Alternative Donor Allogeneic Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

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Allogeneic hematopoietic cell transplantation (alloHCT) provides a potentially curative therapy for patients with high-risk or chemorefractory acute myeloid leukemia (AML). Historically, the applicability of alloHCT has been limited as only 30%–35% of patients have human leukocyte antigen (HLA)-matched siblings and outcomes using other donor types have been markedly inferior due to excess toxicity, graft failure, graft-versus-host disease (GVHD), and consequently non-relapse mortality. Advances in HLA typing, GVHD prophylactic approaches, and other transplantation techniques have successfully addressed these historical challenges. Herein, we review recent alloHCT studies using volunteer unrelated donors, umbilical cord blood units, or HLA-haploidentical donors, specifically focusing on studies that compared outcomes between donor sources. Although none are randomized and most are retrospective, these analyses suggest that current outcomes for AML patients using most alternative donor types are comparable to those seen using HLA-matched siblings.
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The curative potential of allogeneic hematopoietic cell transplantation (alloHCT) in treating patients with acute myeloid leukemia (AML) was first demonstrated over 50 years ago. Although cure was achievable in some patients with chemorefractory disease, alloHCT demonstrated a more dramatic benefit when used to treat AML patients earlier in their disease course.[1] In fact, relapse was lower after alloHCT than after consolidation chemotherapy,[2] suggesting that some patients with AML in first complete remission might benefit by proceeding directly to alloHCT.[3,4] Even so, many patients suffered non-relapse mortality (NRM),[5] stemming from a number of challenges to the success of alloHCT. These included graft failure, graft-versus-host disease (GVHD) in both its acute and chronic forms, and post-grafting opportunistic infections related to long-lasting deficiencies in both humoral and cellular immunity.

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Encouraging results with alloHCT were restricted to the minority of patients who had an HLA-matched sibling donor (MSD). A suitable unrelated donor (whether HLA-matched unrelated donor [MUD], one-locus HLA-mismatched unrelated donor [mmUD], or umbilical cord blood [UCB] unit) can be found for most individuals.[6] Furthermore, HLA-haploidentical (haplo) related donors are available for nearly all individuals. Nevertheless, outcomes were less favorable when alternative donors were used,[7–11] establishing HLA-matched sibling donors as the gold standard donor source. However, advances in transplantation approaches over the past few decades (Figure 1) have led to markedly improved outcomes after alternative donor alloHCT, now challenging whether MSD alloHCT still achieves superior outcomes. Herein, we review the expanding role of alternative donor alloHCT in the treatment of AML patients.

HLA-MATCHED UNRELATED DONORS

Since HLA-matching has been prioritized in donor selection, a patient without an HLA-matched related donor potentially could benefit from alloHCT using a volunteer HLA-matched unrelated donor. Index cases from the early 1980s proved the feasibility of this approach for treating acute leukemia.[12] Although initial studies suggested relative equivalence with MSD alloHCT,[13] a large, prospective case-control, multi-institutional study showed inferior engraftment, higher rates of grade II–IV acute and extensive chronic GVHD, and worse survival for unrelated donor alloHCT compared with MSD alloHCT.[10,11]

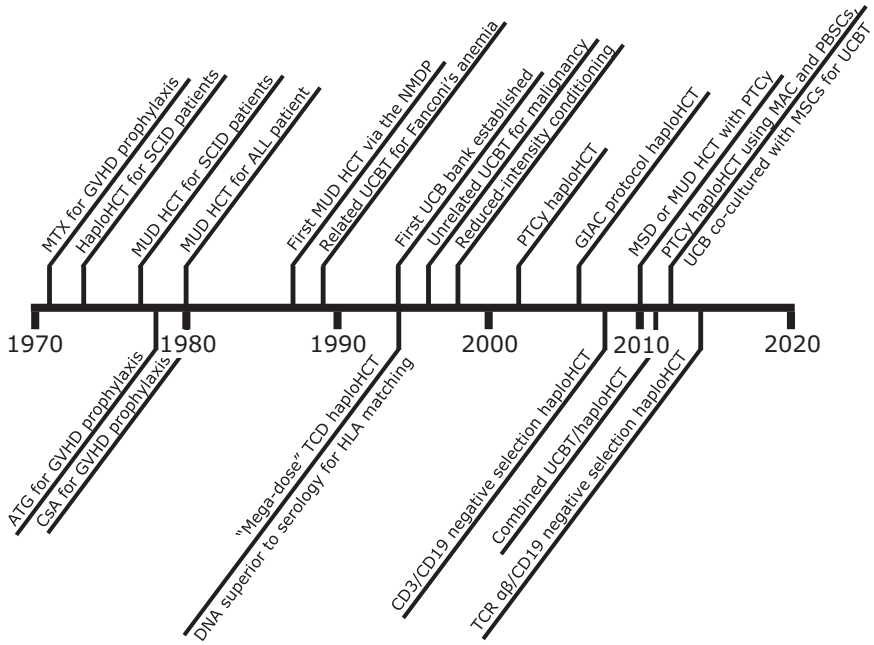

Figure 1. Timeline of important milestones in alternative donor allogeneic hematopoietic cell transplantation. For all milestones, the year of manuscript publication was used. Early unsuccessful transplantations were not included. MTX, methotrexate; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; HCT, allogeneic hematopoietic cell transplantation; HaploHCT, HLA-haploidentical HCT; SCID, severe combined immunodeficiency; MUD, HLA-matched unrelated donor; ALL, acute lymphoblastic leukemia; ATG, anti-thymocyte globulin; CsA, cyclosporine-A; NMDP, National Marrow Donor Program; UCBT, umbilical cord blood transplantation; TCD, T-cell depletion; PTCy, post-transplantation cyclophosphamide; MSD, HLA-matched sibling donor; TCR, T-cell receptor; MAC, myeloablative conditioning; PBSCs, peripheral blood stem cells; MSCs, mesenchymal stromal cells.

Given discrepancies in results between studies and the inclusion in some studies of mmUDs, large registry-based analyses were undertaken to evaluate the relative equivalence of MUD versus MSD alloHCT. The first compared alloHCT patients reported to the International Bone Marrow Transplant Registry between 1985 and 1991.[14] Each of graft failure, grades II–IV and III–IV acute GVHD, chronic GVHD, and NRM (>50%) were higher for all alternative donors (MUDs, one-locus mmUDs, or one- or two-locus HLA-mismatched related donors) when compared with MSDs. A later registry study from the Center for International Blood and Marrow Transplant Research (CIBMTR) reported on alloHCT for 4,099 (941 8/8 MUDs and 3,158 MSDs) adult patients with AML, acute lymphoblastic leukemia, or chronic myelogenous leukemia performed between 1995 and 2004.[15] GVHD, particularly grade II–IV acute GVHD, was slightly more common in the MUD cohort. For AML patients, MUD allografting was associated with higher rates of both NRM and relapse, resulting in significantly lower disease-free survival (DFS) and questioning whether there indeed was a superior graft-versus-leukemia effect associated with MUD compared with MSD allografting.

Based on these and other studies, MUDs standardly have been considered a second-tier donor source. However, simultaneous to the second study above, advances in HLA typing were improving outcomes for MUD alloHCT. HLA typing originally had been performed by serologic methods for HLA-A, HLA-B, and HLA-DR only. The importance of HLA-C serologic matching was later recognized, although "permissive" mismatching in HLA-C may exist that does not deleteriously affect outcomes.[16] By the mid-1990s, it was discovered that serologic typing was inferior to DNA-based typing.[17,18] Indeed, one study published in 1998 performed HLA typing by both serologic and DNA methods and found that only 45% of patients who were serologically matched were in fact HLA-matched by DNA testing at HLA-A, -B, and -DRB1.[19] Furthermore, HLA-C and -DQ testing had not been performed serologically, and 41% of donor-recipient pairs were found to be incompatible at those loci by DNA testing.[19]

Therefore many patients from earlier studies of "MUD" alloHCT may not have in fact received 8/8 HLA-matched allografts. Even single HLA-mismatches in HLA-A, -B, -C, and -DRB1 were found to be associated with worse survival,[20,21] in addition to the negative effects of specific HLA-locus-mismatching on the incidences of graft failure, GVHD, and relapse.[19–22] Matching at HLA-DQ, HLA-DP, and low expression HLA-DR loci also may impact outcomes, although effects of mismatching at these loci is much more prominent in alloHCT using 6/8 or 7/8 mmUDs.[23,24] Beyond better HLA typing, enhanced supportive care has played an important role in improving outcomes for unrelated donor alloHCT. Furthermore, the incorporation of anti-thymocyte