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Transplantation for Myelodysplastic Syndromes 2013

Jennifer E. Vaughn, Bart L. Scott, and H. Joachim Deeg

Clinical Research Division, Fred Hutchinson Cancer Research Center, and the University of Washington School of Medicine, Seattle, WA.

Abstract

Purpose of the review—The only current treatment capable of curing patients with myelodysplastic syndromes (MDS) is allogeneic hematopoietic stem cell transplant (HCT). However, many MDS patients are older, often with substantial co-morbid conditions, and the disease is heterogeneous. As a consequence, results of HCT vary considerably, and the practices of HCT for MDS are evolving.

Recent findings—The newly published modified International Prognostic Scoring System (IPSS-R), developed for non-transplanted patients, also correlates with post-HCT outcome, with the patient's karyotype having the strongest impact. The presence of monosomal karyotype and various genetic and molecular markers have also been shown to have prognostic value. The use of hypomethylating agents, before or after HCT, may reduce the post-HCT relapse risk or delay relapse. Low and reduced-intensity conditioning regimens have allowed transplant for growing numbers of older patients with MDS, and the development of novel regimens may lead to improved relapse-free survival even in patients with high-risk cytogenetics. The optimal stem cell source may differ for different patient populations and different disease risk categories.

Summary—Transplant results for MDS have improved in recent years. Some patients even in the 8th decade of life have been transplanted successfully. Ongoing studies are aimed at further reducing transplant-related toxicity, graft-versus-host disease and post-HCT relapse.

Keywords

Myelodysplastic syndromes; allogeneic hematopoietic cell transplantation; cytogenetics; conditioning regimens; relapse; hypomethylating agents

INTRODUCTION

The ideal treatment of the myelodysplastic syndromes (MDS) remains elusive. Despite significant advances in our ability to characterize the molecular and genetic abnormalities underlying the pathophysiology of MDS, the only current treatment shown to be curative in a large proportion of patients is allogeneic hematopoietic stem cell transplant (HCT). The past two decades have seen significant improvements in both the efficacy and safety of HCT [1], but treatment-related morbidity and mortality [1], as well as disease relapse still pose significant risks to patients.

Multiple efforts, for example in the form of decision analyses, are directed at facilitating the selection of patients for HCT, with the goal of improving post-HCT survival. The

Corresponding author: H. Joachim Deeg, MD, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, D1-100, Seattle, WA, 98109, jdeeg@fhcrc.org.

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implications of pre-transplant disease burden, conditioning regimens, optimal donor selection and stem cell source, and prevention of graft-versus-host disease (GVHD) and post-HCT relapse remain areas of investigation.

DETERMINING THE NEED FOR TRANSPLANTATION

A significant aid in identifying patients who will benefit from HCT was the International Prognostic Scoring System (IPSS) [2] which classifies patients as “low”, “intermediate 1 or 2” and “high” risk for disease progression and disease-related mortality, based on clinical (number of cytopenias), morphologic (number of bone marrow myeloblasts), and cytogenetic characteristics. Patients receiving scores that place them in the intermediate-2 or high-risk categories are generally considered for earlier HCT. Recently, the IPSS has undergone revisions (IPSS-R) that take into consideration different subgroups of cytogenetic abnormalities and the depth of cytopenias, leading to the expansion of risk categories into five groups: “very good”, “good”, “intermediate”, “poor” and “very poor” risk [3**].

While the IPSS and the WHO Prognostic Scoring System (WPSS) remain major validated prognostic models in patients undergoing HCT, recent revisions (5-group classification in IPSS-R, incorporation of hemoglobin values, and consideration of marrow fibrosis in WPSS) reflect our growing ability to identify and understand the contributions of diverse disease characteristics to disease progression and outcome [4, 5*]. Another factor may be the impact of a monosomal karyotype (MK) on prognosis [5*]. MK, defined as the presence of 2 autosomal monosomies or a single monosomy in the presence of additional structural abnormalities [6], is now a well-defined determinant of poor prognosis in acute myeloid leukemia (AML). Patneik et al. showed, similarly, lower overall survival and a trend toward lower relapse-free survival among MDS patients with MK as compared to patients with an otherwise complex karyotype (and therefore very high-risk disease) but without MK [7]. A study by Belli et al. suggested that the prognosis of patients with MK is similar to that of patients with an IPSS-R classification of “poor” but that patients falling into the “very poor” group do worse [8]. We recently evaluated the ability of the five-group cytogenetic risk classification [9**] and the monosomal karyotype to predict post-transplant outcome in patients with MDS and AML evolving from MDS. Results indicate that a “very poor” cytogenetic risk (Fig.1) or a MK prior to HCT was associated with significantly increased overall mortality after HCT. There was also a trend toward a higher relapse incidence with MK, although the difference was not statistically significant [5*]. Not unexpectedly, the presence of a MK is highly correlated with very poor risk cytogenetics [5*,10]. Valcarcel et al. showed that in the non-transplant setting the poor prognostic effect of the MK was not independent of the effect contributed by 3 cytogenetic abnormalities or, in general, “complex” cytogenetics [10]. The MK may represent a predilection toward greater cytogenetic disarray and, therefore, a more advanced or aggressive disease state.

Current molecular techniques have rendered genetic aberrations readily detectable. Bejar and colleagues utilized next generation sequencing and mass spectrometry to identify relevant mutations in 439 MDS patients. In particular, mutations of TP53, EZH2, ETV6 and ASXL1 were found to be significantly associated with more rapid disease progression and increased risk of mortality [11]. These investigators also addressed the effect of molecular lesions on prognosis while concurrently validating the “low risk” prognostic scoring system (LR-PSS) originally proposed by the MD Anderson team in 2010 [12]. They examined the prognostic value of the above-mentioned mutations, as well as DNMT3A [13] and the splicing factor genes SF3B1, SRSF2 and U2AF1 [14–16*]. Mutations involving TP53, ASXL1 and EZH2 were associated with poor prognosis; however, only the EZH2 gene mutation retained prognostic significance (HR for death 2.90; 95% CI 1.85–4.52) when the LR-PSS was incorporated into a multivariate model [17**].

Thus, recent classification systems and the identification of genetic mutations are identifying patients with “high-risk” MDS who should be considered for HCT early in the disease course. However, it is less clear to what extent HCT is able to overcome the poor prognosis of those patients.

IMPLICATIONS AND MANAGEMENT OF DISEASE BURDEN PRIOR TO HCT

Patients with a high myeloblast burden at the time of HCT are at an increased risk of post-HCT relapse [18, 19], suggesting that delaying HCT and allowing for a progressive increase in myeloblasts, i.e. disease progression, may be detrimental. At the same time, however, the substantial risk of transplant-related morbidity and mortality must be considered [20, 21]. Historically, the prevalent strategy has been to reduce pre-HCT disease burden by induction chemotherapy, which, when effective in achieving a remission, has been associated with reduced post-HCT relapse [22, 23]. However, induction chemotherapy may have significant side effects, and may delay or even preclude HCT [24].

As an alternative to induction chemotherapy, the hypomethylating agents azacitidine and decitabine have been used pre-HCT. In a small retrospective study at our center, adjusting for additional risk factors including IPSS score and cytogenetic risk, patients treated with azacitidine prior to HCT had similar overall survival (HR 0.87; 95% CI 0.44–1.69), non-relapse mortality (HR 1.06; 95% CI 0.45–2.54), rates of relapse (HR 0.43; 95% CI 0.15–1.2) and relapse-free survival (HR 0.72; 95% CI 0.38–1.38), as did MDS patients given classic induction chemotherapy [25*]. Another retrospective analysis by the Groupe-Francophone des Myelodysplasies reviewed the outcomes of 163 patients who received cytoreductive therapy prior to HCT. The incidence of 3-year overall survival among patients treated with azacitidine, induction chemotherapy or a combination of azacitidine and chemotherapy was 40%, 37% and 36%, respectively. Again, there were no significant differences in overall survival, non-relapse mortality or relapse [26*]. There are no published randomized prospective studies assessing the benefit of hypomethylating agents versus chemotherapy for disease debulking prior to HCT, and the optimal approach is unknown. However, better tolerability, lower cost, and the suggestion of equivalent efficacy of hypomethylating agents certainly contributes to their appeal. A randomized trial is underway at our Center.

INNOVATIONS IN THE PRACTICE OF TRANSPLANTATION

MDS patients are unique among other HCT patients in that their median age at disease presentation is in the 8th decade of life. The development of the Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI) has allowed us to select more clinically fit individuals who will tolerate HCT despite their advanced age [27]. Additionally, the advent of low-intensity (often referred to as non-myeloablative) and reduced-intensity conditioning (RIC) regimens has permitted to offer allogeneic HCT to increasingly older patients. These regimens are associated with reduced toxicity and rely heavily on the allogeneic graft-versus-tumor effect by donor cells for disease eradication [28]. A retrospective series analyzing HCT outcomes in patients with MDS (including transformation to AML) at the FHCRC failed to show significant differences in 3-year overall survival (27% versus 48%, $p=0.56$) and progression-free survival (28% versus 44%, $p=0.60$) between “myeloablative” (high-dose) conditioning and RIC [29]. Currently, a multicenter randomized clinical trial comparing high-dose conditioning with RIC is underway in the US (BMT-CTN trial 0901).

The selection of regimen intensity is challenging. Martino et al. reported a retrospective analysis of the European Bone Marrow Transplantation (EBMT) group data on patients with MDS and AML with low disease burden (blasts < 10%) who were treated with a spectrum of regimens. Patients treated with low intensity regimens experienced lower non-relapse

mortality (NRM) prior to day 100 than those treated with RIC or high dose regimens (HR 0.21; $p < 0.01$). However, treatment with a low dose regimen also led to a significantly increased risk of relapse in the first 12 months (HR 3.9; $p < 0.01$) and inferior progression-free and overall survival in the reported 7-year follow-up (OS probability for those treated with low-intensity regimens was 29% versus 53%, 56% and 51% for those treated with intermediate RIC, conventional and high-dose myeloablative regimens, respectively $p < 0.01$) [30]. These results echoed previous data presented by the Center for International Bone Marrow Transplantation Research (CIBMTR) registry in which low intensity regimens were shown to be inferior with regards to relapse-free (HR for relapse 1.73, $p < 0.001$) and overall survival (HR for mortality 1.20, $p = 0.006$) [31*]. Recent modifications of higher intensity regimens using, for example, a combination of i.v. treosulfan and fludarabine have resulted in minimal NRM (5% at day 100 and 8% at 2 years), and a 2-year relapse-free survival of 58% in patients with AML, ALL and MDS; survival was 80% in patients who did not have high risk cytogenetics [32] (Fig. 2).

Outcomes of HCT are also influenced by donor selection. Despite multiple studies that have shown equivalent results using HLA-matched related (MRD) and unrelated donors (URD) [33–35], there is no complete agreement. Ho et al. recently presented results showing superiority of matched unrelated donors in reducing relapse rates and improving progression-free survival with a trend toward improvement in overall survival (56% for URD versus 50% for MRD) after RIC. Rates of acute (20% vs. 16%) and 2-year chronic (55% vs. 50%) GVHD were slightly higher in the matched unrelated cohort, but not significantly so. Sixty-four of the 433 patients had MDS [36]. A study by the CIBMTR [37] showed that while MDS patients transplanted from donors matched for 8/8 HLA loci had similar probabilities of survival at 3 years (47% for MRD versus 38% for matched URD), patients who were allele-level matched at 7 of 8 HLA loci fared significantly worse (31%) [37].

Among older patients, there has been some concern about the use of HLA-matched sibling donors, generally close in age to the patient, because of age-related health issues. Yet, data by Alousi, et al. suggest that in older patients with good performance status, the use of an older (age > 50 years) matched sibling donor may be superior to an unrelated younger donor (age < 50) [38*].

The use of cord blood as a stem cell source is an emerging field with promising results [39, 40]. Similarly encouraging are results with HLA-haploidentical donors [41, 42], although data in MDS are limited.

The optimal source of stem cells for allogeneic HCT is currently under debate. Recent results from a multi-center, phase III trial comparing HCT with stem cells harvested from peripheral blood (PBSC) to HCT with bone marrow cells showed that the greater graft-versus-tumor effect derived from PBSC may not translate into improved survival (2-year overall survival with PBSC was 51% versus 46% among bone marrow recipients; $p = 0.29$). In addition, PBSC conveyed a higher rate of morbidity from chronic GVHD (53% versus 41% at 2 years; $p = 0.01$) [43**]. There was no difference in risk of graft failure between the two groups. These results have led the transplant community to reconsider standard practice in selecting the stem cell source [44].

PREVENTION AND SALVAGE OF POST-HCT RELAPSE

Despite advances, post-HCT relapse remains a significant problem in patients with MDS. In patients with high-risk cytogenetics, relapse rates of 30 to 40% have been reported [45, 46]. Relapses often occur early, and patients who relapse within 100 days of HCT have a very poor prognosis [47]. The utility of hypomethylating agents as both maintenance and salvage

therapy post-HCT has recently been examined. De Lima et al. presented results of a Phase I trial which suggested that doses of 32 mg/m² of azacitidine daily for 5 days delayed relapse [48]. A Phase II trial of 5-azacitidine as salvage therapy in patients with AML, MDS and chronic myelo-monocytic leukemia (CMML) who relapsed or who were found to have minimal residual disease after HCT is underway at our Center. Preliminary results in 25 patients who relapsed within 100 days of HCT suggest improvement in overall survival compared to patients not given azacitidine (Fig. 3) [49]. The phase I RELAZA trial, reported by Platzbecker et al., enrolled patients who were felt to be at imminent risk of disease relapse after HCT as indicated by a decline in donor CD34+ chimerism below 80%. Treatment with azacitidine in those patients resulted in improved donor chimerisms in > 50% of patients and either a delay or prevention of hematologic relapse [50]. Given the available evidence, hypomethylating agents appear to be an attractive and well-tolerated means by which to improve overall survival in patients who relapse after transplantation.

Additionally, several new agents targeting molecular mutations, such as midostaurin and AC-220, are under investigation for the prevention of relapse in patients with the FLT3-ITD mutation. Donor lymphocyte infusion (DLI) following RIC in an effort to prevent disease recurrence [51, 52] or to treat patients with documented relapse [53] has also been reported. Newer cellular therapies, such as infusion of genetically modified cells, for example directed at WT-1 or donor NK cells provide interesting new approaches.

CONCLUSIONS

While our knowledge of the role of cytogenetic and molecular defects in the pathophysiology of MDS has grown exponentially, thanks to the advent of new technologies, our efforts to cure MDS still center on allogeneic HCT. Hypomethylating agents offer a bridge to or allow delay of HCT by serving as an effective and well tolerated means to reduce disease burden; however, it is not clear that they are also beneficial in patients with high risk cytogenetics. Importantly, if patients are candidates for HCT, the transplant should be carried out before the patient's disease shows progressing on hypomethylating therapy [54]. The use of RIC regimens has revolutionized the field of HCT for MDS, as many older patients can undergo HCT with little risk of severe toxicity. Methods to reduce the risk of relapse after RIC conditioning are an area of intensive research. It is likely that combinations of pre-HCT interventions, modified conditioning regimens and exploitation of post-HCT manipulations, including cellular therapy, will be necessary to further reduce the relapse incidence and improve survival.

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* of special interest

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KEY POINTS

- An improved understanding of the impact of various cytogenetic and molecular aberrations on prognosis has improved our ability for prognostication, thereby assisting in the decision making process for (or against) HCT.
- HCT is used with increasing frequency to treat patients with MDS, in part due to the development of novel conditioning regimens that allow to offer HCTs to older individuals.
- However, the selection of the optimal donor, conditioning regimen and stem cell source for patients with MDS undergoing HCT remain areas of intense investigation.
- Hypomethylating agents have shown efficacy in the treatment of MDS, allowing to use them as a bridging approach to HCT and for tumor debulking before HCT.
- Methods to prevent and treat post-HCT relapse of MDS are unsatisfactory. The use of donor lymphocyte infusion, treatment with hypomethylating agents and, possibly, novel cellular strategies, are useful in some patients.

FIGURE 1. Impact of monosomal karyotype (MK) on posttransplant relapse and overall survival (OS)

Incidence among patients with poor-risk karyotype (by 5-group classification), without or with concurrent MK. (This figure was originally published in *Blood*. H.J. Deeg, B.L. Scott, M. Fang, H.M. Shulman, B. Gyurkocza, D. Myerson, J.M. Pagel, U. Platzbecker, A. Ramakrishnan, J.P. Radich, B.M. Sandmaier, M. Sorror, D.L. Stirewalt, W.A. Wilson, R. Storb, F.R. Appelbaum, T. Gooley. Five-group cytogenetic risk classification, monosomal karyotype, and outcome after hematopoietic cell transplantation for MDS or acute leukemia evolving from MDS. *Blood*. 2012;120(7):1398–1408. © the American Society of Hematology.)

FIGURE 2. RFS by disease risk (A) and cytogenetic risk (B)

(A) Disease risk was classified using CIBMTR criteria. Low risk: ALL or AML in first remission or MDS-RA; standard risk: AML or ALL in second or greater remission; high risk: relapsed or primary refractory ALL or AML, RAEB and RAEBT. (B) Cytogenetic abnormalities were classified as favorable if t(8;21), t(15;17) or inversion 16 for AML or hyperdiploidy for ALL were present; high risk included 11q23 abnormalities, monosomy 7, monosomy 5, deletion 5q or abnormalities of 3q, t(9;22), extreme hypodiploid for ALL or complex abnormalities (≥ 3 chromosomes); intermediate risk included all other abnormalities. (This figure was originally published in *Biology of Blood and Marrow Transplantation*. E.R. Nemecek, K.A. Guthrie, M.L. Sorrow, B.L. Wood, K.C. Doney, R.A. Hilger, B.L. Scott, T.J. Kovacovics, R.T. Maziarz, A.E. Woolfrey, A. Bedalov, J.E. Sanders, J.M. Pagel, E.J. Sickel, R. Witherspoon, M.E. Flowers, F.R. Appelbaum, H.J. Deeg. Conditioning with Treosulfan and Fludarabine followed by Allogeneic Hematopoietic Cell Transplantation for High-Risk Hematologic Malignancies. *Biology of Blood and Marrow Transplantation*. 2011;17(3):341–350. © Elsevier.)

FIGURE 3. Survival curves comparing overall survival in patients treated with azacitidine at the first sign of relapse (including MRD) after allogeneic transplantation for MDS/AML as compared to historical controls [47] from our Center

Survival for the patients treated with azacitidine is calculated from the start of treatment.

Survival for historical controls is calculated from the date of relapse. **(A)** Improved OS prolonged survival for patients treated with azacitidine compared to the controls population if relapse occurred prior to day 100 (n=17). **(B)** In patients relapsing after day 200, no improvement in overall survival was seen compared to the historical population, but numbers were small (n=6).