Selection of Patients With Myelodysplastic Syndrome for Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative option for patients with myelodysplastic syndrome (MDS). Because MDS predominantly affects an older population, age-associated comorbidities can preclude patients from cure. HSCT is associated with the risk of morbidity and mortality; however, with safer conditioning regimens and improved supportive care, eligible patients with an appropriately matched donor can receive this therapy without exclusion by older age alone. We discuss the role of improved MDS prognostic scoring systems and molecular testing for selection for HSCT, and review the pre-HSCT tolerability assessment required for this advanced aged population.

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Introduction

Myelodysplastic syndrome (MDS) encompasses a heterogeneous spectrum of malignancies characterized by ineffective hematopoiesis and morphologic dysplasia, with a predisposition toward leukemic transformation.[1] Allogeneic hematopoietic stem cell transplantation (HSCT) is the only potentially curative therapy currently available for MDS. MDS predominantly affects older persons; thus, until recently, many patients were precluded from this curative treatment option because of age alone. However, with the development of safer transplant conditioning regimens and supportive care measures, transplantation can now be offered to a wider patient population. Thus, the HSCT volumes for MDS have increased by 3.7-fold during the past decade in the United States, and MDS is currently the second most common indication for transplantation.[2,3] Comprehensive patient evaluation for transplant tolerability remains an area of active investigation, given the potential for treatment-related complications to offset the benefits of transplantation. Furthermore, with the advent of newer models with improved prognostic capacity, the indications for transplantation need to be refined and updated.

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Transplantation for MDS: Comparison With Non-HSCT Therapy

For patients with advanced MDS who are eligible for transplantation, the superiority of HSCT compared with non-HSCT therapies has been reported in both retrospective and prospective analyses. Platzbecker et al[4] compared DNA-hypomethylating therapy (n = 75) to allogeneic HSCT (n = 103), using a donor versus no donor retrospective analysis of patients with MDS aged 60 to 70 years. Those patients who did not have a search for a donor because of age ≥ 60 years or those with an unsuccessful donor search were used as the control arm. The estimated 2-year overall survival was 39% (95% confidence interval [CI], 30%-50%) for patients who received transplantation compared with 23% (95% CI, 14%-40%) for those who had received azacitidine (AZA). Using a multivariate Cox regression analysis, the benefit for HSCT was evident > 1 year after transplantation, with significantly lower overall mortality compared with those who had received AZA (hazard ratio for hematopoietic cell transplantation [HCT] vs. AZA, 0.3; $P = .007$).

The benefits of HSCT compared with non-HSCT therapies were also noted by a French group, who reported on the only prospective nonrandomized donor to no donor analysis to date.[5] Patients aged 50 to 70 years who had intermediate-2 (int-2) or high-risk disease according to the International Prognosis Scoring System (IPSS) or isolated high-risk features such as a poor-risk karyotype and thrombocytopenia were enrolled prospectively. Subjects with proliferative chronic myelomonocytic leukemia and transformed MDS were also enrolled. Hypomethylating agents or induction

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chemotherapy were given at the discretion of the treating physician while the donor search was ongoing. The primary comparison for the analysis was to evaluate the survival between patients with an appropriately human leukocyte antigen (HLA)-matched sibling or unrelated donor (n = 112) and those without such a donor (n = 50). Most (72%) of the subjects in the donor cohort had undergone transplantation at a median of 8 months after study enrollment. The survival benefit of transplantation for high-risk MDS became apparent approximately 2 years after HSCT. The 4-year survival was 37% in the donor group compared with 15% in the no donor group ($P = .02$).

The optimal method for assessing the value of HSCT is to randomize patients eligible for transplantation and perform a donor to HSCT versus no-HSCT trial. However, given that HSCT is the only potential curative option available to patients and that consensus groups have endorsed transplantation for MDS, it is unlikely that a truly randomized HSCT trial will ever be conceived. However, 2 large prospective studies are ongoing to confirm the advantages of allogeneic HSCT compared with non-HSCT approaches for MDS using biologic randomization. The Blood and Marrow Transplantation Clinical Trial Network study (BMT-CTN 1102) will assess the benefits of transplantation for those patients with high-risk MDS, as defined by the IPSS, during any period of their disease course (ClinicalTrials.gov Identifier, NCT02016781).[3] Patients referred for HSCT will be biologically assigned to transplant versus non-HSCT therapy according to the availability of a suitably HLA-matched sibling or unrelated donor. Patients aged 50 to 75 will be eligible for the trial, which is anticipated to enroll a minimum of 338 subjects according to donor availability. The primary study endpoint will be overall survival at 3 years after enrollment. The study will also address the patient quality of life and a cost-effectiveness analysis. The German MDS study group will evaluate, in a prospective trial, patients aged 55 to 70 years with high-risk MDS defined by IPSS and compare the outcomes of HSCT and no-HSCT, also based on donor availability (ClinicalTrials.gov identifier, NCT01404741).[4] All subjects will receive 4 to 6 cycles of AZA and subsequently will be biologically assigned to transplantation on the basis of donor availability, with either an HLA-matched sibling or unrelated donor. Patients without a suitable donor will continue with AZA treatment for their MDS. The trial will assess comorbidities at study entry and before transplantation. The primary study objective will be to compare the 3-year overall survival between the 2 arms.

Usage of Prognostic Models

Several prognostic systems have been developed to better predict MDS outcomes, including leukemic transformation and survival. The IPSS was first published in 1997 to predict MDS prognosis, including the time from diagnosis to progression to acute myelogenous leukemia (AML) or death. This model incorporates the blast percentage, presence of cytopenias, and cytogenetic risk category to stratify the disease into low, intermediate-1 (int-1), int-2, and high-risk categories at diagnosis. For patients with int-2 and high-risk disease, the average time to leukemic transformation was 1.1 and 0.2 years, and the average time to death was 1.2 years and 0.4 year, respectively.[6] The IPSS has been the most widely adopted tool in clinical practice for the management of MDS, and the goals of treatment for those patients with int-2 or high-risk disease have included disease-modifying strategies that can improve survival, such as HSCT. Since then, several models were developed to predict MDS outcomes and further refine the IPSS schema.

The World Health Organization Prognosis Scoring System (WPSS) incorporates the World Health Organization category and transfusion requirements and cytogenetic risk.[7] Another multinational collaborative effort, known as the International Working Group for the Prognosis of MDS (IWG-PM) project, has revised the IPSS (IPSS-R) to further refine its prognostic value.[8] The model classified 7012 patients into 5 risk groups (very low, low, intermediate, high, and very high risk) compared with the 4 groups in the IPSS and WPSS. The new classification incorporates the depth of cytopenias with the hemoglobin level, platelet counts, and neutrophil count cutoffs. In contrast, the previous model incorporated simply the presence or absence of cytopenias. The percentage of marrow blasts has also been further divided into 3 groups. The increase in cytogenetic categories for conventional karyotyping underscores the importance of genetic abnormalities in MDS. The newer classification notes 16 cytogenetic abnormalities compared with the previous 6 recognized in the IPSS, which are now classified within 5 risk categories. The median survival in the absence of therapy for the high- and very-high-risk categories was 1.6 years and 0.8 year, with a corresponding time to leukemic transformation in these groups of 1.4 years and 0.7 year.

Several retrospective studies have highlighted the validity of the IPSS-R. In a single institution database analysis of 1088 patients, the median overall survival according to the IPSS-R risk categories was 90 months for the very-low-, 54 months for the low-, 34 months for the intermediate-, 21 months for the high-, and 13 months for the very-high-risk groups ($P < .005$).[9] Additionally, this analysis demonstrated the survival benefit of using disease-modifying agents such as AZA and HSCT in patients with higher risk MDS according to the IPSS-R. Patients in the high and very high IPSS-R risk groups who received AZA experienced significant improvement in survival compared with those patients who had not received AZA (median survival, 25 vs. 18 months for high risk, $P < .028$; and median survival, 15 vs. 9 months for very high risk, $P = .005$). Similarly, patients with lower risk MDS by IPSS-R did not show a survival benefit from HSCT, although the use of HSCT approached statistical significance for 42 intermediate-risk patients ($P = .08$). The benefits of HSCT were observed for patients with high- and very-high-risk disease, with significantly longer survival compared with the no-HSCT group (median survival, 40 vs. 19 months, $P < .005$ for high risk; median survival, 31 vs. 12 months, $P < .005$ for very high risk).

To further identify the factors predictive for the outcomes of those patients who receive HSCT, Della Porta et al[10] evaluated the survival and relapse in 519 patients with MDS or oligoblastic AML (< 30% marrow blasts) who had undergone allogeneic transplantation. On multivariate analysis, the IPSS-R risk group significantly affected survival (hazard ratio [HR], 1.41; $P < .001$) and relapse (HR, 1.81; $P < .001$). The study used the Akaike criterion to demonstrate that the IPSS-R is more indicative of prognosis than the IPSS. Compared with the IPSS-based prognostic stratification, the IPSS-R risk group changed for 65% of patients, with most patients reclassified into higher risk categories with a less favorable