Chapter 10
Hematopoietic Cell Transplantation for MDS Patients

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Introduction

Allogeneic hematopoietic cell transplantation (HCT) remains the only potential curative therapy for a small subset of fit patients with myelodysplastic syndromes (MDS) [1], because currently available targeted therapeutic agents may lead to prolongation of overall survival but no cure of MDS. Individual stratification based on age, comorbidities, and MDS risk scores [2] is important to select patients for HCT, because overall only 10% of patients are potential candidates. In general, the earlier the transplantation takes place during the disease course, the better the chances of long-term cure [3]. Contrarily, patients with less advanced disease and without high-risk cytogenetic and molecular features should not be exposed to the risk associated with this procedure, because within the first year after HCT there is an approximately 20% risk of treatment-related mortality (TRM) [4]. Thus, the selection of the right patient population, the appropriate timing of HCT, and the optimal conditioning regimen are key questions that must be addressed. The introduction of reduce-intensity conditioning (RIC) regimens have substantially extended the use of HCT also to older patients with reduced fitness or present comorbidities [2]. Nevertheless, careful consideration should be given to who will optimally benefit from an HCT approach. In addition, relapse remains the main cause of failure for HCT and novel conditioning regimens and post-HCT prophylactic approaches are demanded [4].

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A. Nazha (ed.), *Diagnosis and Management of Myelodysplastic Syndromes*,
https://doi.org/10.1007/978-3-030-51878-3_10

Indication and Timing for Allogeneic Hematopoietic Stem Cell Transplantation

Because the clinical course of MDS is highly variable, an accurate assessment of the prognosis by IPSS/IPSS-R is essential before deciding about HCT [2]. Cutler et al. made an attempt to facilitate the decision process and carried out an analysis to determine which approach offers the longest life expectancy [5]. Results showed that in transplant-eligible patients with lower-risk disease, HCT may be best carried out when progression occurs to IPSS intermediate-2 risk [5]. Patients with less advanced disease and good quality of life should not be exposed to the substantial risk of mortality of this procedure due to the favorable prognosis with standard treatment alone [1]. Nevertheless, the earlier the HCT is performed during the disease course, the better are the long-term results [6]. A prior study by the European Society for Blood and Marrow Transplantation (EBMT) in 246 IPSS low/intermediate-1 patients demonstrated a 3-year survival rate of 58% and a 30% overall non-relapse mortality rate [7]. Thus, clinically fit patients with lower-risk MDS failing first-line standard of care treatment options and harboring poor-risk features including frequent RBC transfusions (≥2 units per month), life-threatening cytopenias (neutrophil counts, <0.5 × 109/L, or platelet counts, <30 × 109/L), very poor prognostic cytogenetic or molecular markers like RUNX1, EZH2, NRAS, TP53, or ASXL1 should be considered for HCT as appropriate candidates if no clinical trial is available [6].This may be especially important for the large group of lower-risk patients with a high transfusion burden and lack of response to erythropoietin-stimulating agent (ESA) [1, 6].

For higher-risk (IPSS intermediate-2 and high risk) transplant-eligible patients, HCT should be performed as early as possible in the disease course, since any delay appears to be associated with a loss in life years [1, 5]. On the other hand, considering the potential treatment-related complications associated with HCT, that is, GvHD and infections, the stringent selection of patients by identifying the patient- and disease-related factors is unavoidable and an important predictor of outcome after HCT [6, 8]. HCT should be considered in patients up to the age of 70–75 years, in MDS patients with intermediate-2/high or IPSS-R high/very high in good clinical condition, and without severe comorbidities if an HLA-matched donor is available [9].

Moreover, patients that do not respond or lose response to established non-transplant therapies like hypomethylating agents (HMA) including azacitidine and decitabine are also potential candidates [1, 2]. In fact, higher-risk MDS patients who fail HMA treatment typically have very poor prognosis with a median survival of 5–6 months with best supportive care only [10, 11]. Given the dismal prognosis of HMA failure and the current lack of available other treatment options, HCT should be considered for those patients. Overall, choosing the optimal candidate and timing for transplant and integrating HCT into the therapeutic algorithm remains a challenge in many cases and the pros and cons of this procedure should be discussed in detail with the patients [1].

Risk Factors Influencing Outcome After Allogeneic Hematopoietic Cell Transplantation

Comorbidities, frailty, performance status (e.g., Karnofsky score), and age are relevant patient-related factors that determine outcome after HCT [12, 13]. In addition to conventional prognostic scoring systems like IPSS and IPSS-R, tools like the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) demonstrated a strong prognostic impact on outcome after HCT [3, 12, 14]. The HCT-CI was developed to enable HCT-related risk assessment and to identify relevant comorbidities in the HCT population [3]. The comorbidity index comprises 17 different categories of organ dysfunction influencing non-relapse mortality and overall survival (OS) in the HCT setting. Positive findings are summated into a total score that enables the classification of patients into three risk groups: low risk (non-relapse mortality 14% at 2 years), intermediate risk (non-relapse mortality 21% at 2 years), and high risk (non-relapse mortality 41% at 2 years) [3].

Regarding pre-transplant blast count, patients with less than 5% bone marrow blasts showed a better outcome after HCT in prior studies [15]. For the rest of the primarily HCT-treated MDS patients, the overall survival was not significantly influenced by the percentage of bone marrow blasts [6], but fit, higher-risk patients with bone marrow blasts of more than 10% should be considered for early HCT after prior HMA or intensive chemotherapy treatment [6]. Concerning cytogenetic risk classification, complex karyotype abnormalities and monosomal karyotype predict for increased mortality, higher rates of relapse, and inferior survival after HCT [16]. When considering the mutational profile of the transplant-eligible patients, high risk somatic mutations like *TP53*, *RUNX1*, and *ASXL1* are independently associated with adverse outcome and shorter survival after allogeneic HCT [17]. In a prior small study including 87 transplant eligible patients, Bejar et al. demonstrated that mutations in *TP53*, *TET2*, or *DNMT3A* identify patients with shorter OS after HCT [18]. Subsequent larger studies could not confirm these results and showed that *TET2* and *DNMT3A* mutations had no impact on transplant outcomes [19]. Moreover, Della Porta et al. showed that in patients with MDS/AML, somatic mutation like *ASXL1*, *RUNX1*, or *TP53* are independently associated with unfavorable outcomes and shorter survival after allogeneic HCT [17]. Lindsley et al. also evaluated the association of mutations with transplantation outcomes like overall survival, relapse, and death without relapse in 1514 patients with MDS. Again, *TP53* mutations were associated with shorter survival and a shorter time to relapse compared to TP53 wild-type patients. Moreover, the emergence of *TP53* mutation in combination with a complex karyotype resulted in an unfavorable outcome and early relapse after HCT in prior studies [18]. In patients without *TP53* mutation, the presence of RAS pathway mutations was associated with shorter survival and a high risk of relapse. *JAK2* mutations were also associated with shorter survival and a high risk of death without relapse [20]. Thus, alternative conventional therapies (e.g., APR236) or disease-specific post-transplant strategies to prevent relapse are demanded for this patient population carrying high-risk somatic mutations.

Cytoreductive Treatment Prior to Allogeneic Hematopoietic Stem Cell Transplantation

Upfront HCT in higher-risk MDS patients is currently recommended in patients with less than 10% bone marrow blasts [6]. In the absence of randomized trials, the value of prior induction chemotherapy to reduce the percentage of bone marrow blasts prior HCT remains unclear [1]. A few retrospective studies have addressed the question, which cytoreductive approach prior to HCT conditioning is associated with superior outcome [21, 22]. Comparing intensive chemotherapy versus HMA therapy prior to the HCT, the relapse rates post HCT were similar for both cohorts after adjustment for several prognostic factors including cytogenetic risk [22]. Thus, a reduced toxicity approach using HMA treatment in order to "bridge" the time up to the identification of a compatible donor [1, 2] prior to conditioning for HCT is currently the preferred treatment in many centers. Nevertheless, there remains a substantial number of patients who display disease progression or severe infectious complications during the first 4 months of pre-transplant therapy and therefore cannot undergo subsequent transplantation.

In patients with an anticipated short-term benefit of HMAs (e.g., due to the presence of a complex karyotypes), HCT should be planned as early as possible because of the dismal prognosis of patients failing HMA therapy with a median survival time of less than 6 months [10]. In these cases, exposition to HMAs should be limited with the goal to achieve the highest potential reduction in disease burden prior to transplantation [1, 6]. The VidazaALLO study compared the 3-year overall survival after single agent azacitidine treatment with azacitidine followed by HCT according to donor availability in elderly patients with newly diagnosed untreated high-risk MDS aged 55–70 years (NCT01404741). Within the first 3 years, patients treated with azacitidine followed by HCT had an overall survival of 49% (95% CI: 36–61%) compared to 22% (95% CI: 6–44%) with azacitidine monotherapy. Thus, the VidazaALLO study demonstrated an improved event-free survival and overall survival in favor of HCT [23].

When considering remission-induction using intensive chemotherapy regimens, prior studies demonstrated considerable toxicity leading to treatment-related mortality (TRM) in up to 16% of transplant-eligible patients [24]. The higher response rates and better tolerability of the liposomal cytarabine-daunorubicin formulation (CPX-351) compared to conventional chemotherapy makes it an attractive treatment opportunity prior to transplant. Within the German MDS study group, the randomized PALOMA study is currently comparing CPX-351 versus azacitidine versus intensive chemotherapy treatment prior to HCT in patients with higher-risk MDS and oligoblastic AML (NCT04061239).

Moreover, it is widely accepted that systemic iron overload directly contributes to outcome after HCT in MDS [25, 26]. Available data showed that patients with either higher ferritin or a pre-transplant liver iron content greater than or equal to 125 μmol/g had an increased incidence of non-relapse mortality after HCT [27]. The results of the ALLIVE study demonstrated that elevated labile plasma iron (LPI) levels before or during HCT predict an increased incidence of

treatment-related non-relapse mortality (33% vs 7%) and a decreased overall survival in patients with AML or MDS [27]. Therefore, eligible patients should receive appropriate iron chelation prior to HCT.

Conditioning Intensity Prior to Allogeneic Hematopoietic Stem Cell Transplantation

As the intensity of transplant conditioning is linked to mortality, the development of reduced intensity conditioning (RIC) regimens has allowed the successful application of HCT in older patients with MDS [1, 28]. Recent retrospective analyses have suggested that HCT in older higher-risk MDS patients undergoing RIC regimens is superior compared to treatment with HMA, although the observed benefit occurred later following HCT [29, 30]. Many retrospective studies have assessed the value of RIC regimens compared with conventional myeloablative conditioning (MAC) regimens in patients with MDS. Kröger et al. demonstrated that RIC resulted in at least a 2-year relapse-free survival and overall survival similar to MAC in patients with MDS or secondary AML and a median age of 50 years [29]. In contrast to these results, Scott et al. showed a non-significant higher overall survival following MAC compared to RIC [30]. Moreover, RIC was associated with a lower treatment-related mortality but higher relapse rates compared with MAC [30]. These results support that higher-risk patients with good performance status and no comorbidities are candidates for MA regimens, but less fit and comorbid patients should be considered for RIC schedules [6].

Post-transplantation Strategies

Since HCT represents an intensive and possible curative treatment for eligible MDS patients, relapse after HCT remains one of the most important causes of treatment failure and mortality with very limited salvage therapies. While many patients have a high early mortality from relapse, some respond to salvage treatment and achieve sustained remissions. In fact, the risk of relapse is mainly determined by the disease stage at the time of transplantation and the relapse rate of patients is significantly influenced by the cytogenetic risk, exceeding 50% in patients with very poor-risk karyotype according to the IPSS-R [1, 2, 8]. Declining donor chimerism or mixed chimerism early after HCT are usually considered signs of imminent relapse. Measurement of chimerism in sorted CD34 cells has been used as minimal residual disease (MRD) monitoring after HCT in MDS [6]. Therapeutic options for MDS relapse after HCT consist of treatment with HMA or intensive chemotherapy, donor lymphocyte infusions (DLIs), second HSCT, or palliative care [1, 6]. DLIs can be administered prophylactically at the time of persisting or declining mixed donor chimerism or therapeutically in cases of confirmed relapse.

Oral azacitidine is currently under investigation as maintenance therapy following HCT in higher-risk MDS or AML patients [1]. Recently, the phase 3, randomized, placebo-controlled QUAZAR AML-001 study demonstrated that maintenance treatment with oral azacitidine (CC-486) [31] results in a significant improvement in overall survival compared to placebo in newly diagnosed AML patients after achieving the first complete response (CR) or complete response with incomplete blood count recovery (CRi) with prior induction chemotherapy [31].

Alternative approaches include pre-emptive MRD-triggered azacitidine treatments as shown by the recently published results of the multicenter prospective RELAZA2 trial [32]. Patients who had achieved a CR after conventional chemotherapy or HSCT were prospectively screened for MRD by either quantitative PCR for mutant *NPM1*, leukemia-specific fusion genes (DEK-NUP214, RUNX1-RUNX1T1, CBFb-MYH11), or analysis of donor-chimerism in flow cytometry-sorted CD34-positive cells. MRD-positive patients in confirmed CR received azacytidine treatment. After the first six cycles, MRD status was reassessed and patients with major responses (MRD negativity) were eligible for a treatment de-escalation. Six months after initiation of azacitidine, 58% patients were relapse-free and alive ($p < 0.0001$). Thus, MRD-guided pre-emptive therapy with azacitidine was able to prevent or delay hematological relapse in these MRD-positive patients with MDS or AML who are at a high risk of relapse [32]. Further studies may incorporate novel strategies to prevent relapse as either pre-emptive or maintenance therapy into their concepts.

Conclusion

HCT remains the only potential curative therapy for patients with MDS. Choosing the right candidates and the optimal moment for transplant remains a challenge in many cases. Fit patients with IPSS intermediate 2 or high-risk MDS should be transplanted early in their disease course, if a suitable HLA-matched related or unrelated donor is available [1, 6]. In MDS patients with lower-risk IPSS and without poor-risk features, HCT can be postponed until disease progression to higher-risk disease. Older patients (>60 or 65 years of age) and patients with clinically relevant comorbidities can still be candidates for lower-intensity conditioning regimens [1, 6]. Clinical trials, which investigate less toxic but intensive regimens prior HCT and further prophylactic strategies to prevent relapse are currently recruiting and results are eagerly awaited.

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