTS

- Considerable progress has been made with allogeneic HCT in patients with MDS. Regimen-related toxicity has been reduced substantially with the development of a spectrum of different intensity conditioning regimens.
- However, post-HCT relapse and GVHD remain major issues. Therefore, any patient who is being counseled regarding HCT for MDS must be fully informed that HCT offers the potential, but does not guarantee the cure.
- GVHD occurs in at least half of all patients. It can be fatal, particularly with severe gut manifestations, and patients with chronic GVHD may require immunosuppressive therapy for years.
- Chronic GVHD can severely impact quality of life, and in particular, older individuals tend to tolerate treatment (with steroids) poorly.
- An overall treatment plan including the possibility of HCT should be developed early after diagnosis since prolonged or non-effective non-transplant therapy may negatively impact post-HCT outcome.
- Transplant results with fully HLA-matched unrelated donors are comparable to those with HLA genotypically HLA-identical sibling donors.
- Older patients can be transplanted successfully, but other medical conditions have a negative effect on transplant outcome. Biologic age appears to be more important than chronologic age.

RESEARCH AGENDA

Efforts must be directed at further reducing GVHD and non-relapse mortality in all patients, and regimens must be developed that can overcome the barrier of high risk cytogenetics. Information on somatic mutations that may affect the course of MDS and the probability of responding to therapy must be incorporated into treatment planning. Research must be directed at identifying molecular pathways that can serve as targets for novel therapeutic interventions before or after HCT. The role of hypomethylating agents both before and after HCT must be further defined. Immunotherapeutic strategies deserve to be explored in MDS.

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Figure 1. Impact of IPSS risk category on transplant outcome

A) Probability of RFS, B) Probability of relapse. All patients were conditioned with a busulfan/cyclophosphamide regimen and transplanted with marrow or PBPCs from siblings or unrelated donors. This research was originally published in *Blood*. Deeg HJ, Storer B, Slattery JT, Anasetti C, Doney KC, Hansen JA, Kiem H-P, Martin PJ, Petersdorf E, Radich JP, Sanders JE, Shulman HM, Warren EH, Witherspoon RP, Bryant EM, Chauncey TR, Getzendaner L, Storb R, Appelbaum FR. Conditioning with targeted busulfan and cyclophosphamide for hemopoietic stem cell transplantation from related and unrelated donors in patients with myelodysplastic syndrome. *Blood* 2002; 100: 1201-1207. © the American Society of Hematology

Figure 2. 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 hematopoietic cell transplantation for high-risk hematologic malignancies. E.R. Nemecek, K.A. Guthrie, M.L. Sorrow, B.L. Wood, K.C. Doney, R.A. Hilger, B.L. Scott, T.J. Kovacsovics, R.T. Maziarz, A.E. Woolfrey, A. Bedelov, J.E. Sanders, J.M. Pagel, E.J. Sickel, R. Witherspoon, M.E. Flowers, F.R. Appelbaum, H. Joachim Deeg, *Biology of Blood and Marrow Transplantation* 2011; 17:341-350. © 2011, with permission from Elsevier.