Allogeneic transplantation for aplastic anemia

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Objective: To discuss the role of allogeneic transplantation for the treatment of severe aplastic anemia.

Methods: Published reports for treatment of severe aplastic anemia were searched with Medline. Search terms included severe aplastic anemia, HLA-matched sibling, unrelated donor, hematopoietic stem cell transplantation.

Results: Survival after HLA-matched sibling donor transplantation is approximately 80% in patients aged less than 20 years. Survival rates are lower in older patients ranging from 50–70%. The risks of transplant-related morbidity and mortality increase with age and explain the observed lower survival rates in older patients. Unrelated donor transplantation is reserved for patients who lack a matched related donor and have failed at least one course of immunosuppressive therapy. Survival after unrelated donor transplantation has also improved in recent years and largely attributed to the selection of donors who are fully HLA-matched to the patient. The risks of transplant-related complications are higher than after HLA-matched sibling transplantation. Graft-versus-host disease (GVHD) is higher; GVHD can lead to significant morbidity and mortality. Other frequent complications include graft failure and pulmonary complications. The use of peripheral blood progenitor cells has also contributed to higher GVHD risks and consequently excess deaths.

Discussion: The results of allogeneic transplantation, from related and unrelated donors have improved substantially in the last decade. Early referral for transplantation, selection of HLA-matched donors and improved supportive care has contributed to the success of this treatment. The choice of graft used for transplantation is important regardless of donor type; bone marrow is the preferred graft.

Keywords: Aplastic anemia, Allogeneic transplantation, Survival

Introduction

In most cases, aplastic anemia is an immune-mediated disorder; T lymphocytes destroy hematopoietic progenitor cells resulting in pancytopenia.1 Treatments for aplastic anemia include immune suppressive therapy (IST) with antithymocyte globulin (ATG), which lyses lymphocytes, and cyclosporine, which blocks T lymphocyte function, and hematopoietic stem cell transplantation (HCT), which replaces all hematopoietic progenitor cells, including lymphopoietic cells.2 There is general agreement that, when a human leukocyte antigen (HLA) matched sibling is available, HCT is first-line treatment for severe aplastic anemia (SAA). IST may be used as first-line therapy for older patients with an HLA-matched sibling. A similar strategy is generally employed for patients who do not have an HLA-matched sibling and must seek an alternative donor.3 Whether alternative donor HCT should be performed after failing one or more than one course of IST is uncertain and depends, in part, on patient factors predicting the likelihood of further response to IST and the likelihood of good outcome with HCT, as well as timely availability of a suitable donor.

HLA-Matched Sibling Donor Transplantation

Matched sibling HCT is the treatment of choice for patients with SAA. While some support this treatment as first-line therapy for patients up to the age of 50–55 years, others limit transplantation as first-line treatment to those younger than 40 years. There is general agreement that risks of mortality after HCT increase with age and consequently so too the desire to avoid this procedure in older persons. In a recent report from the Center for International Blood and Marrow Transplant Research (CIBMTR), mortality risks were higher in patients aged 20 years and older compared to those aged <20 years.4 Among those aged 20 years and older, mortality risks were higher in those over 40 years compared to those aged 20–40 years.4 In that report, the 5-year probabilities of overall survival were 82, 72, and 53% in patients aged <20 years, 20–40 years and >40 years, respectively.4 There was a 10–20% difference in absolute difference in overall survival between the three age groups. Acute and chronic graft-versus-host disease (GVHD) risks are higher in older patients and both acute and chronic GVHD are associated with...
lower survival. Other factors that had an adverse effect on survival included Karnofsky performance score less than 90 and an interval between diagnosis and transplantation that was longer than 3 months. Others have shown use of IST or androgens prior to transplantation also has an adverse effect on survival which compel physicians to weigh the risk of mortality after HLA-matched sibling transplantation versus offering IST as first-line therapy in older patients. Importantly, the choice of graft is associated with survival. Use of peripheral blood progenitor cells leads to higher GVHD, especially chronic GVHD, which translates to lower overall survival in children and adults who undergo HLA-matched sibling transplantation for SAA. Consequently, the recommended graft when considering HLA-matched sibling transplantation is bone marrow (BM).

Unrelated Adult Donor Transplantation

Unrelated donor transplantation is an effective therapy for SAA, but is limited by the availability of a suitably matched unrelated donor and is associated with higher risks of graft failure, GVHD and mortality than HLA-matched sibling transplantation. Selecting an appropriately matched donor for HCT is an important component of success. Large studies, primarily in patients with hematologic malignancies, indicate that donor-recipient matching at HLA-A, -B, -C or DRB1 (7/8 HLA match) is associated with higher risks of transplant-related mortality, grade 2–4 acute GVHD and overall mortality. Several groups, including the CIBMTR, have attempted to compare outcomes of transplantation for aplastic anemia using 8/8 HLA-matched versus HLA-mismatched grafts. Among 118 children and adolescents with aplastic anemia transplanted between 1989 and 2003 with unrelated adult donor BM grafts, mortality risks were lower after HLA-matched versus mismatched transplants. Ten-year probabilities of overall survival were 57% after 8/8 HLA-matched transplants compared to 39% after ≤7/8 HLA-matched transplants. In a more recent cohort of patients reported to the CIBMTR, survival probabilities after 8/8 HLA-matched unrelated donor BM transplantation was higher at 75%.

Transplantation Strategies: Conditioning Regimen

In general, the intensity of transplant conditioning regimen for HLA-matched sibling and unrelated donor transplantation is lower than regimens used for treatment of hematologic malignancies. The accepted transplant conditioning regimen for HLA-matched sibling donor transplantation is cyclophosphamide and ATG. On the other hand, unrelated donor transplants have higher rates of graft failure, regimen-related toxicity and GVHD than HLA-matched sibling transplants, even when the donor and recipient are 8/8 HLA-matched. Unrelated donor transplantations performed in the eighties and nineties incorporated high doses of total body irradiation (TBI) to prevent graft failure. However, high dose TBI-containing regimens are associated with severe acute toxicity and secondary malignancies. Therefore, to lower early toxicity and secondary malignancy, recent transplant conditioning regimens have used lower doses of TBI in combination with cyclophosphamide and ATG. Deeg and colleagues identified 200 cGy of TBI administered as a single dose together with cyclophosphamide (200 mg/kg) and equine ATG (90 mg/kg) as the optimal regimen in a radiation dose de-escalation study; graft failure occurred in 5% of patients and 5-year survival was 55%. Regimen-related toxicity (grade 3 or higher) and death decreased with de-escalation of the TBI dose. Age was an important predictor of survival; the 5-year probability of overall survival in younger patients (<20 years) was 73% compared to 46% in older patients (P=0.05). Lowering the dose of TBI had no impact on graft failure.

Conclusion

The selection of more closely HLA-matched donors and lowering the intensity of transplant conditioning regimens, have had a significant impact on survival after transplantation for SAA. BM is the preferred graft source. The role of UCB transplantation in patients without an HLA-matched adult donor needs
further exploration. An important unanswered question is the timing of unrelated donor transplantation. Although most people agree that alternative donor HCT should be reserved for patients failing IST, there may be a small group of patients whose likelihood of IST response is sufficiently low and whose likelihood of good HCT outcome is sufficiently high to consider alternative donor HCT early in the treatment course. Among patients who fail a first course of IST, more data are needed to identify those better served by alternative donor HCT versus a second course of IST. However, given the fact that infection, multiple transfusions and poor performance score greatly decrease the likelihood of HCT success, inordinate delay should be avoided.

References