Timing of allogeneic stem cell transplantation for myelodysplastic syndromes and aplastic anemia

Corey Cutler¹

¹Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) for myelodysplastic syndrome (MDS) is the only known curative procedure for myelodysplastic disorders (MDS) and severe aplastic anemia (SAA), which is currently the third most common indication for HSCT, as reported to the Center for International Blood and Marrow Transplantation Research.¹ MDS is a disease predominantly of older persons, and reduced-intensity conditioning (RIC) HSCT is now used routinely among persons >70 years of age. As a result, HSCT volumes for MDS continue to increase. In recent years, with the emergence of novel therapies to treat MDS, the role of HSCT has been called into question because these novel agents can improve hematologic parameters, reduce transfusion requirements, and even prolong survival.² Therefore, several analyses designed to determine the optimal timing of allogeneic HSCT for the treatment of MDS have been performed. These analyses and a discussion on the timing of HSCT for severe aplastic anemia (SAA) are reviewed here.

Transplantation for MDS: comparison with non-HSCT therapy

Retrospective reviews have often suggested that HSCT is superior to non-HSCT approaches for patients with advanced MDS who are eligible (based on age, comorbidity, and donor status) for HSCT. However, the inherent bias of these analyses makes them unreliable, and important secondary outcomes, such as quality of life, cannot be ascertained retrospectively. Nonetheless, more recent analyses have attempted to control for some of the imbalances of patient characteristics, perhaps adding some important information to the field.

Platzbecker et al compared allogeneic HSCT with DNA-hypomethylating therapy in patients 60-70 years of age in a donor versus no donor analysis using a cohort who received therapy with azacytidine after an unsuccessful donor search or no search attempt (as a departmental standard) as a control.³ In this analysis, an advantage for transplantation was evident approximately 2 years after HSCT, with a multivariate Cox regression analysis showing that HSCT was associated with a significantly better overall survival (hazard ratio = 0.3, P = .007), at times >1 year from transplantation. Interestingly, there did not appear to be a decrement in early survival in the transplantation arm, possibly dispelling the myth that early, up-front nonrelapse mortality is the price to be paid for the chance at cure with allogeneic HSCT. The broader generalizability of this retrospective review was limited by a 100% transplantation rate in the donor group, which is not likely to be possible even with early recognition of potential transplantation candidates.

More important than retrospective studies are prospective nonrandomized comparisons, of which only one has been completed to date. Robin et al presented the results of a French study in abstract format at the ASH Annual Meeting in 2013.⁴ In that study, subjects with high and intermediate-2 risk MDS [International Prognostic Scoring System (IPSS)], as well as subjects with intermediate-1 risk MDS with poor cytogenetics or thrombocytopenia were enrolled prospectively. Subjects with transformed MDS or proliferative chronic myelomonocytic leukemia were also offered participation. During their donor search, non-HSCT therapy was offered at the treating physician’s discretion. Those with a donor and ≤10% BM blasts underwent RIC transplantation; those with ≥10% blasts or no donors did not. The primary comparison was between those subjects who were eligible for HSCT (with ≤10% BM blasts) and was divided by the presence of a donor (n = 129) or no donor (n = 34). Of those with a donor, 70.5% underwent HSCT. There was an overall survival advantage for those subjects with a fully matched donor over those without a donor (P = .03); this advantage became apparent after 2.5 years of follow-up. There also appeared to be a nonstatistical advantage in the no-donor group over HSCT using a 9/10 donor, although this comparison was limited by sample size (P = .11, n = 34 no donor vs n = 16 9/10 donor).

In addition to this completed study, 2 larger prospective studies are being performed to demonstrate the relative advantage of HSCT over non-HSCT approaches. A German study will biologically assign 250 newly diagnosed MDS patients age 55-70 years with higher-risk MDS IPSS intermediate-2, high, or intermediate-1 with poor-risk cytogenetics) to HSCT or no HSCT on the basis of donor status.

Learning Objectives

- To understand the role of transplantation for myelodysplastic disorders (MDS) and severe aplastic anemia (SAA)
- To understand the appropriate timing of transplantation for MDS and SAA in the context of alternative available therapies
A Markov modeling approach to determine the optimal timing of HSCT for MDS has been previously performed.10 Using several data sources, this analysis demonstrated that, for low and intermediate-1 risk groups, the decision to delay HSCT from the time of diagnosis maximized overall survival. However, for patients with intermediate-2 and high-risk disease, immediate HSCT at the time of diagnosis was associated with a greater number of life-years than HSCT at a delayed time point. These recommendations were even stronger when the model was analyzed in a cohort of patients under the age of 40 years, and no changes to this recommended strategy occurred when quality of life considerations were factored into the decision model.

Given that the majority of patients with MDS are older, myeloablative HSCT usually cannot be used safely in this population. Generally safer than myeloablative HSCT, RIC HSCT can be safely performed in individuals well into their eighth decade of life.6 However, the role of RIC HSCT in MDS until recently has been less clear, largely because the approval of DNA-hypomethylating therapy has added options beyond supportive care for affected patients. In addition, prospective trials comparing these 2 approaches have not been performed.

We recently completed a decision analysis examining the role of RIC HSCT compared with non-HSCT therapies for older patients.7 This analysis included data from over 500 patients aged 60-70 enrolled in clinical trials and prospectively registered in MDS databases. Given the therapeutic options previously unavailable to patients with MDS, this analysis evaluated the role of best supportive care and/or erythropoiesis-stimulating agents in comparison with RIC HSCT for patients with lower-risk MDS and evaluated the role of DNA-hypomethylating therapy compared with RIC HSCT for patients with higher-risk MDS. Both traditional Markov modeling and Monte Carlo simulation techniques were used, and quality of life was factored into the decision models. This analysis, similar to the analysis for myeloablative transplantation, suggested a plateau in the HSCT survival curve associated with an overall benefit in quality-adjusted life-years with immediate transplantation for subjects with intermediate-2 and high-risk MDS, and recommended a non-HSCT approach for subjects with lower-risk disease. It should be noted that these recommendations are for groups of patients and not necessarily individuals, because outcome curves crossed to demonstrate transplant superiority in the higher-risk group only at approximately the 3-year mark.

Using a continuous-time multistate Markov model, Alessandrino et al recently compared HSCT with best supportive care alone in >1100 patients with MDS.8 In this analysis, the strategy that optimized outcomes was to proceed to HSCT at the time of MDS progression from low to intermediate-1 risk or from low to intermediate risk according to the World Health Organization Prognostic Scoring System. However, this analysis assumes that all subjects present with low-stage disease and progress in an orderly fashion through higher-risk MDS. Despite this, when faced with the decision to perform transplantation at the time of a higher-risk diagnosis, HSCT maximized overall outcomes, again with quality of life factored into the model.

Although these 2 analyses concordantly suggest HSCT as a preferred strategy for subjects with higher-risk MDS, Brand et al have argued that these decision models are fraught with incorrect statistical assumptions, most important those revolving around the unmeasured hazards of death before HSCT.9 They performed their own multistate decision model based on a much smaller cohort of subjects (N = 384, including 74 with >20% blasts at the time of diagnosis and 29 with AML at the time of HSCT). These investigators could not demonstrate an advantage to HSCT, but acknowledge that very high transplant-related mortality in their database likely contributed to this fact. Nonetheless, with 1 prospective registration trial completed and 2 trials ongoing, it remains our current practice to continue to recommend HSCT for those patients who are eligible for the procedure and who have HLA-matched, related or unrelated donors. HSCT from mismatched or alternative donors should be considered investigational given the poorer results noted in registry trials10 and should be reserved for special circumstances.
It is important to note that the Markov models published to date have all used the older IPSS scoring system. With the general acceptance of the newer IPSS-R, it is unclear at what IPSS-R score HSCT should be recommended; however, it is known that IPSS-R scores correlate with HSCT outcome. There is excellent concordance for IPSS-R high and very high score and HSCT should be recommended for these patients. The correct treatment for intermediate-risk subjects is not currently known. In addition, the evolving field of molecular prognostic factors in MDS will play a critical role in determining the appropriate use of HSCT for MDS.

**Pre-HSCT therapy**

Because most patients who present for HSCT evaluation are not newly diagnosed and do not have immediately available donors, there is often time to contemplate the role of cytoreductive therapy before HSCT. Whereas the role of HSCT in the algorithmic treatment of MDS is firmly established, the sequencing of pre-HSCT therapies, if any are in fact required, is not.

Numerous retrospective analyses have examined the impact of pre-HSCT hypomethylating agent therapy and AML induction-type chemotherapy on HSCT outcomes. Although most of these analyses demonstrate comparable baseline patient and disease characteristics, there clearly are unmeasured factors that contribute to the decision to pursue one form of therapy over another, thus biasing these studies’ results. The largest of these retrospective studies included 163 consecutive patients who underwent HSCT after azacitidine, leukemia-type induction chemotherapy, or both. In this study, there were no differences in relapse rates, nonrelapse mortality, event-free survival, or overall survival after HSCT comparing the azacitidine and induction chemotherapy groups (although the group that received both azacitidine and induction chemotherapy, presumably due to disease progression before HSCT, fared significantly worse). A similar, but smaller, study from Seattle demonstrated a slight advantage to pre-HSCT therapy with azacitidine over induction chemotherapy, potentially due to reduced toxicity. However, both of these studies lack the size of the original patient population initially considered for transplantation, the denominator, without which it is impossible to determine the role of one pre-HSCT approach versus another because patients who do not proceed to HSCT are not captured in these analyses. To determine accurately which pre-HSCT strategy is superior, registration or, more optimally, randomization at the time of pre-HSCT therapy initiation is required. Further, if this question is to be posed in a formal fashion, a no-therapy arm should be included because it is unclear whether any disease-modifying therapy is required before HSCT. In retrospective analyses, when pre-HSCT azacitidine was compared with no treatment, no benefit was noted with azacitidine; however, selection bias is very likely here as well. In the absence of prospective data, but given the acceptable toxicity and potential for cytoreduction, we recommend pre-HSCT azacitidine or decitabine therapy for patients in whom HSCT is being contemplated. We perform BM examinations after every other course of therapy and continue as long as the disease burden is diminishing. Once a donor is identified, we move toward HSCT as long as the blast count is <10%, particularly when RIC conditioning is planned. A prospective randomized trial comparing induction chemotherapy with hypomethylating therapy before transplantation is now accruing subjects (www.clinicaltrials.gov identifier NCT01812252).

In summary, allogeneic HSCT for MDS continues to be applied broadly as a curative therapy. As the population ages and as MDS becomes more prevalent, HSCT will continue to be used, even among older adults in whom HSCT was not possible <20 years ago. Determining the most appropriate of novel therapeutics before HSCT and determining the optimal, if any, timing of HSCT will remain a priority for the HSCT research community.

**Transplantation for SAA**

Allogeneic HSCT for SAA is far less controversial than HSCT for MDS. Widely agreed to be a curative procedure, HSCT for SAA is often performed urgently as close to the time of diagnosis as possible to avoid HLA-sensitization during transfusion. SAA is an uncommon condition and <200 HSCTs from HLA-matched donors (related and unrelated) using calcineurin-inhibitor based GVHD prophylaxis were reported to the Center for International Blood and Marrow Transplant Research between 2008 and 2011 (CIBMTR, personal communication). This small number of procedures makes research difficult, but makes a standard algorithm to the approach to this disease very important.

Given the long duration of immunosuppressive therapy and the high relapse rate with immune suppression discontinuation, coupled with the rapid recovery of hematopoiesis associated with allogeneic HSCT, HLA-matched, related donor HSCT is the treatment of choice for eligible patients with newly diagnosed SAA. This recommendation is based largely on anecdotal evidence of efficacy; even a recent Cochrane review was unable to demonstrate superiority of matched, related donor allogeneic HSCT over traditional immunosuppressive therapy when older nonrandomized trials were pooled. Although some degree of conditioning is required, treatment-related toxicity is low and contemporary studies report very high long-term cure rates. Results with syngeneic transplantation are even better. Unfortunately, <25% of patients presenting with SAA will have an HLA-matched related donor available for BM donation, so alternative therapies are required.

In general, immunosuppressive therapy is initiated in patients in whom a suitable HLA-matched related donor is not available and allogeneic HSCT is reserved for those who are refractory to immunosuppressive therapy. In this scenario, allogeneic HSCT has a survival advantage over further immunosuppressive therapy or supportive care alone. With improvement in HLA matching, supportive care, and general transplantation technology over the past decade, several investigators have suggested that early HSCT be offered to older individuals with HLA-matched, sibling donors. More importantly, they have posed the question of whether alternative donor allogeneic HSCT should be used earlier in the disease course for SAA. Retrospective analyses have demonstrated that, although in multivariable regression analyses, the use of an HLA-matched related donor was associated with improved outcome, in a propensity-adjusted case control series, long-term outcomes comparing HLA-matched related and unrelated donors provided the same long-term outcomes.

To continue to improve the outcomes of HSCT for SAA, investigators have undertaken 2 approaches. The first is to add the T-cell immunosuppressive agent fludarabine to conditioning regimens so that the cytotoxic agent cyclophosphamide can be reduced. The second is to search for better T-cell-depleting agents for use in the conditioning regimen. In a randomized phase 3 trial of cyclophosphamide (200 mg/kg) and anti-thymocyte globulin (ATG) versus cyclophosphamide (100 mg/kg), fludarabine, and ATG in 83 subjects, Kim et al were able to demonstrate reduced rates of regimen-related toxicity in the lower-dose cyclophosphamide arm.
without compromising engraftment of survival. At this time, the BMT CTN is completing a dose-minimization study of cyclophosphamide with fludarabine and ATG to determine how low cyclophosphamide doses can be dropped before engraftment is compromised (BMT CTN Study 0301). Early results suggest that some amount of cyclophosphamide is required in unrelated donor transplantation, because graft failure occurred in 3/3 subjects in whom this drug was omitted. However, cyclophosphamide at a dose of 150 mg/kg was associated with excess nonrelapse mortality. Others have chosen to study the use of the immunodepleting monoclonal anti-CD52 antibody alemtuzumab as a replacement for ATG preparations in allogeneic HSCT for SAA. For example, Marsh et al have demonstrated good long-term survival with low rates of chronic GVHD when alemtuzumab was used with cyclophosphamide and fludarabine.

Although non-HSCT therapies have improved somewhat for the treatment of MDS and SAA, there have been larger advances in HSCT, predominantly due to improvement in HLA-typing, the acceptance of RIC, and the supportive care of the HSCT patient. Moving forward, HLA-matched related and unrelated donor HSCT will likely become the treatment of choice for most patients with higher-risk MDS and newly diagnosed SAA.

Disclosures
Conflict-of-interest disclosure: The author declares no competing financial interests. Off-label drug use: None disclosed.

Correspondence
Corey Cutler, Associate Professor of Medicine, Harvard Medical School, Division of Hematologic Malignancies, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215. Phone: 617-632-5946; Fax: 617-632-5168; e-mail: corey_cutler@dfci.harvard.edu.

References
24. Kim H, Lee JH, Joo YD, et al. A randomized comparison of cyclophosphamide vs reduced dose cyclophosphamide plus fludarabine for allogeneic hematopoietic cell transplantation in patients with...

