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Allogeneic hematopoietic cell transplantation for myelodysplastic syndrome: the past decade

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Abstract

Hematopoietic cell transplantation (HCT) is the only therapy with curative potential for patients with myelodysplastic syndrome. Many conditioning regimens have been developed that, along with the use of cord blood or HLA-haploidentical donors, allow doctors to offer HCT to a growing proportion of patients. New classification schemes identify more narrowly characterized risk groups, which may facilitate decisions with regard to HCT. Disease stage and cytogenetics remain the major determinants of HCT outcome. The use of peripheral blood progenitor cells may offer an advantage over marrow for engraftment and relapse prevention, but graft-versus-host disease remains a problem. The age of patients undergoing HCT has increased significantly over the past 25 years, and comorbid conditions are the major patient characteristic impacting transplant success. Recent studies show that drugs used in the non-HCT setting may be beneficial in the context of HCT.

Keywords

conditioning regimen; cytogenetics; disease stage and transplant outcome; donor selection; hematopoietic cell transplantation; MDS; patient age

Hematopoietic cell transplantation (HCT) is curative for a proportion of patients with myelodysplastic syndrome (MDS). The lead patients who underwent HCT have now been followed for more than 25 years in unmaintained remission. However, both relapse of MDS and treatment-related, nonrelapse mortality (NRM), often related to graft-versus-host disease (GVHD), have remained major roadblocks to universally successful HCT. While intensification of HCT conditioning regimens has been effective in reducing relapse frequency, the associated increase in toxicity and NRM was prohibitive [1].

Pre-HCT ‘debulking’ with classic induction chemotherapy with the objective of reducing post-HCT relapse will induce remissions in 30–40% of patients with MDS, but mortality

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rates of 10–15% have been reported. The approval of azacitidine, decitabine and lenalidomide (drugs with limited toxicity) for the treatment of MDS has changed the landscape and has affected HCT in several ways. First, many patients will undergo treatment with these non-HCT modalities rather than going directly to HCT. Second, patients so treated may present for HCT either as ‘responders’ or as treatment failures, very likely representing a selection of patients who will also have different prognoses after HCT [2]. Third, treatment over extended periods of time may generate new comorbidities before HCT. Fourth, owing to their low toxicity it may be possible to use those agents even after HCT in a prophylactic or therapeutic fashion.

The trend has been to offer HCT to ever older patients with MDS (the median age at diagnosis is in the early 1970s), who typically have more frequent or more severe comorbid conditions. Those, in turn, exert a major negative impact on transplant outcome. The negative effect of comorbidities has been partially neutralized by the use of reduced/low intensity conditioning regimens, albeit with the risk of increased relapse frequency [3]. The increasing use of cord blood cells or HLA-haploidentical HCT has further broadened the availability of HCT. Finally, new insights into the potential role of acquired gene mutations, refined characterization of karyotype subgroups, and the demonstration of the role of transfusion support or marrow fibrosis for the prognosis of MDS are altering the decision-making process with regard to HCT. In addition, the proportion of patients considered to have ‘secondary’ MDS has clearly increased.

In a recent population-based study, we showed (using the database of the Group Health Cooperative and data from the Surveillance, Epidemiology, and End Results Program) that 26% of all cases carried a prior diagnosis of cancer for which cytotoxic therapy, either chemotherapy or irradiation, had been given [4]. These are important epidemiological data as 90% or more of patients with secondary, presumably treatment-related MDS, have clonal cytogenetic abnormalities identifiable by classic banding techniques, and the majority of these would be classified as high-risk cytogenetics. Finally, the median age of patients with MDS coming for HCT transplantation has risen from 33 years in the late 1980s to 54 years in 2005; again, an important development as comorbid conditions are frequent in older individuals and high-intensity treatment regimens are poorly tolerated.

Classification & staging of MDS

The French–American–British classification, based on dysplastic features of marrow cells and the proportion of myeloblasts (in marrow and blood) [5], having served well for nearly three decades, is being replaced by the International Prognostic Scoring System (IPSS; also considers peripheral blood cytopenias and cytogenetics) [6], the WHO classification (recognizing multilineage dysplasia, subdividing refractory anemia [RA] and RA with excess blasts [RAEB] and eliminating RAEB in transformation) [7], and the resulting WHO-based prognostic scoring system (WPSS, which replaces the French–American–British classification used in IPSS with the WHO categories and substitutes red blood cell transfusion dependence for peripheral blood cytopenias). While the IPSS distinguishes four risk groups (low, intermediate-1, intermediate-2 and high, with median life expectancies ranging from 5.7 to 0.4 years for all patients), the WPSS shows five risk groups (very low to very high risk, with median life expectancies of 11.3–0.7 years). Among patients in the WPSS ‘very low’ category, only 7% are expected to develop leukemia by 10 years, while in the ‘very high’ risk group 50% will do so by 8 months.

Schanz *et al.* recently described a five-group cytogenetic risk classification with median survivals of patients ranging from 61 months in the ‘very good’ category to 6 months in the ‘very poor’ category [8]. In a preliminary analysis we showed that this new classification

distinguished risk groups for post-HCT relapse more precisely than do the three cytogenetic risk categories of the IPSS (see below; Deeg *J et al.*, Unpublished Data).

Bejar *et al.* determined mutations in myeloblasts from patients with MDS, and showed that regardless of classic cytogenetics and IPSS score, the presence of a single mutation in the panel assessed in their study (e.g., TET2 and AXSL) significantly shortened the median life expectancy in nontransplant patients; additional mutations further reduced the probability [9]. Therefore, while the relevance of these mutations has not been examined in the setting of HCT, the data suggest that patients in whom certain mutations, especially *ASXL1*, *RUNX1*, *TP53*, *EZH2* and *ETV6* are identified, should probably be considered for aggressive management, including HCT, earlier than they would be considered based on conventional criteria [10].

Other documented or potential risk parameters are so far not reflected in MDS classifications. Bone marrow fibrosis is associated with more rapid disease progression, and Scott *et al.* showed that the presence of marrow fibrosis also adversely affected HCT outcome, mostly in patients with advanced MDS [11]. This was recently confirmed by Kröger *et al.* in an analysis of 721 patients [12].

Flow cytometric scoring systems have been developed, which show a correlation between the flow phenotype and disease progression. Importantly, one group demonstrated a correlation between the severity of flow-cytometric aberrancies on marrow cells and the probability of relapse after HCT; this observation held true even for patients with less than 5% marrow myeloblasts [13]. Presumably, differences in gene expression underlie the observed immunophenotypic abnormalities, and gene-expression profiling has been shown to predict the risk for progression of MDS to acute myeloid leukemia [14]. Furthermore, the expression of HLA-DR15 has been suggested to be a marker for high probability of response of MDS to immunosuppressive therapy [15]. The impact on outcome after HCT is controversial [16]; however, a significant correlation between *HLA-DR15* and *TNF* polymorphisms at position -308 has been observed in MDS [17], and the *TNF-308* AG genotype conferred an increased risk of treatment-related mortality (TRM) compared to the GG genotype. Conversely, the *TNF-863* AA genotype was correlated with decreased overall mortality and TRM compared with the CC genotype. Clearly, additional work is needed to further dissect the heterogeneity of the disease [18].

Other risk factors

Comorbid conditions impact overall treatment success, including the outcome of HCT. Several scoring systems have been developed, including the HCT-specific comorbidity index [19,20] or a risk score based primarily on pulmonary function [21]. With rare exceptions [22], studies show that an elevated risk score, be it due to a prior solid tumor, the presence of cardiac or pulmonary (or other organ) insufficiency, or metabolic and psychiatric disorders, among others, significantly interferes with long-term HCT success. For example, we recently showed in a cohort of 85 patients with chronic myelomonocytic leukemia (CMML) transplanted from related or unrelated donors that those with an HCT-specific comorbidity index score of 0–2 had a relapse-free survival (RFS) of 53% compared with 27% among those with scores of 3 or greater [23]. The impact of comorbidity is observed with both high-dose and reduced-intensity conditioning (RIC) regimens [19,24].

Multiple studies suggest that iron status pre-HCT, as indicated by high levels of serum ferritin (e.g., >1000 µg/l), and liver iron content correlate with increased NRM and inferior survival after HCT [25]; both disease biology and blood transfusion burden are likely to contribute [26,27]. Some potential consequences of iron overload include an increased risk of blood stream infections, invasive fungal infections and sinusoidal obstruction syndrome

[28,29]. However, ferritin levels may reflect processes other than iron overload, and it is unclear if iron chelation will minimize the identified risks in MDS patients. Prospective clinical trials are not available, but are needed to clarify this issue [30].

Who is a candidate for HCT?

MDS is primarily a disease of older age. Until not too long ago, few patients older than 55 or 60 years of age underwent HCT. This has changed dramatically over the past decade, and as indicated earlier, the median age of patients transplanted for MDS at our center has increased from 33 years in the late 1980s to currently approximately 54 years. However, in parallel with increasing age comes an increasing prevalence of comorbid conditions, which may interfere with transplant success, as older individuals have a poor tolerance for high intensity therapy, including conditioning for HCT, which may lead to a reluctance to offer HCT to older patients.

An American Society of Blood and Marrow Transplantation consensus paper recommended early HCT for patients with IPSS intermediate-2 or high-risk at diagnosis, who have suitable donors and meet the transplant center's eligibility criteria [31]. It also recommended HCT for selected patients with less advanced disease at diagnosis who have poor prognostic features (e.g., older age, refractory cytopenias and transfusion dependence). It is expected that incorporation of newer prognostic tools, such as flow cytometry or molecular markers, will improve our ability to select patients for HCT. Newer risk models and individual risk factors (such as comorbidities) will hopefully identify covariates that are likely to affect outcomes across nontransplant and HCT therapies. Age considerations have typically been determined by institutional policies or research interests.

Many years of clinical research have been directed at reducing the toxicity of transplant conditioning regimens, using the day-100 mortality as a landmark. As the tolerability of high-intensity regimens declines with age, MDS represented an important target for the development of low/reduced intensity conditioning. However, the rationale for those developments was multifold. First, clinical trials had shown convincingly that beyond a certain level of intensity, overall survival and RFS were not further improved, since any gain in relapse reduction was counterbalanced by an increase in NRM. Second, murine models and earlier clinical analyses had shown that allogeneic donor cells exerted an immunologic graft-versus-tumor (GVT) effect that enhanced disease eradication without intensifying the conditioning regimen [32,33]. In fact, it may be possible to reduce the cytotoxic intensity and exploit the immunological activity of donor cells. Third, Schmid *et al.* showed that the infusion of donor lymphocytes in patients who had relapsed after HCT induced remissions, and Slavin *et al.* observed that donor lymphocytes by themselves could be used as immunotherapy [34,35]. Fourth, Storb *et al.* showed in a canine model that low-dose total body irradiation, is insufficient to ablate the recipient's marrow and associated with only mild toxicity, allowed for engraftment of allogeneic peripheral blood progenitor cells (PBPCs) [36].

Concurrently, the shift from high-dose total body irradiation to chemotherapy-only conditioning regimens, particularly with combinations of busulfan (BU) plus cyclophosphamide (CY), or fludarabine plus BU or melphalan, substantially reduced conditioning-related toxicity while securing engraftment of marrow or PBPCs from both related and unrelated donors [37–39]. In several studies, the incorporation of thymocyte globulin into the conditioning regimen, originally intended to facilitate engraftment of cells from unrelated donors, was shown to reduce GVHD, particularly in its chronic form, without increasing the risk of relapse post-HCT [40–44].

MDS stage & timing of HCT

The IPSS categories 'intermediate-2' or 'high-risk' or, more recently, the WPSS categories 'intermediate' to 'very high', are generally thought to identify patients for whom HCT should be considered early in the disease course. Cutler and collaborators showed that in patients with advanced MDS, upfront HCT was associated with a greater number of added life years [45]. For patients in the IPSS low category, delaying HCT until disease progression offered the longest life expectancy, while for patients with 'intermediate-1' risk delayed HCT offered a slight advantage. However, the study was based on several assumptions, and the IPSS does not take into consideration the impact of age and clinical determinants, such as transfusion dependence [45,46], which are reflected in other prognostic scoring systems [46,47]. When considering age, time from diagnosis to HCT, year of HCT, disease stage, source of stem cells, donor type and conditioning intensity, the WPSS was shown to provide an independent prognostic criterion for overall survival and relapse, but not for TRM [48].

Selection of donor & stem cell source

Historically, HLA-identical siblings have been the first choice as donors for HCT, and most transplant teams have maintained this approach. However, numbers of HCT from HLA-matched unrelated donors (URD) have grown rapidly, and at certain centers URD transplants are done more frequently than sibling transplants. In addition, umbilical cord blood cells are used with increasing frequency, particularly for patients from ethnic minorities for whom HLA-matched URDs are often difficult to identify. Finally, the development of novel HCT strategies allows for the use of HLA-haploidentical-related donors, thereby providing a donor for almost any patient to be considered for HCT, although experience in patients with MDS is still limited [49].

When considering a stem cell source other than cord blood cells, another question is whether cells harvested directly from the marrow or granulocyte-colony stimulating factor (G-CSF)-mobilized PBPCs should be used. PBPCs can be obtained by leukapheresis, not requiring anesthesia of the donor, and they provide more rapid engraftment than marrow. However, PBPCs also convey a higher risk of GVHD, particularly chronic GVHD. Nevertheless, retrospective analyses suggest that PBPCs result in superior survival in MDS patients undergoing related donor HCT, due to lower relapse rates [50,51]. For example, Guardiola and collaborators showed significantly improved 2-year RFS with PBPCs in 234 MDS patients (50 vs 39%, respectively) [52]. However, a recently completed randomized trial with URD transplants showed comparable outcomes with marrow and PBPCs, albeit with a higher incidence of GVHD in PBPC recipients [53].

What can patients expect from HCT?

HLA-matched siblings & unrelated donors

An earlier analysis from the National Marrow Donor Program including 510 URD transplants for MDS showed a RFS of 29% at 2 years and 26% at 4 years [54]. A study from our center involved 109 patients with MDS conditioned with BU targeted to plasma concentrations of 800–900 ng/ml plus CY, and transplanted from siblings (n = 45) or URD (n = 64) [55]. RFS at 3 years was 56% for related and 59% for unrelated recipients. Relapse occurred in 16 and 11% of patients, respectively. The 3-year NRM was 28 and 30%, respectively. This study established that selection of URDs based on high-resolution HLA typing leads to HCT outcomes similar to those with HLA-matched siblings.

A study by the Italian Cooperative Group (GITMO) showed a 5-year overall survival of 80% in patients with RA, 57% with refractory cytopenia with multilineage dysplasia, 51% with RAEB-1, and 28% with RAEB-2 [48]. Yet another series of 374 patients with low-risk MDS (median age of 39 years) showed a 4-year overall survival of 52% [56], similar for HLA-identical sibling and HLA-matched URD transplants. The best results were achieved with HCT early after diagnosis. A recent study of 118 patients <18 years of age showed an 8-year RFS of 65% for patients with refractory cytopenias with multilineage dysplasia and 48% among patients with RAEB [57], representative of all trials, showing superior results with less advanced disease [58,59].

Studies at our own center are in agreement with those findings showing RFS in the range of 75% for low-risk MDS and 30–35% for high-risk disease, the difference being due almost exclusively to relapse [55]. A European Group for Blood and Marrow Transplantation study showed 5-year relapse probabilities of 34, 35 and 57%, and TRM of 33, 42 and 46%, respectively, among patients with good, intermediate and poor risk cytogenetics by IPSS (discussed in [31]). An analysis by Armand *et al.* in 476 patients [60] supports those data, which were further validated in a multicenter study using only two ‘transplantation-specific’ cytogenetic risk groups (good/intermediate versus poor risk) [61].

We recently examined the impact of the newly proposed five-category cytogenetic risk classification [8] in comparison to the IPSS classification in 1042 patients who underwent HCT at our center. The 3-year probabilities of relapse for the five cytogenetic risk categories were 8, 17, 19, 26 and 48%, respectively, while overall survival at 3 years declined from 46% in the ‘very good’ risk group to 8% in the ‘very poor’ risk group. However, even with this five-group categorization, increased myeloblasts still added further information, that is, contributed to HCT outcome [Deeg J *et al.*, Unpublished Data].

Finally, several studies suggest that the replacement of BU with treosulfan may offer an advantage for HCT outcome, with as many as 80% of MDS patients without high-risk cytogenetics surviving in remission [62,63]. Across the board, however, results remained unsatisfactory in patients who presented with high-risk cytogenetics. The high frequency of high-risk cytogenetics is also the reason for poor overall results in patients with secondary MDS [64,65].

Clearly, myeloblast count and clonal karyotype remain the major determinants of HCT outcome.

Cord blood

A Japanese study in 33 adult MDS patients given umbilical cord blood cells showed 5-year TRM and relapse rates of 14 and 16%, respectively; survival was 70% [66]. Similar results were reported by Parikh and collaborators in pediatric patients [67]. The Minnesota group reported results with HLA-matched related donors (n = 47) and with cord blood (n = 43, including ten with MDS) in patients <55 years of age prepared with RIC, and showed 3-year RFS of 30 and 34%, respectively (p = 0.98) [68]. There was no difference with regard to acute GVHD, but cord blood recipients had less chronic GVHD (17 vs 40% at 1 year). Currently, most centers prefer allele-level-matched URDs over cord blood, but the use of cord blood is expected to expand further. The selection algorithms for less well-matched donors are highly center-specific and beyond the scope of this review.

HLA-haploidentical donors

Any person with a living parent or child will have a potential HLA-haploidentical donor. While early results with HLA non-identical HCT were disappointing [69], recent research and the use of CY after RIC HCT have substantially improved the success rate. de Witte *et*

al. reported on 1378 MDS patients, including 91 patients transplanted from HLA-nonidentical related donors [70]. The 3-year survival was 28%, but TRM was 66%, rather typical of earlier studies. A retrospective analysis of results in 185 patients with hematologic malignancies suggested that the number of HLA locus mismatches was not associated with RFS, relapse or NRM [71]. At the MD Anderson Cancer Center (TX, USA), 28 patients underwent T-cell-depleted HLA-haploidentical HCT after conditioning with fludarabine, melphalan, thiotepe and ATG [72]. Survival was 42% for patients with <15% myeloblasts and 0% for more advanced disease; day-100 (1-year) TRM was 9% (32%). Chen *et al.* reported on 36 patients with high-risk MDS who underwent HLA-mismatched/HLA-haploidentical HCT with G-CSF-primed marrow and G-CSF-mobilized PBPCs, and showed a 2-year RFS of 65% [73]. Patients transplanted within 7 months of diagnosis had better outcomes (89% RFS) than those transplanted later (43%). These data demonstrated the feasibility of the technique, but more developmental work is needed.

Can pre-HCT therapy improve post-HCT outcome?

Various efforts have been undertaken to ‘debulk’ patients with advanced MDS before HCT. Conventional induction-type chemotherapy with anthracyclins plus cytosine arabinoside or topotecan combinations, as well as myelotarg, have resulted in remissions, generally of short duration, in 30–40% of patients. However, mortality related to treatment was in the range of 10–15%.

The availability of the hypomethylating agents 5-azacitidine and decitabine, widely used as non-HCT therapy for MDS, has changed that strategy. Treatment can be given in an ambulatory setting and is associated with very low toxicity and mortality. However, controlled trials are not available, and retrospective analyses are not conclusive. Field *et al.* analyzed results in 54 consecutive patients with MDS or CMML who underwent HCT from HLA-matched donors [74]. Among these, 32 patients had received 5-azacitidine, and 24 had not. The 1-year post-HCT survival was 47 and 60%, RFS was 41 and 51%, and relapse incidence was 20 and 32%, respectively. The authors concluded that there was a trend towards a lower relapse incidence in 5-azacitidine-treated patients, but it was not clear whether patients in both subcohorts were comparable with regard to disease risk. Similar data were reported by De Padua Silva *et al.* and by Lubbert *et al.* in smaller numbers of patients [75,76].

Data relevant to the question whether patients on hypomethylating therapy should continue treatment until therapy fails, or should go to HCT while still responding to treatment, have been presented recently. In 67 patients with MDS and 20 with CMML who had received decitabine, Jabbour *et al.* observed a median survival of 4.3 months, and an estimated 1-year survival of 28% [77]. The outcome was comparable for all MDS risk categories (defined by IPSS). Prébet *et al.* examined the outcome in patients treated with 5-azacitidine for at least 4 or 6 months but did not tolerate 5-azacitidine or show disease progression [2,78]. Median survival after 5-azacitidine failure was 4.1 months. Of note, 37 patients who underwent allogeneic HCT (14% of all patients) at 1–26 (median 5) months after 5-azacitidine failure had a median survival of 19.5 months. Among the 14 patients transplanted for progressive disease, the median survival was 17 months, while it was not reached in the 14 patients who had stable disease.

Although limited, the data indicate that patients whose disease progresses on/after hypomethylating therapy have a poor prognosis. Therefore, if these patients are candidates, HCT should be carried out before there is evidence of disease progression.

Post-transplant therapy

Post-HCT relapse has remained a major cause of failure in patients with high-risk MDS [31,79,80]. Intensification of the HCT conditioning regimen has reduced relapse incidence, but was associated with prohibitive NRM [1]. Current efforts are, therefore, directed at exploiting the immunological GVT effect of donor cells or adding post-HCT ‘adjuvant’ therapy. Hypomethylating agents, with minimal toxicity, provide a means of post-HCT treatment, as prophylaxis or preemptively. Hypomethylating agents may have the added benefit of increasing expression of various gene products that would represent targets for the donor cell-mediated GVT reaction and eradication of residual MDS cells [81].

The MD Anderson group has treated patients with 5-azacitidine, beginning at 6–7 weeks after HCT, and has shown that a dose of 32 mg/m² given for 5 consecutive days was well tolerated [82]. Among 45 patients with high-risk MDS/acute myeloid leukemia they observed a 1-year RFS of 58%. The incidence of chronic GVHD was lower in 5-azacitidine-treated patients than in historical controls, an observation supported by a report from Washington University, USA, which emphasized, in addition, that the beneficial effect on GVHD did not compromise GVT effects [81].

Platzbecker and colleagues screened patients with MDS or acute myeloid leukemia post-HCT for a decline in donor CD34⁺ chimerism and administered 5-azacitidine for ‘imminent relapse’ if and when chimerism fell below 80% [83]. A total of 20 out of 59 screened patients qualified and were started (median day 169) on 5-azacitidine at 75 mg/m²/day for 7 days. Sixteen patients showed an increase in CD34⁺ donor chimerism or stabilized at 80%. Hematologic relapse eventually occurred in 13 patients (65%), but was delayed to days 56–558 (median 231) after documentation of declining CD34 chimerism to below 80%. The data suggested that preemptive treatment with 5-azacitidine was safe, and it delayed or even prevented hematological relapse.

Cure, quality of life or both?

One aspect of HCT often neglected in discussions with patients, particularly in older individuals, is quality of life (QoL). HCT is the only treatment with curative potential in MDS, and progressive modifications of transplant regimens have reduced toxicity and mortality; even patients in their 70s have been transplanted successfully. However, GVHD has remained a major obstacle. While GVHD manifestations may occur later and tend to be milder with RIC transplant regimens, the frequency is not significantly different from that in patients conditioned with high-intensity regimens. Standard therapy for acute and chronic GVHD is still with glucocorticoids, which are poorly tolerated in older patients. In addition to the increased risk of infections, morbidity related to musculoskeletal effects interferes with activity and QoL. Patients may require extensive rehabilitation and may spend the remainder of their life in skilled-care facilities. More importantly, preliminary data indicate that particularly patients with low or intermediate-1 risk MDS (by IPSS), have a longer life expectancy if they do not undergo HCT early in their disease course. This perspective is different for patients with advanced MDS. However, for this latter group it will be important to consider not only HCT survival statistics, but also life expectancy related to medical conditions other than MDS. Furthermore, Koreth *et al.* showed recently that even with advanced MDS, HCT will offer an advantage to older patients only by about 5 years after HCT [84]. If non-HCT therapy without significant morbidity and mortality can modify the natural course of the disease, the net gain may be higher without HCT. There is agreement that not the chronologic, but rather the biologic age of patients determines the probability of success with HCT. Therefore, careful evaluation of older patients may lead to the selection of those for HCT who are biologically younger than, say 60 or 65 years. Finally, nonmedical

and even nonbiologic factors need to be considered. The psychological and financial stress associated with HCT can be overwhelming. While discussions of the economic impact of HCT on the family are typically avoided, expenses associated with HCT may exhaust a family's reserves. We should ask, therefore, whether such an outcome – for the family – is justifiable if the probability of failure is high and it is likely that the patient will not regain productivity and QoL.

Expert commentary

MDS, long on the sidelines of medical research, has clearly been 'discovered' as an exciting area of research at the applied clinical level as well as in basic investigations. HCT is currently the only treatment modality with proven curative potential. Over the past decade, considerable progress has been made with regard to improving transplant regimens, identifying suitable donors for a growing number of potential transplant candidates, and managing post-HCT complications. However, GVHD and relapse of MDS, particularly in patients with high-risk cytogenetics, have remained stumbling blocks on the road to uniformly successful HCT. Novel cytogenetic classifications and a developing understanding of the role of acquired mutations have improved our prognostic accuracy and may allow for the design and application of more disease stage-specific treatment algorithms. There is preliminary evidence that genetically or functionally modified donor cells (T cells and NK cells) can be infused after HCT to eliminate residual MDS cells (with the objective of reducing relapse) without increasing the risk of GVHD. While ever older patients are being transplanted with some success, the impact of HCT on QoL and the financial stress associated with a treatment that may prove futile, deserves further study.

Five-year view

HCT in MDS patients has undergone considerable changes over the past decade. There is now a broad spectrum of conditioning regimens that allows clinicians to offer HCT to many patients, even those with comorbid conditions and of advanced age. With the use of cord blood and HLA-haploidentical donors, the option of HCT is now available for the vast majority of patients. The post-HCT administration of CY or, as may be the case, hypomethylating agents, may further improve results. However, additional work is needed to prevent GVHD and to reduce the relapse incidence in patients with high-risk cytogenetics and advanced disease. Whether novel immunotherapeutic strategies, including radioimmunotherapy, can achieve that goal remains to be determined. It is likely that transplant regimens will be further refined, probably by removing or adding back selected cell populations, such as NK cells or regulatory T cells; QoL considerations must be part of patient counseling, and physicians advising patients need to be prepared to discuss the potential futility of HCT.

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Key issues

- Novel classification schemes for myelodysplastic syndrome allow for more accurate prognostication and, as a consequence, recommendations for hematopoietic cell transplantation (HCT) or non-HCT therapy.
- Validation of comorbidity scoring systems has provided the basis for risk assignment to a given patient.
- Development of a broad range of conditioning regimens has allowed clinicians to offer HCT dependent upon disease stage and patient characteristics.
- The increasing use of unrelated donors and the establishment of protocols for cord blood and HLA-haploidentical HCT has made HCT available to a rapidly growing number of patients.
- Post-HCT relapse is a major hurdle to greater success, particularly in patients with high-risk cytogenetics.
- Graft-versus-host disease both in its acute and chronic forms is a frequent cause of morbidity after HCT.
- While HCT is being carried out in ever older patients, the enthusiasm to do so has overshadowed the impact of the procedure and its complications, such as graft-versus-host disease, on quality of life and socioeconomic stress.
- Novel non-HCT modalities need to be further integrated into the overall HCT strategy.