Alternative Donor Transplantation for Aplastic Anemia

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Patients with severe aplastic anemia who do not have a human leukocyte antigen (HLA)-identical sibling generally receive immunosuppressive therapy as a first-line therapy, with allogeneic transplantation being reserved for those who do not have an adequate sustained response. Barriers to the use of unrelated-donor transplantation for aplastic anemia include identifying a suitable alternative donor, and risks of graft failure, regimen-related toxicity, and graft-versus-host disease (GVHD). Despite the more than 14 million adults registered with donor registries worldwide, only approximately 50% of patients of Caucasian descent will have an available and fully HLA-matched unrelated adult donor; the rate is substantially lower for non-Caucasians. While umbilical cord blood allows transplantation with greater donor-recipient HLA disparity (without excessive risk of GVHD), risks of graft failure and transplant-related mortality are higher than after transplantation of adult donor grafts. Among patients with a suitable donor, recent changes in pre-transplant conditioning regimens have lowered the risks of organ toxicity and graft failure. Although advances in donor HLA typing and selection practices and improved GVHD prophylaxis have lowered the risk, GVHD remains an important obstacle to long-term symptom-free survival. Despite these limitations, unrelated-donor transplantation offers the best chance of long-term survival for many patients in whom current immunosuppression strategies are not effective. Wider applicability of alternative-donor transplantation for aplastic anemia will require better approaches to prevent graft failure and GVHD and to expand the pool of unrelated-donor grafts. This includes exploring strategies to effectively use alternative grafts such as umbilical cord blood.

Introduction

In most cases, aplastic anemia is an immune-mediated disorder; T lymphocytes destroy hematopoietic progenitor cells, resulting in pancytopenia.[1–3] Treatments for aplastic anemia include immunosuppressive therapy (IST) with anti-thymocyte globulin (ATG), which lyses lymphocytes; cyclosporine, which blocks T-lymphocyte function; and hematopoietic stem-cell transplantation (HCT), which replaces all hematopoietic progenitor cells, including lymphopoietic cells.[2–6] There is general agreement that when a human leukocyte antigen (HLA)-matched sibling is available, HCT is the first-line treatment for patients with severe aplastic anemia who are younger than 40 to 45 years of age. While some also advocate HCT as a first-line treatment for older patients with an HLA-matched sibling, more commonly, IST is given as a first-line treatment in older patients and HCT is only offered if IST fails. A similar strategy is generally employed for patients who do not have an HLA-matched sibling and must seek an alternative donor.[7,8] Unrelated-donor transplantation is an effective therapy for aplastic anemia, but is associated with higher risks of graft failure, graft-versus-host disease (GVHD), and transplant-related mortality than HLA-identical sibling transplantation. Whether alternative-donor HCT should be done after the failure of one or more than one course of IST is uncertain, and depends on patient factors predicting the likelihood of further response to IST, the likelihood of good outcome with HCT, and the timely availability of a suitable donor.

As of 2008, more than 14 million adults were registered as potential donors with unrelated-donor registries worldwide.[9] However, only 50% to 60% of patients of Caucasian descent will find a fully HLA-matched and available unrelated adult donor; the probability is substantially lower for non-Caucasians. Only about 20% of Asians and 17% of African Americans will find a fully HLA-matched (at HLA-A, HLA-B, HLA-C, and HLA-DRB1) and available unrelated adult donor (data from the National Marrow Donor Program). Requirements for more stringent matching (i.e., at HLA-DQ and HLA-DP) further decrease the likelihood of a finding an acceptable donor and may not improve outcome (see below).

Identifying the Optimal Unrelated-Adult Donor: Donor-Recipient HLA Match

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, HLA-B, HLA-C, and HLA-DRB1 (an 8/8 HLA match) offers highest likelihood of survival.[10,11] A single mismatch at either the allele or antigen level (a 7/8 HLA match) is associated with higher risks of transplant-related mortality, grade 2 to 4 acute GVHD, and overall mortality. Some data suggest that donor-recipient mismatches at HLA-B or HLA-C are somewhat more tolerated than mismatches at HLA-A or HLA-DRB1. In contrast to earlier, smaller studies, recent analyses using the large database maintained by the National Marrow Donor Program and the Center for International Blood and Marrow Transplant Research (CIBMTR) suggest that mismatching at the HLA-DQ locus is not associated with adverse outcomes when the donor and the recipient are matched at HLA-A, HLA-B, HLA-C, and HLA-DR.[10,11] Mismatches at HLA-DP increase GVHD but do not adversely affect overall survival in patients transplanted for malignancy.

Studies that effectively examine the impact of donor-recipient HLA match require thousands of patients with genetic data at the level of individual HLA loci. Consequently, most studies focus on patients with hematologic malignancies, the most common indication for allogeneic HCT. 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 bone marrow grafts, mortality risks were lower after HLA-matched than after HLA-mismatched transplants.[12] Ten-year probabilities of overall survival were 57% after 8/8 HLA-matched transplants, compared with 39% after ≤ 7/8 HLA-matched transplants ($p = 0.01$).[12] In that report, there were no significant differences in acute GVHD, but the chronic GVHD risk was higher in the mismatched cohort (relative risk [RR] 2.05; $p = 0.03$). In a more recent cohort of patients reported to the CIBMTR, survival probabilities were higher, but the effect of HLA mismatching was still seen; the 2-year probability of survival was 78% after 8/8 HLA-matched transplants, compared with 60% after 7/8 or lower HLA-matched transplants (unpublished data, CIBMTR). Matching at the HLA-DQ and HLA-DP loci were not considered in this analysis, because a single mismatch at HLA-DQ or HLA-DP was not associated with adverse outcomes in the report by Lee et al. that analyzed more than 4000 donor-recipient pairs.[10] The European Group for Blood and Marrow Transplantation reported their experience with unrelated-donor HCT,[13] in which more recent transplantations were associated with better survival: 5-year probabilities of survival were 34% versus 57% for transplantations before versus after 1998 ($p < 0.001$). A limitation to that report was the lack of information on the degree of donor-recipient HLA match at HLA-A, HLA-B, HLA-C, and HLA-DRB1, the accepted standard now, but it is presumed that recent improvements in outcome result, at least in part, from better donor selection.

Adult Donor Graft Sources

Hematopoietic stem cells may be harvested from marrow or, after stimulation of the donor with hematopoietic growth factors, from peripheral blood. Over the past decade, the use of peripheral blood progenitor cells (PBPCs) has surpassed the use of bone marrow as the preferred source of allogeneic grafts for adults. Worldwide, PBPC collections from unrelated donors numbered 7260 (69%) and bone marrow collections 3221 (31%) in 2008.[9] Data from the CIBMTR suggest that approximately 25% of unrelated-donor HCTs for aplastic anemia use PBPC grafts. PBPC collection avoids general anesthesia and surgery, and consequently lowers the risks of donation. PBPC transplants are associated with faster neutrophil recovery but higher rates of GVHD, particularly chronic GVHD. The higher rate of chronic GVHD after HLA-matched sibling PBPC transplantation was associated with lower overall survival, particularly in children, in a study of patients with aplastic anemia.[14] Similarly, in an analysis of unrelated-donor transplants for aplastic anemia reported to the CIBMTR, mortality risks were higher with PBPC than with bone marrow grafts (RR 1.74; $p = 0.05$), with 2-year probabilities of overall survival of 76% and 55% with bone marrow and PBPC, respectively (unpublished data, CIBMTR), despite faster neutrophil recovery with PBPC. In summary, the data thus far suggest that bone marrow is the preferred graft source for adult-donor transplantation in aplastic anemia.

Other Unrelated-Donor Grafts: Umbilical Cord Blood

Unpublished data from the CIBMTR indicate that approximately 10% of unrelated-donor transplants for aplastic anemia performed in recent years have used umbilical cord blood (UCB) grafts. UCB as an alternative to unrelated-adult donor grafts is very attractive. Placental lymphocytes are immunologically naive, allowing for transplantation of UCB units with degrees of donor-recipient HLA disparity that would be associated with prohibitively high risks of GVHD when using bone marrow or PBPC grafts. UCB transplantation, almost always with some degree of donor-recipient mismatch, is used extensively for hematological malignancies. Two reports confirm rates of leukemia-free survival similar to that obtained with HLA-matched bone marrow transplants in children and adults with acute leukemia.[15,16] Although UCB transplantation is used for aplastic anemia, the data thus far are not as encouraging. Forty-five patients with aplastic anemia who received a single UCB unit as their first allograft were reported to the CIBMTR (unpublished data). Approximately 70% of these transplants were mismatched at two HLA-loci (antigen-level typing at HLA-A, HLA-B, and allele-level typing at HLA-DRB1). The median total nucleated cell dose at cryopreservation was 4×10^7/kg. Neutrophil recovery was slow, with d 28 and d 60 recovery probabilities of only 35% and 70%, respectively. The observed graft failure rate of 30% was higher and the 2-year overall survival rate of 35% lower than that seen with HLA-matched or mismatched bone marrow grafts. Data from Eurocord also suggest high graft failure rates and 2-year overall survival probabilities of about 40%.[17] Chan et al.,[18] in their report on nine patients, observed sustained engraftment in the five patients who received the combination of fludarabine (175 mg/m^2) + rabbit ATG (9 mg/kg), cyclophosphamide (120–150 mg/kg) + total body irradiation (TBI) (200 cGy). Three patients had primary graft failure (one receiving busulfan + fludarabine + ATG and two receiving fludarabine + ATG + cyclophosphamide 50 mg/kg + TBI 200 cGy). At the time of this writing, seven of nine patients are still alive, although two patients required a second UCB transplantation. The Japan Cord Blood Bank Network reported 2-year overall survival of 42% (13 of 31 patients are alive) after UCB transplantation for aplastic anemia.[19] These patients received various transplant conditioning regimens. The investigators identified the combination of TBI (200–500 cGy) + fludarabine + cyclophosphamide (50–100 mg/kg) as the optimal regimen; four of five patients receiving this regimen are alive as of this writing. This observed success in very small numbers of patients needs to be validated in a larger series. It is also likely that some of the reason for poor outcomes is the fact that these transplants are often done only in patients who have failed multiple courses of IST. There are no direct comparisons of outcomes after a second (or third) course of IST, an unrelated-donor HCT, and UCB transplantation. Controlled trials are needed to better understand the appropriate role and timing of these strategies.

Transplantation Strategies: Conditioning Regimen

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 1980s and 1990s incorporated high doses of TBI to prevent graft failure.[20] However, high-dose TBI regimens are associated with severe acute toxicity[21] and secondary malignancies.[22,23] Therefore, to lower early toxicity and secondary malignancy, recent pre-transplant conditioning regimens have used lower doses of TBI in combination with cyclophosphamide + ATG.[8] The doses of cyclophosphamide + ATG are similar to those used for HLA-matched sibling transplants. Deeg et al.[8] 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 the 5-year survival rate 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 with 46% in older patients ($p = 0.05$). Lowering the dose of TBI had no

impact on graft failure. Importantly, the survival rate in young patients approached that seen with HLA-matched sibling transplants.

In two other reports, one from the CIBMTR[12] and the other from the Japan Marrow Donor Program,[24] survival was lower and graft failure higher (10%) than that reported by Deeg et al.[8] The latter two studies included patients who had received pre-transplant conditioning regimens of varying intensity; in general, regimens with greater intensity were associated with higher regimen-related toxicity. The European group recommends a non-irradiation regimen with fludarabine + cyclophosphamide + ATG in patients age 14 years of age and younger.[25] This regimen, when it was offered to patients of all ages, resulted in an 18% graft failure rate and a 2-year survival rate of 73%. However, in older patients (>14 years), the graft failure rate was much higher at 35%. Consequently, this group now recommends the addition of TBI 200 cGy for patients older than 14 years, and reports graft failure rates of approximately 10%.[26]

In the United States, the Blood and Marrow Transplant Clinical Trials Network initiated a trial in 2004 (BMT CTN 0301) to explore the impact of replacing cyclophosphamide with fludarabine to lower regimen-related toxicity while preserving engraftment. All patients received TBI 200 cGy (single dose) and equine ATG (90 mg/kg). The study was designed such that the dose of cyclophosphamide de-escalated or escalated, based on engraftment and toxicity, among four dose levels: 150, 100, 50, and 0 mg/kg. The dose levels of 150 and 0 mg/kg have since been discontinued due to toxicity and graft failure, respectively; enrollment to the dose levels of 100 and 50 mg/kg continues. Interestingly, Chan et al.[18] identified the combination of fludarabine + ATG + cyclophosphamide 120 to 150 mg/kg + TBI 200 cGy as the optimal regimen for UCB transplantation, although only five patients received this regimen. However, it is possible that the optimal pre-transplant conditioning regimen will differ depending on the type of graft used.

GVHD

Acute and chronic GVHD rates are high after unrelated-donor transplantation. After transplantation of 8/8 HLA-matched bone marrow for aplastic anemia, the probably at d 100 of acute GVHD is approximately 30% and the 2-year probability of chronic GVHD is 30% (unpublished data, CIBMTR). This CIBMTR analysis showed that transplantation of 8/8 HLA-matched PBPC grafts resulted in higher risks of grade 2 to 4 acute GVHD compared with bone marrow (RR 1.83; $p = 0.01$); chronic GVHD risks were not different. GVHD risks are higher after HLA-mismatched transplants regardless of the type of graft source. The treatment for acute or chronic GVHD is further immunosuppression, which increases the risk of opportunistic infections and mortality. With extended follow-up, the excess chronic GVHD after HLA-matched sibling PBPC transplant is reported to lead to lower survival in younger patients (≤20 years).[14] Chronic GVHD is also associated with significant morbidity. Active chronic GVHD has been shown to impair health-related quality of life in long-term survivors,[27] and chronic GVHD is a risk factor for solid tumors in long-term survivors of allogeneic HCT.[23,28] Better strategies for preventing and treating GVHD are needed. While the risk of GVHD is higher after unrelated-donor transplantation, data thus far have not shown significant differences in rates of second cancer by donor source.

In addition to chronic GVHD, radiation in the pre-transplant conditioning regimen is a known factor for solid tumors in long-term survivors, with about 15 excess cases per 10,000 patient years in 1-year survivors.[28] Risk is highest with TBI doses of 1000 cGy or greater and age younger than under 30 years at exposure.[28] The recent practice of very-low-dose TBI (200 cGy) is expected to lower the risk of second cancers, although longer follow-up is necessary to be certain that this is the case.

Conclusion

The selection of more closely HLA-matched donors and lowering the intensity of the pre-transplant conditioning regimen have had a significant impact on survival after transplantation for aplastic anemia. Results are now much closer to those observed with HLA-identical sibling transplants, with graft failure rates of 5% to 10% and long-term survival rates of 60% to 80% with current regimens. The data favor low-dose TBI + cyclophosphamide + ATG as an appropriate pre-transplant conditioning regimen; the addition of fludarabine is still being actively investigated, but seems helpful in some studies. Bone marrow is the preferred graft source for most patients. 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 would agree that alternative donor HCT should be reserved for patients failing IST, there may be a small group of patients whose likelihood of sustained IST response is sufficiently low (e.g., in those with certain cytogenetic abnormalities) and who have factors indicating a high likelihood of good HCT outcome (e.g., young age, well-matched donor, untransfused) in whom alternative donor HCT should be considered early in the treatment course. Better biomarkers to predict IST response would be helpful in these decisions. 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.

Disclosures

Conflict-of-interest disclosure: Authors declare no competing interests. Off-label drug use: Fludarabine and ATG used in the setting of hematopoietic cell transplantation for aplastic anemia.

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