Hematopoietic Cell Transplantation for Myelodysplastic Syndrome

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OVERVIEW

Although high-dose chemotherapy may cure a small subset of patients with myelodysplastic syndrome (MDS), allogeneic hematopoietic cell transplantation (HCT) is the only currently available modality that is curative in a large proportion of patients. Approximately 30% to 40% of patients with high-risk MDS and 60% to 80% of patients with low-risk MDS survive long-term in remission. Disease classification and risk assessment schemes, such as the World Health Organization (WHO) Prognostic Scoring System (WPSS), the Revised International Prognostic Scoring System (IPSS-R), and patient characteristics as assessed by the HCT Comorbidity Index (HCT-CI) or other scores, provide guidance for patient management. First, by defining the prognosis of patients without HCT, these tools help physicians decide who should and who should not be transplanted. Second, they predict at least in part how successful a transplant is likely to be. Pretransplant cytogenetics and marrow myeloblast count are the strongest risk factors for post-transplant relapse. The HCT-CI allows physicians to estimate the probability of nonrelapse mortality after HCT; recent data suggest that there is also a relationship to the development of graft-versus-host disease (GVHD). In general, the emphasis has shifted from high-dose therapy, aimed at maximum tumor-cell kill, to reduced-intensity conditioning (RIC), relying on the donor cell-mediated graft-versus-tumor (GVT) effects to eradicate the disease. GVT effects are most prominent in patients who also develop GVHD, especially chronic GVHD. Thus, ongoing work is directed at reducing GVHD while maintaining potent GVT effects and at exploiting the growing knowledge of somatic mutations for the development of targeted therapies.

Although high-dose chemotherapy may cure a small subset of patients with MDS, allogeneic HCT is currently the only modality shown to be curative for 30% to 80% of patients, depending on patient and disease characteristics, the source of stem cells, and the transplant strategy applied. The availability of human leukocyte antigen (HLA)-matched unrelated donors, HLA-identical siblings, (HLA-nonidentical) cord blood, and HLA-haploidentical relatives allows for the identification of suitable stem cell donors for the vast majority of patients. However, despite considerable progress, problems remain in regards to the prevention of GVHD while maintaining the desired graft-versus-leukemia (GVL) effect—an essential factor in disease eradication and optimization of transplant conditioning regimens.

DISEASE CLASSIFICATION AND TRANSPLANTATION

The WHO classification,[1] evolving from the classic French-American-British (FAB) schema,[2] has identified MDS subcategories, such as del(5q) with superior prognosis or, conversely, refractory cytopenia with multilineage dysplasia with inferior prognosis relative to refractory anemia, and has categorized all patients with 20% or more marrow myeloblasts as having acute myeloid leukemia (AML; Table 1). An additional poor risk factor is the presence of marrow fibrosis.[3] These parameters are important when considering indications for HCT. The incorporation of cytogenetic information and transfusion needs and the degree of peripheral blood cytopenias in risk assessment scores such as the WPSS[4] or the IPSS-R[5] (Table 2 and the inclusion of age, for example, in the MD Anderson score,[6] have refined our prognostic ability and thereby provided guidance for HCT—specifically a more conservative, observing strategy for good risk and a more aggressive, intensive treatment approach for patients with poor-risk disease.

TRANSPLANT RISK ASSESSMENT

Patient Characteristics

Older age has long been considered a contraindication for transplantation. Studies over the past decade have shown that more than chronologic age, comorbid conditions that may be associated with advanced age (but could also be present in younger patients) are the dominant factors that negatively affect transplant outcome. Those conditions have been cataloged in the HCT-CI, and results clearly show inferior outcome with increasing HCT-CI scores, which include prior diagnosis of a solid

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tumor, hypertension, or impaired pulmonary function, among others.[7] Other classification schemes have also included transplant characteristics, in particular, the stem cell source,[8] and more recently have applied a modified system to patients transplanted with reduced-intensity conditioning (RIC) regimens.[9]

Conditioning Regimens

The optimum conditioning regimen has not been determined. In general, however, the emphasis in allogeneic HCT has shifted from high-dose (myeloablative) therapy, aimed at cytotoxic tumor-cell kill, to low (nonmyeloablative) or RIC, relying on immune effects mediated by GVT effects to eradicate the disease.[10-13] RIC regimens have reduced the incidence and severity of treatment-related toxicity and day 100 mortality to less than 10% or even 5% but generally have resulted in a higher incidence of MDS relapse than observed with high-intensity regimens.[14] In fact, a recent multiinstitutional U.S. trial involving patients with MDS or AML (BMT CTN 0901) was closed prematurely because of inferior outcome in patients conditioned with RIC regimens.

Donor-Host Immunity

Allogeneic HCT carries the risk of the adverse effects of the bidirectional reactivity of donor and host cells. Host-versus-donor reactivity leading to rejection of the graft is an infrequent event. Donor-versus-host reactivity leading to clinical manifestations, however, occurs in about half of all patients.[15,16] Although GVT effects contribute to disease eradication, those effects are most prominent in patients who also show clinical evidence of GVHD. In fact, the most prominent GVL effects are observed in patients who develop chronic GVHD, which occurs in 40% to 60% of patients transplanted with unmanipulated donor cells[17]; the incidence tends to be lower in patients receiving T cell–depleted grafts[18] and, possibly, patients administered post-transplant cyclophosphamide,[19] which appears to be capable of inactivating host-reactive donor cells.

KEY POINTS

- Hematopoietic cell transplantation provides curative therapy for patients with myelodysplastic syndrome.
- The clonal karyotype is the strongest predictor of post-transplant relapse.
- The availability of human leukocyte antigen (HLA)-matched related and unrelated donors, HLA-haploidentical relatives, and umbilical cord blood helps identify donors for the vast majority of patients.
- Additional research is needed to prevent graft-versus-host disease while maintaining the graft-versus-tumor effect.
- As myelodysplastic syndrome is primarily a disease of older age and quality of life is a top priority for most older individuals, discussions regarding transplantation in older patients must include not only the acute effects of transplantation but also delayed effects.

Further, immune-incompetence early after HCT and GVHD-associated immunosuppression severely increases the risk of systemic infections—another cause of post-HCT morbidity and mortality.[20]

Stem Cell Source

Peripheral blood progenitor cells are currently the preferred source of stem cells, because of their rapid kinetics of engraftment and more potent GVL effect than marrow cells, albeit at the risk of a higher incidence of GVHD.[15] Cord blood cells are typically associated with slow engraftment and the associated risk of bleeding and infections.[21,22] The incidence of relapse, however, in many studies has been lower than with stem cells obtained from adult donors. Transplantation of HLA-haploidentical cells carries an increased risk of graft rejection, although recently used conditioning regimens have reduced that risk, and the incidence of GVHD has been similar to or lower than that observed with HLA-matched donor cells, presumably related to the post-transplant administration of cyclophosphamide.[23] Data from patients with MDS are too limited to draw firm conclusions regarding the effect on relapse.

TRANSPLANT INDICATIONS AND OUTCOME

Based on several retrospective and decision analyses, HCT is typically offered to patients with intermediate-2 or high-risk disease (by IPSS criteria) or (intermediate) poor- and very poor–risk by IPSS-R (or similarly by WPSS) criteria, whereas patients in lower-risk categories are often managed more conservatively, for example, with hypomethylating agents, since significant advantages of HCT in regard to duration of survival have been shown only in those patients at higher risk.[24-26] Nevertheless, there is a tendency to offer HCT also for lower-risk disease, particularly for younger patients.[12,27] Not unexpectedly, long-term survival in remission (following HCT from HLA-matched related or unrelated donors and high-intensity conditioning) is in the range of 75% for patients with low-risk disease, approximately 60% with intermediate-1, 45% with intermediate-2, and 30% for patients with high-risk MDS.[27,28] The major factors with a negative effect on relapse-free survival are pre-HCT karyotype and marrow blast count. Patients with very poor cytogenetics, including monosomal karyotype, have a 10% or less probability of long-term survival.[27,29]

Caution is indicated when advising patients who are considered transplant candidates to undergo a trial with hypomethylating agents. Clearly, a proportion of patients (approximately 45%) will respond to hypomethylating therapy, on average, for 9 to 10 months. However, when transplantation is carried out in patients whose disease has progressed while receiving such therapy, results are poor, although the median survival is prolonged to about 14 months in comparison to only 5 to 6 months for all "5-azacitidine failures." On the other hand, patients who are responding or not progressing while receiving hypomethylating treatment have an approximately 30% probability of being transplanted successfully.[30]

The effect of disease risk is modified by the presence of comorbidities; patients with HCT-CI scores of 3 or higher experience

TABLE 1. WHO Classification

Disease	Blood Findings	Bone Marrow Findings
RCUD (RA, RN, RT)	Unicytopenia or bicytopenia*	Unilineage dysplasia ≥ 10% of the cells in one myeloid lineage
	No or rare blasts (< 1%)**	< 5% blasts
		< 15% of erythroid precursors are ring sideroblasts
RARS	Anemia	≥ 15% of erythroid precursors are ring sideroblasts
	No blasts	Erythroid dysplasia only
		< 5% blasts
RCMD	Cytopenia(s)	Dysplasia in ≥ 10% of the cells in ≥ 2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes)
	No or rare blasts (< 1%)**	< 5% blasts in marrow
	No Auer rods	No Auer rods
	$< 1 \times 10^9$/L monocytes	± 15% ring sideroblasts
RAEB-1	Cytopenia(s)	Unilineage or multilineage dysplasia
	< 5% blasts**	5%-9% blasts**
	No Auer rods	No Auer rods
	$< 1 \times 10^9$/L monocytes	
RAEB-2	Cytopenia(s)	Unilineage or multilineage dysplasia
	5%-19% blasts†	10%-19% blasts†
	Auer rods ±†	Auer rods ±†
	$< 1 \times 10^9$/L monocytes	
MDS-U	Cytopenias	Unequivocal dysplasia in 10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS
	< 1% blasts**	< 5% blasts
MDS associated with isolated del(5q)	Anemia	Normal to increased megakaryocytes with hypolobated nuclei
	Usually normal or increased platelet count	< 5% blasts
	No or rare blasts (< 1%)	Isolated del(5q) cytogenetic abnormality
		No Auer rods

Abbreviations: WHO, World Health Organization; RCUD, refractory cytopenia with unilineage dysplasia; RA, refractory anemia; RN, refractory neutropenia; RT, refractory thrombocytopenia; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, refractory anemia with excess blasts; MDS-U, Myelodysplastic syndrome-unclassified.
*Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.
**If the marrow myeloblasts percentage is < 5% but there are 2% to 4% myeloblasts in the blood, the diagnostic classification is RAEB-1; cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS-U.
†Cases with Auer rods and < 5% myeloblasts in the blood and less than 10% in the marrow should be classified as RAEB-2. Although the finding of 5% to 19% blasts in the blood is, in itself, diagnostic of RAEB-2, cases of RAEB-2 may have < 5% blasts in the blood if they have Auer rods or 10% to 19% blasts in the marrow or both. Similarly, cases of RAEB-2 may have < 10% blasts in the marrow but may be diagnosed by the other two findings, Auer rod+, and/or 5% to 19% blasts in the blood.

TABLE 2. IPSS-R Prognostic Scores[5]

	Score						
Variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
Marrow blasts (%)	≤ 2		> 2-< 5		5-10	> 10	
Hemoglobin	≥ 10		8-< 10	< 8			
Platelets	≥ 100	50-< 100	< 50				
Neutrophils	≥ 0.8	< 0.8					

Abbreviation: IPSS-R, Revised International Prognostic Scoring System.

survival rates that may be substantially lower than for patients without scored comorbidities.[11,31,32] We have shown, for example, in patients transplanted for chronic myelomonocytic leukemia (considered under the heading of MDS) from HLA-matched related or unrelated donors that the overall survival in remission was 40%. However, a breakdown by HCT-CI showed a probability of 53% for patients with HCT-CI scores of 0 to 2 but only 26% for patients with scores of 3 or higher.[31]

As MDS is primarily a disease of older individuals who often present with comorbid conditions and who are less likely to tolerate high-intensity conditioning regimens, recent studies have analyzed the relevance of disease classi-

fication for the decision of transplantation. Koresh et al[33] used a Markov decision model and quality-of-life utility estimates to assess transplant success in 514 patients with de novo MDS who were age 60 to 79. Results showed that for patients with low- or intermediate-1-risk MDS (by IPSS criteria)[34] and conditioned with reduced-intensity regimens, life expectancy was 38 months on average, compared to 77 months in patients with nontransplanted disease. In patients with intermediate-2 or high-risk MDS, the corresponding figures were 36 and 28 months, clearly showing an advantage for transplantation, associated with a quality-adjusted survival benefit. These data support the recommendation for or against transplantation on the basis of disease stage.

Encouraging results have been achieved recently with treosulfan-based regimens, which are associated with low toxicity and excellent efficacy. In a trial conducted at the Fred Hutchinson Cancer Research Center, 60 patients with MDS or AML were prepared with a regimen of fludarabine (30 $mg/m^2 \times 5$) and treosulfan (12 g or 14 $g/m^2 \times 3$) for HCT from HLA-matched related or unrelated donors. Two-year nonrelapse mortality was less than 10%, and relapse-free survival for patients with standard- or intermediate-risk cytogenetics was 80%.[35] Patients with high-risk karyotype, in contrast, showed long-term relapse-free survival of only 35% to 40%. Ongoing trials suggest that with the addition of low-dose (2 Gy) total body irradiation to fludarabine and treosulfan, relapse-free survival may increase to 65%, even among patients with high-risk cytogenetics.[36]

Although cytogenetics have been shown to have the strongest effect on post-transplant relapse and, as a result, relapse-free survival,[27] emerging data suggest that somatic mutations further modify the outcome. Bejar et al have shown that mutations in p53, DNMT3A, or TET2 each decrease the probability of post-transplant survival by a factor of three to four.[37] On the other hand, data show that mutations in SF3B1 are associated with a superior leukemia-free and overall survival, possibly affecting the decision on and the timing for transplantation.[38]

OUTLOOK

Clearly, more effective strategies are needed for the prevention of GVHD and relapse. Various strategies of post-HCT therapy, for example, with hypomethylating agents or cellular therapy with natural killer cells or genetically modified T cells (directed, for example, at Wilms tumor 1), are currently being explored in efforts to prevent relapse.[39] The use of post-HCT administration of cyclophosphamide, in the hands of several investigators, has been effective in preventing GVHD after HLA-haploidentical transplants and is also being tested in patients receiving HLA-matched transplants where acute or chronic GVHD (or both) occur about in half of all patients and, particularly with unrelated HCT, involvement of the intestinal tract proves life threatening.[23]

The use of HCT in growing numbers of older patients with MDS, even in their 70s, poses special challenges, particularly with the intensity of conditioning. Currently those patients are highly selected, and results cannot be extrapolated to that age segment in general. Further, first-line therapy with steroids, although effective in a portion of patients, is often poorly tolerated in older individuals.[40] Metabolic abnormalities, infections, and long-term effects on muscles and skeleton can severely affect quality of life. Thus, not only comorbidities before HCT but also complications developing after HCT must be prioritized when discussing HCT with older patients, for whom quality of life (rather than quantity of life) is often a top priority.

Clearly, the rapidly expanding understanding of the effect of various mutations in clonal cells will affect disease risk classification and may also lead to novel antirelapse strategies aimed at molecular targets.[41,42]

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