Current Hematologic Malignancy Reports (2020) 15:268–275
https://doi.org/10.1007/s11899-019-00551-7

MYELODYSPLASTIC SYNDROMES (M SAVONA, SECTION EDITOR)

Indications for Allogeneic Hematopoietic Cell Transplantation in Myelodysplastic Syndrome

Nathalie Danielson[1] · Michael Byrne[2]

Published online: 3 March 2020

Abstract

Purpose of Review Myelodysplastic syndromes (MDS) are heterogeneous diseases that principally affect older adults. Allogeneic hematopoietic cell transplantation (HCT) is the only potentially curative therapy; however, non-relapse mortality (NRM) accounts for as many as 40% of deaths after HCT and underscores the need for careful patient selection. We review the common indications and causes of failure after HCT in MDS.

Recent Findings Appropriate patient selection is necessary to optimize HCT outcomes and maximize the life-expectancies of MDS patients. The international prognostic scoring systems (IPSS) and revised IPSS (IPSS-R) are used to identify high-risk patients and guide decision making. Neither scoring system incorporates molecular mutations, which are now recognized as important predictors of disease biology and clinical outcomes. Patient and disease characteristics including age, comorbid conditions, iron overload, blast percentage, and other features may impact post-HCT outcomes.

Summary An accurate assessment of the disease risk and patient qualities that affect NRM is necessary to optimize post-HCT outcomes. In this review, we summarize the risk factors for, and common causes of NRM, as well as markers of poor-risk disease that should lead providers to consider allogeneic HCT in MDS patients.

Keywords Myelodysplastic syndrome · Allogeneic stem cell transplantation

Introduction

Myelodysplastic syndromes (MDS) are clonal diseases of ineffective hematopoiesis characterized by bone marrow (BM) dysplasia and peripheral blood (PB) cytopenias. Signs and symptoms of BM failure may lead patients to seek medical attention while others' PB cytopenias are incidentally discovered during routine healthcare examinations. Without treatment, patients may experience the consequences of ineffective hematopoiesis (i.e., infection, bleeding, or insufficiency ischemia) and/or transform to acute myeloid leukemia (AML). Patients with secondary AML experience poor clinical outcomes and reduced overall survival (OS) [1]. Treatment is aimed at ameliorating the signs or symptoms of the disease, reducing risk of leukemic transformation, and improving survival.

Providing optimal treatment in MDS may be challenging. Myelodysplastic syndrome is generally considered a disease of the elderly with a median age at diagnosis after the seventh decade of life [2, 3]. In this age demographic, comorbid conditions, disease biology, patient preferences, and other factors may influence treatment decisions and patient outcomes [4]. Low-risk patients may be observed or growth factors may be offered to symptomatic, low-risk individuals. Other treatment options include lenalidomide, which improves red blood cell transfusion independence and delays leukemic transformation in patients with the del 5q31 chromosomal abnormality [5]. Higher-risk patients may be treated with DNA methyl transferase inhibitor (DNMTi) to slow the progression of their disease, reverse PB cytopenias, and reduce the risk of leukemic transformation. Between 50 and 60% of patients respond to the DNMTi 5'azacitdine, which is associated with improved OS [6, 7]. Patients who fail to respond, are intolerant, or

This article is part of the Topical Collection on *Myelodysplastic Syndromes*

✉ Michael Byrne
michael.byrne@vumc.org

[1] Division of Hematology and Medical Oncology, Tennessee Valley Veterans Affairs Health System, Nashville, TN, USA

[2] Division of Hematology and Medical Oncology, Department of Medicine, Vanderbilt University Medical Center, 777 Preston Research Building, 2220 Pierce Avenue, Nashville, TN 37232, USA

progress during treatment experience a short OS (median OS of 5.6 months; 2 year OS of 15%). [8]

Allogeneic HCT is the only potentially curative therapy, and poor-risk patients managed without HCT have a 3-year OS of < 10% [9]. In comparison, approximately 40–50% of patients survive beyond 2 years with allogeneic HCT, and long-term disease control is feasible [10–12]. Comparisons of patients with and without HCT donors consistently demonstrate a survival benefit with HCT. The European Intergroup Trial showed a 4-year OS of 54% vs. 41%, favoring allogeneic HCT, in patients < 55 years old [13]. In a French prospective study, 162 patients with higher-risk MDS were "randomized" based on the availability of an HLA-matched donor. Those who underwent allogeneic HCT experienced a superior OS relative to those without a donor (4-year OS of 37% vs. 15%) [14]. A retrospective analysis that categorized MDS patients by revised International Prognostic Scoring Systems (IPSS-R) group reported similar conclusions. Patients with high- and very high-risk MDS experienced an OS benefit with HCT (high 40 vs. 19 months, and very high 31 vs. 12 months) [15].

Although allogeneic HCT is potentially curative, it carries a risk of non-relapse mortality (NRM) that exceeds 40% in some series [16–18]. Appropriately identifying high-risk patients and optimizing the timing of HCT are necessary to maximize the life expectancy and likelihood of cure. This review focuses on the indications, barriers, and innovations in allogeneic HCT for MDS patients.

Non-relapse Mortality

Over the last two decades, safer conditioning regimens, improvements in supportive care, and new therapies for acute and chronic graft versus host disease (GVHD) have reduced NRM [19–22]. In spite of these improvements, the long-term outcomes remain suboptimal. A recent registry analysis from the European Society for Blood and Marrow Transplantation (EBMT) reported a 2, 5, and 10-year OS of MDS and secondary AML patients of 53%, 43%, and 35%, respectively, indicating that < 50% of MDS patients become long-term survivors [20]. Non-relapse mortality is an important cause of death and reflects the consequences of administering an intensive therapy in an aging population with medical comorbidities. The risk of NRM remains high within the first year and several series associate advancing age with NRM [16–18, 20, 21, 23, 24].

Recipient Age

Advancing age may correlate with frailty, comorbid conditions, loss of organ reserve, and a diminished capacity to withstand stress [25]. These changes, which are associated with the natural aging process, correlate closely with NRM. An analysis of 221 older MDS patients and 92 older secondary AML patients who underwent allogeneic HCT showed a 1-year NRM of 32% and a 3-year OS of 34% [26]. Separately, Sorror and colleagues established a link between advancing age and NRM with hazard ratios of 1.21, 1.48, 1.75, and 1.84 in patients ages 20–39, 40–49, 50–59, and ≥ 60 years relative to recipients < 20 years of age [27]. In a registry analysis of MDS and AML patients who underwent reduced intensity conditioning, HCT did not show significant differences in relapse, NRM, DFS, or OS between age groups [28]. In summary, the literature does not support an "age cutoff" for high-risk MDS patients; however, recipient age and other age-associated comorbidities should be considered during HCT planning.

Comorbidities and Effect on HCT Outcomes in MDS

In addition to recipient age, comorbid conditions are also closely correlated with NRM. The impact of comorbidities was reported in a retrospective analysis of 600 MDS patients, the majority of whom were managed without HCT. Comorbidity severity was associated with significant differences in median OS, ranging from 9.7 to 31.8 months, and patients with severe comorbidities experienced a 50% reduction in OS irrespective of age or IPSS risk [29]. A separate study reported similar conclusions with a 2-year NRM of 14%, 21%, and 41% in the low-, moderate-, and high-risk comorbidity groups [30]. Although comorbid conditions and Karnofsky performance status are weakly correlated, combining the two scoring systems allows patients to be divided into four groups with 2-year survivals of 32%, 41%, 58%, and 68% [31]. A second study confirmed that recipient age and comorbid conditions are highly predictive of NRM [27].

Accurately attributing NRM to HCT may be challenging due to competing risks. While GVHD-associated NRM is easily attributed to HCT, other post-HCT complications may be less clear. A recent EBMT landmark analysis addressed this challenge by calculating hazards based on age, sex, and geographic location to determine the death rate of the general population. "Excess" NRM, attributed to HCT, was then calculated by age group. Younger patients (age < 45 years) had an estimated 5-year population mortality of 0.5% compared to 8% of older patients (age ≥ 65 years). At a 2-year landmark, the 1- and 5-year risk of mortality was 9% and 26%. In the 5-year post-landmark analysis, NRM accounted for 8% of the deaths in younger patients, and 31% of the deaths in older patients. Consistent with prior studies, increased age correlated with excess mortality. Of the 208 late deaths, mortality was evenly divided between relapse and NRM; 23% of deaths were attributed to GVHD, 15% to infection, and 36% to secondary malignancies; and 23% of patients experienced cardiovascular events [20]. In a second series, organ failure (7.7%), infectious complications (7.6%), and acute or chronic GVHD (4.1%) were the principal causes of NRM [21].

Disease Biology and Relapse-Related Mortality

Due to a biologically aggressive disease and limited number of effective therapies, 23–30% of patients with MDS that undergo allogeneic HCT will relapse and face poor clinical outcomes with short OS [16–18, 20, 32, 33]. Many of the high-risk disease features that identify patients for HCT also predict for poor outcomes after allogeneic HCT, particularly complex and/or monosomal karyotypes and *TP53* mutations [34–38]. Accurately characterizing the disease biology is necessary to determine the appropriateness of allogeneic HCT in MDS. Disease features, patient history, and molecular data are used to identify high-risk patients. These variables and their impact on HCT decision-making are summarized in the following sections.

Scoring Systems

The IPSS and IPSS-R are validated assessment tools for newly diagnosed, untreated MDS patients and are commonly used to guide clinical decision-making [39, 40]. Neither incorporates data from later in the disease course, including treatment response, a recognized limitation of these systems. The IPSS-R improves upon the IPSS by stratifying patients with cytopenias and BM blast counts as continuous variables and complete cytogenetic risks; however, molecular mutations by next-generation sequencing (NGS) are not incorporated. There is growing recognition that these mutations are an important predictor of disease biology, and ultimately treatment outcomes, and their absence from the IPSS and IPSS-R represents a second limitation. Efforts to incorporate these data into future scoring systems are underway.

In spite of these shortcomings, the IPSS and IPSS-R are widely used to guide the appropriate timing of HCT. Using a Markov decision model, life expectancies of HLA-identical sibling transplant recipients who underwent immediate HCT were compared to the outcomes of patients who underwent HCT at disease progression. In IPSS low- and intermediate-1 risk groups, delayed HCT led to a superior life expectancy whereas intermediate-2 and higher-risk groups benefitted from early allogeneic HCT [41]. These outcomes were confirmed in a second analysis of 514 older patients with de novo MDS. IPSS intermediate-2 and high-risk disease experienced a life expectancy of 36 months with HCT compared to 28 months without [42].

Although this approach is generally adopted for low-risk patients, three registry studies reported a survival benefit when early allogeneic HCT is utilized [12, 43, 44]. Using the IPSS-R scoring system, patients with low-, intermediate-, high-, and very-high risk disease had 5-year survivals of 71%, 58%, 39%, and 23%, respectively. The incidence of relapse was 4%, 12%, 23%, and 39%, respectively [45]. While these data seem to support early HCT in lower-risk patients, they do not incorporate the time between diagnosis and HCT, which can be significant for low-risk patients when HCT is delayed.

In summary, lower-risk patients may experience extended event-free survivals and improved OS when allogeneic HCT is delayed until disease progression. Alternatively, appropriately selected high-risk patients should proceed to HCT after a donor is identified.

Cytogenetics

Cytogenetics is an important component of the IPSS and IPSS-R scoring systems. A recent machine learning analysis that censored patients at HCT identified cytogenetic risk category by IPSS-R as the single most important predictor of OS [46]. A large EBMT registry analysis reported a 5-year progression free survival (PFS) and OS of 22% and 28%, respectively, in adults with chromosome 7 abnormalities [47]. Separately, a series of MDS and oligoblastic AML patients linked a monsomal karyotype with a higher probability of relapse and 5-year OS of 10%, significantly worse than patients without these abnormalities [45]. Finally, patients with poor-risk and very poor-risk cytogenetics by the IPSS-R experienced a 5-year OS of 28% and 15%, respectively [45]. Collectively, these data indicate that the presence of a complex and/or monosomal karyotype is associated with poor-risk disease and should prompt HCT discussions early in the disease course.

Next-Generation Sequencing

The majority of MDS patients have at least one molecular mutation by NGS, and testing at diagnosis is routinely performed at many centers [48, 49]. Several recent studies characterized the impact of these mutations on clinical outcomes. Mutations in *TP53*, *ASXL1*, *TET2*, *DNMT3A*, and others are linked with poor treatment outcomes whereas *SF3B1* is generally associated with refractory anemia with ringed sideroblasts, a more favorable disease phenotype [50, 51].

Mutations in the tumor suppressor gene *TP53* are the most well-characterized and are near-uniformly associated with poor-risk disease. A prognostic model, driven exclusively by molecular data, placed *TP53* mutations in the "very unfavorable" category with a 3-year OS of 0% [52]. Further, these mutations are associated with other adverse-risk disease features, including advancing age, therapy-related disease, complex karyotype, increased transfusion needs, and neutropenia which also negatively impact treatment outcomes [53, 54]. Refractoriness to induction and/or salvage chemotherapy may present challenges in obtaining pre-HCT disease control and further contribute to the poor treatment outcomes in this population [53]. A series of 359 MDS patients with complex karyotype reported that *TP53* mutations were associated with fewer somatic mutations, but a

higher incidence of monosomal and highly complex karyotypes (> 4 cytogenetic abnormalities), both of which were associated with shorter OS [55].

Allogeneic HCT outcomes for *TP53*-mutated patients are poor. In one series, 38% of patients with *TP53* mutations with a complex karyotype died within 100 days of HCT and > 80% died within 2 years. Interestingly, a series that compared *TP53*-mutated patients, with and without a complex karyotype, reported that the latter was associated with better outcomes raising the question of whether the mutation itself, or the mutation in combination with other, co-occurring adverse-risk features, drive the poor post-HCT outcomes [56]. In line with this, a small series that compared therapy-related MDS patients, with and without mutations in *TP53*, revealed no significant differences in RFS or OS [57]. Lastly, a large registry study confirmed a shortened PFS and OS in *TP53*-mutated MDS relative to wild type patients. As many as 20–25% *TP53*-mutated patients survived > 2 years indicating there is clinical benefit with HCT in this population [35].

The significance of other adverse-risk molecular mutations, their impact on HCT planning in otherwise low-risk patients, and the prognostic impact of compound mutations (i.e., both low- and high-risk mutations) are less well-established. In an analysis of 439 MDS patients, mutations in *TP53*, *EZH2*, *ETV6*, *RUNX1*, and *ASXL1* predicted for poor OS [49]. A separate analysis linked *DNMT3A*, *TET2*, *IDH1*, and *IDH2* mutations with multilineage dysplasia while *ASXL1* and *TP53* mutations were independently associated with inferior survival in MDS [58]. In a study of 87 post-HCT MDS patients, mutations in *TP53*, *TET2*, and *DNMT3A* were associated with a shorter OS [59]. Finally, a machine learning model listed mutations in *TP53*, *RUNX1*, *STAG2*, *ASXL1*, and others as predictors of disease biology; however, these mutations fell behind IPSS-R cytogenetic risk, mutation number, PB counts, and other features in their prognostic ability [46]. There is limited data to support an association between the number of mutations and post-treatment outcomes.

Secondary MDS

Secondary myeloid neoplasms occur several months to years after a genotoxic exposure and are associated with complex and/or monosomal karyotype, including chromosome 5 and/or chromosome 7 abnormalities and *TP53* mutations [60]. Secondary MDS is a biologically aggressive disease with increased risk of leukemic transformation and shortened OS. Allogeneic HCT is the only potentially curative therapy for these patients and should be considered regardless of the disease risk by the IPSS or IPSS-R.

In spite of optimal management, approximately 30% with therapy-related MDS/AML will relapse after allogeneic HCT. In multivariate analysis, abnormal cytogenetics and advanced age were associated with relapse and increasing age again correlated with NRM [61]. An analysis from the City of Hope showed no significant difference in 5-year OS between de novo and therapy-related MDS in spite of having a higher cytogenetic risk and IPSS score (49.9% vs. 53.9%) [57].

Percent Bone Marrow Blasts

The majority of MDS patients undergo HCT in < CR indicating that some measure of their primary disease is intact [6, 7]. Bone marrow blast percentage at diagnosis is a driver of disease risk in the IPSS and the IPSS-R. In line with this, a retrospective series of HCT patients with > 10% BM blasts at diagnosis experienced a higher incidence of post-HCT relapse and reduced OS relative to those with < 5% and 5–10% blasts [45]. The prognostic impact of BM blast count prior to HCT is not as well-characterized.

Retrospective studies link lower disease volume with superior post-HCT outcomes. A report of 82 MDS patients after allogeneic HCT confirmed superior 5-year OS with low pre-HCT BM blasts (≤ 2%) compared to patients with > 10% blasts [62]. A second series of 35 MDS patients reported superior 1-year OS with < 5% blasts and a third, older study of BM transplant recipients showed superior DFS and OS with < 5% blasts [63, 64]. In line with these data, improved post-HCT outcomes are observed in high-risk MDS patients who achieve a treatment response prior to HCT [47, 65]. Reflecting these data, an international panel concluded that the post-HCT outcomes of MDS patients are more favorable when HCT occurs with < 5% blasts [66].

Transfusion Dependence and Iron Overload

Transfusion-dependence may be associated with poor post-HCT outcomes, either as a reflection of poor-risk disease, indicator of BM fibrosis, iron overload, alloimmunization, or other factors. In an analysis of nearly 600 MDS/AML patients, those with increased ferritin experienced an inferior OS, driven by increased NRM, and a trend toward increased veno-occlusive disease (VOD) [67]. This correlation between elevated ferritin and VOD was confirmed in a second series [68]. In other series, increased ferritin and iron overload were associated with higher NRM, driven by infection and organ failure, lower DFS, reduced chronic GHVD, and lower OS [69, 70]. Combined, these data support allogeneic HCT earlier in the treatment course, particularly in transfusion-dependent patients. In lower-risk patients, when delayed HCT is preferred, iron chelation therapy may be an appropriate step toward improving treatment outcomes.

Psychosocial and Financial Barriers

Psychiatric illness is considered a comorbid condition on validated risk scales, and psychological disease is an important

driver of post-HCT outcomes, including OS [27, 30, 31]. In one series, patients with major depression during hospitalization for HCT were at greater risk of death at 1 and 3 years after HCT [71]. Similar findings were reported in a second analysis where patients reporting a depressive syndrome at the 6-month follow-up were at threefold higher risk of mortality in the following 6 months [72]. Younger, married, educated, well-adjusted, and less-depressed transplant patients had superior outcomes in a third analysis while optimism may be associated with better short-term outcomes in autologous and allogeneic HCT recipients [73, 74].

Financially, allogeneic HCT may lead to a significant financial burden for patients and their families [75]. The majority of patients that undergo allogeneic HCT may experience reduced earnings/household income, increased out-of-pocket expenses, and other financial challenges. In a survey from the Mayo Clinic group, 73% of allogenic HCT recipients reported an adverse financial impact, including 35% of patients who failed to pursue optimal medical care due to financial hardship [76]. These data were confirmed in a second report indicating that 57% of patients reported financial challenges and 46% reported a decline in income after HCT [77]. More than 50% of patients who previously contributed to their household no longer worked after HCT, and a significant percentage of patients were unable to pay for their medical care during the years following allogeneic HCT [78].

Conclusions

In carefully selected MDS patients, allogeneic HCT is the only potentially curative treatment option with 40–50% of high-risk patients living more than 2 years, and 80% of 2-year survivors living ≥ 10 years after HCT. These outcomes are superior to non-HCT approaches.

Although allogeneic HCT has become safer over the course of the last decade, NRM accounts for as many as 40% of patient deaths and is an important barrier to survivorship. Recipient age and medical comorbidities are non-modifiable risk factors for NRM. While no clear "cutoff" exists for either, an awareness of these risk factors is necessary in order to appropriately select MDS patients for allogeneic HCT and reduce the incidence of NRM. Likewise, neither psychosocial nor socioeconomic status should be considered a barrier to allogenic HCT; however, additional consideration should be given to patients with depressive symptoms or those with limited financial means as both may impact post-HCT outcomes.

Accurately assessing the disease biology in MDS is necessary to appropriately manage these patients, guide decision-making around allogeneic HCT, and to maximize the life expectancies of MDS patients. The IPSS and IPSS-R are validated tools that rely on disease features at diagnosis, but fail to integrate treatment response or molecular data. The literature supports early allogeneic HCT in patients with intermediate-2 and high-risk disease by the IPSS, as well as patients with high-risk molecular markers, such as complex and/or monosomal karyotypes and mutations in *TP53*. The integration of poor-risk molecular mutations in otherwise low-risk patients and the impact of compound mutations (i.e., SF3B1 and TP53), is an important clinical challenge and area of active clinical research. In the future, novel therapies such as APR-246 in *TP53*-mutated patients, may enhance disease control prior to HCT and improve post-HCT outcomes [79].

In instances where allogeneic HCT is planned, pre-HCT disease control should be obtained, ideally with BM blasts < 5%, and iron chelation therapy should be offered in an effort to reduce the NRM associated with iron-overload.

In the future, it is anticipated that allogeneic HCT will become safer, and post-HCT outcomes continue improving for MDS patients. In parallel, an enhanced understanding of mutational data, and how it integrates with established disease markers to support patient care, is expected to better identify patients' with poor-risk disease who will benefit from early allogeneic HCT.

Compliance with Ethical Standards

Conflict of Interest Authors have no conflicts of interest to report.

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- • Of importance
- •• Of major importance

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