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Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes: Lingering Uncertainties and Emerging Possibilities

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The landscape of transplantation in myelodysplastic syndrome (MDS) has evolved rapidly in the last decade, driven mostly by advances in patient selection through better risk stratification, increasing age of allogeneic recipients, introduction of reduced-intensity conditioning regimens, increased availability of unrelated donors, new donor sources, and improvements in transplant technology and supportive care. Despite these advances, several issues, mostly centering on approaches to improve post-transplant survival while minimizing transplant-related mortality, continue to present significant challenges. Advances in understanding the molecular pathogenesis of MDS have made it feasible to construct clinically useful risk models that integrate prognostic genes with conventional risk parameters for better selection of patients likely to benefit from hematopoietic cell transplantation. Simultaneous research efforts in several areas, including comorbidity assessment, novel preparative regimens, optimal pretransplant cytoreductive strategy, and post-transplantation therapies, are expected to improve long-term disease-free survival and quality of life.

INTRODUCTION

Myelodysplastic syndromes (MDS) is a heterogeneous collection of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis leading to peripheral cytopenias and related complications and a variable risk of progression to acute myeloid leukemia (AML). According to Surveillance Epidemiology and End Results, MDS is the most common myeloid malignancy in the United States, with most patients (88%) older than 60 years at diagnosis [1]. Allogeneic hematopoietic cell transplantation (HCT) is the only known treatment modality with curative potential in MDS. Although HCT outcomes in MDS have improved over the last decade, several challenges pertaining to transplant-related mortality (TRM) and morbidity remain. This review summarizes the advances made in the last decade, focusing mainly on more nuanced disease risk stratification, transplant implications of newly identified molecular mutations, the emerging role of haploidentical and umbilical cord blood (UCB) grafts, the role of pretransplant cytoreductive therapy, and the optimal timing of transplantation.

EPIDEMIOLOGY OF TRANSPLANTATION IN MDS: A TALE OF UNMET NEEDS

Over the last decade, the number of transplants performed for MDS has risen dramatically, particularly in older adults, mainly because of increasing numbers of unrelated donor (URD) and reduced-intensity conditioning (RIC) transplants (Figure 1) [2]. This has been accompanied by significant decreases in overall mortality (by 40%) and improved long-term survival because of decreased transplant-related complications, notably infections, organ toxicities, and severe acute graft-versus-host disease (GVHD) [3]. These results are even more promising considering that transplanted cohorts in recent years are on average older by 2 decades compared with their counterparts from the late 1980s and the proportion of URD recipients increased from 6% to 57% in the same interval (exceeding related donors) [4].

The Center for International Blood and Marrow Transplant Research (CIBMTR) reports MDS as the third most common indication for allogeneic HCT, with 1016 transplants registered between 2008 and 2010 [2]. A comparable trend has been reported in Europe, where the European Group for Blood and Marrow Transplantation (EBMT) registered a

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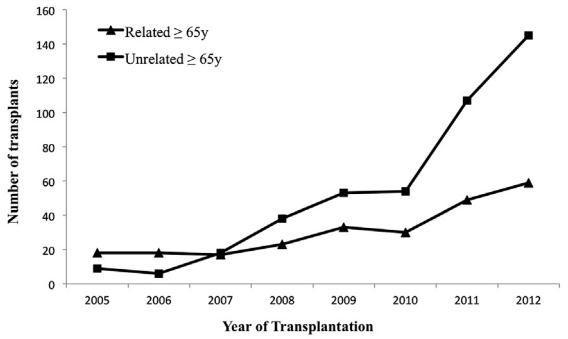

	2005	2006	2007	2008	2009	2010	2011	2012
Related ≥ 65y	18	18	17	23	33	30	49	59
Unrelated ≥ 65y	9	6	18	38	53	54	107	145

Figure 1. Number of allogeneic HCTs for MDS patients ≥65 years of age in the United States, 2005-2012. Data compiled by CIBMTR. Figure provided by Dr. Mary Horowitz and adapted with permission.

doubling in the number of allogeneic HCT for MDS/secondary AML (sAML) from 737 to 1636 between the years 2001 and 2010, paralleled by a 10% to 33% increase in HCT use in patients over age 60 [5]. Although these temporal trends are impressive, when considered in the context of the entire pool of high-risk MDS patients in the United States, statistics from various epidemiologic sources suggest a staggeringly low use of transplantation in this population, as shown in Figure 2 [6-10]. A prospective feasibility study of RIC HCT in 259 higher risk MDS/AML patients reported that only 14 patients (5%) harboring unfavorable cytogenetics eventually received transplantation [11]. The findings of a cross-sectional survey of US physicians from different geographic regions and a wide variety of practice settings are even more sobering, with only 4% of recently diagnosed MDS patients referred for HCT [8]. With 21 million potential marrow donors worldwide, including more than 600,000 UCB units, it is expected that a suitable URD or UCB unit can be found to meet the needs of approximately 12,000 patients in the United States who need URD transplantations every year. Despite this and results comparable with those with HLA-identical sibling donors, the estimated usage of these donor sources is strikingly low, at 10% for 65- to 74-year-olds, the demographic cohort with the highest MDS rates [10]. Figures from 2012 show that a formal search was initiated for only 62% of these patients of which only 60% actually proceeded to HCT [12].

Although the reasons for low utilization of HCT are multifactorial, most of the concerns center around the high risk of TRM or diminution of quality of life due to chronic GVHD or other delayed effects of HCT, especially so in older patients with diminished physiologic reserves because of the combined effect of their advanced age and existing comorbidities. Limited understanding of referring physicians regarding transplant eligibility, late transplant referrals, delay in HLA typing, and underuse of URD transplantation is also responsible. The feasibility of surmounting some of these barriers was demonstrated in a recent study in which a combination of pragmatic strategies, including use of alternative donors, different graft sources, and RIC regimens (42%), allowed 67% of AML patients in complete remission to proceed to HCT [13]. A concerted effort in educating the clinicians providing care for MDS patients would result in more frequent and earlier consideration of this modality.

WHO NEEDS A TRANSPLANT? SEPARATING THE GOOD FROM THE BAD AND THE UGLY

Selection of the appropriate transplant candidate has undergone refinements over the past decade, aided by improved understanding of disease risk, use of disease-modifying therapies that improve survival (since 2004), more sensitive tools to assess transplant vulnerability, and increased HCT opportunities in the elderly with the advent of RIC and nonmyeloablative (NMA) regimens. As shown in Table 1, upfront HCT is currently recommended for fit MDS patients stratified as higher risk based on clonal chromosomal abnormalities, blast percentage, peripheral cytopenias, and additional features depending on the particular prognostic model applied. Originally designed to prognosticate for nontransplanted patients, several risk models, such as the International Prognostic Scoring System (IPSS), the World Health Organization classification-based Prognostic Scoring System (WPSS), and the revised IPSS (IPSS-R), also predict survival and relapse in the transplant setting [4,14,15], even in those receiving RIC [14,15]. The newly

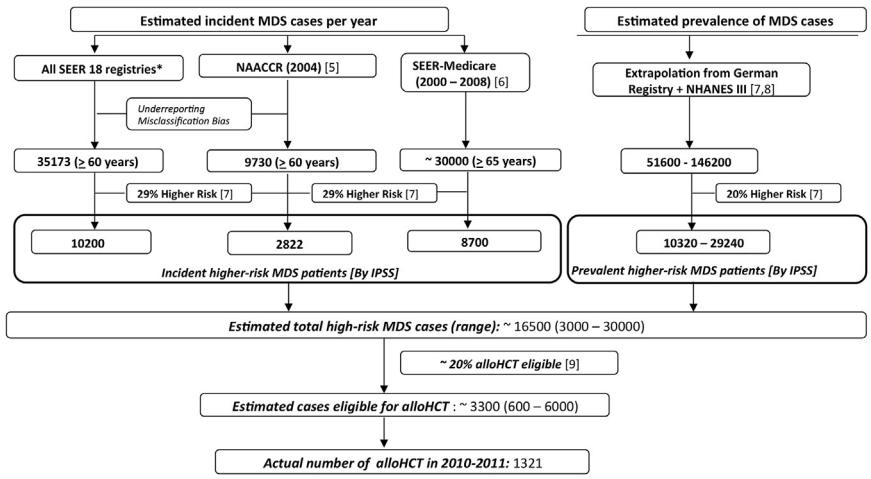

Figure 2. Crude estimation of transplant-eligible older MDS patients (age >60-65 years) in the United States with data extrapolated from contemporaneous population registries highlighting the staggeringly low uptake of allogeneic HCTs in this age group. SEER indicates Surveillance Epidemiology and End Results; NAACCR, North American Association of Central Cancer Registries; NHANES III, National Health and Nutrition Examination Survey III; alloHSCT, allogeneic hematopoietic stem cell transplantation. * MDS cases equal to or greater than 60 years were extracted from all 18 SEER registries using the R package SEERaBomb available at http://cran.r-project.org/web/packages/SEERaBomb/index.html (courtesy of Dr. Tomas Radivoyevitch).