Haploidentical transplantation for hematologic malignancies: where do we stand?

Ephraim J. Fuchs[1]

[1]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD

Abstract

The fundamental obstacle to the successful application of partially HLA-mismatched related donor, or HLA-haploidentical stem cell transplantation, is the strength of the host and donor T-cell response to allogeneic HLA molecules, which results in increased incidences of graft failure, GVHD, and nonrelapse mortality. The holy grail of haplo-SCT is to mitigate host-versus-graft and graft-versus-host responses while preserving immune responses to infection and the patient's malignancy. Two strategies have been taken to achieve this goal. The first strategy is to supplement a T cell–depleted graft with pathogen-specific T cells or populations of T cells in which alloreactivity can be controlled. The second strategy is to eliminate alloreactive T cells selectively from a T cell–replete graft. Substantial progress has been made with both approaches so that the safety of haplo-SCT now approaches that of SCT using grafts of umbilical cord blood or from HLA-matched donors. In light of the rapid and near universal availability of HLA-haploidentical related donors, it should now be possible to identify and mobilize a donor for every patient referred for allogeneic SCT. Prospective comparisons between haploidentical SCT and unrelated donor SCT should be performed to identify the most efficacious approach to alternative donor transplantation.

Introduction

Donor availability remains one of the major challenges to the success of allogeneic stem cell transplantation (allo-SCT) in the treatment of hematologic malignancies. An HLA-matched sibling donor (MSD) or HLA-matched unrelated donor (MUD) cannot be identified or mobilized in time for as many as 40%-50% of patients, and the availability of MUDs can be quite low for members of underrepresented minorities such as African Americans. In contrast, a partially HLA-mismatched, or HLA-haploidentical, first-degree relative can be identified rapidly for nearly any patient. Potential HLA-haploidentical donors include biological parents or children of a patient, and each sibling has a 50% chance of sharing exactly one HLA haplotype. In our center's experience, we have been able to identify at least 1 HLA-haploidentical first-degree relative for > 95% of patients, and the average number of HLA-haploidentical donors per patient is 2.7.[1] Although rapid and near universal donor availability is the major advantage of haploidentical SCT (haplo-SCT), the major drawback is intense bidirectional alloreactivity that results in high incidences of graft failure, GVHD, and nonrelapse mortality (NRM) after transplantation of a T cell–replete graft. Two important differences in the repertoires of T cells reactive to HLA versus non-HLA (minor) histocompatibility antigens account for the higher toxicity of HLA-mismatched compared

with HLA-matched allo-SCT. First, the frequency of T cells reactive to allogeneic HLA molecules is as high as 1 in 10 (10%), whereas the frequency of T cells reactive to minor histocompatibility antigens may be as low as 1 in 50 000 (0.002%). Second, the repertoire of HLA-reactive T cells may contain memory T cells that were immunized to environmental antigens such as viruses, but cross-react against allogeneic HLA molecules.[2,3] Therefore, a relatively high frequency of alloreactive memory cells may make GVHD more difficult to control after HLA-mismatched compared with HLA-matched SCT.

Early trials of T cell–replete haplo-SCT reported incidences of severe GVHD and NRM approaching or exceeding 50%.[4-6] Whereas transplantations from donors mismatched for only one HLA antigen were associated with survival comparable to that for MSD BM transplantation (BMT), the outcome of transplantations from donors mismatched for 2 or 3 HLA antigens (HLA-A, HLA-B, and HLA-DR) was poor, with long-term survival of approximately 10%.[7] In light of evidence that T cells are responsible for causing GVHD,[8,9] attempts were made to improve the outcome of haplo-SCT by removing T cells from the donor graft. Ex vivo depletion of graft T cells reduces the risk of severe GVHD after partially HLA-mismatched SCT, but is accompanied by an increased risk of fatal graft failure.[10-12] To overcome the problem of graft failure after T cell– depleted haplo-SCT, investigators in Perugia, Italy pioneered "megadose" SCT involving the infusion of a product containing a median of 13.8×10^6 CD34$^+$ cells/kg and a median of only 1×10^4 CD3$^+$ cells/kg.[13] Patients (n = 104) were conditioned with 8 Gy of total body irradiation (TBI), thiotepa, fludarabine, and rabbit antithymocyte globulin. With this intensive conditioning regimen and the high dose of donor stem cells, primary engraftment was achieved in 94 of 101 evaluable patients; 6 of the remaining 7 patients engrafted with donor cells after a salvage transplantation procedure. Nevertheless, 38 patients (36.5%) died of nonrelapse causes, mostly from infection. Three-year event-free survival was 47% for patients receiving transplantations in remission but only 4% for patients with active disease at the time of transplantation.

These early studies of haplo-SCT illustrate the fundamental challenges inherent in crossing the HLA barrier. If donor T cells are left in, there is excessive GVHD and associated mortality. If T cells are depleted from the graft and the recipient's immune system is not ablated, there is an unacceptable incidence of graft failure. If the recipient is intensively conditioned and receives a T cell– depleted graft, immune reconstitution is unacceptable and too many patients die from opportunistic infections. Clearly, there is a need to obtain engraftment and mitigate GVHD while preserving immunity to infection after haplo-SCT. This can be approached by augmenting immune reconstitution in recipients of T cell– depleted grafts or by selectively depleting alloreactive lymphocytes from T cell–replete grafts.

Augmenting immune reconstitution after T cell–depleted haplo-SCT

Infusion of pathogen-specific T cells

Some of the first approaches to rebuilding immunity after T cell–depleted haplo-SCT involved infusing pathogen-specific T cells after transplantation. Perruccio et al generated clones of T cells specific for *Aspergillus* or CMV antigens, screened them for cross-reactivity against recipient alloantigens, and infused nonalloreactive clones soon after haplo-SCT. Pathogen-specific T cells persisted over time, did not cause GVHD, and were associated with control of *Aspergillus* and CMV antigenemia and infectious mortality.[14] Polyclonal CMV-specific T cells have been generated by ex vivo stimulation with CMV pp65 and have been infused to control refractory CMV viremia or disease after HLA-MUD or haplo-SCT.[15] Similar approaches have been taken to prevent or control infections with

adenovirus or EBV.[16-18] However, the time, expense, and technical expertise required to produce pathogen-specific T cells limit the broad applicability of these approaches.[19]

Infusion of T cells engineered to express suicide genes

Polyclonal T cells can be engineered to express suicide genes. If GVHD occurs after the infusion of the engineered cells, they can be killed by the administration of a drug that activates expression of the suicide gene. Donor lymphocytes expressing the HSV thymidine kinase (HSV-TK) gene were infused into 28 recipients of haplo-SCT. Ten patients developed acute GVHD and one patient developed chronic GVHD, which was controlled by the administration of ganciclovir. Rapid immune reconstitution was achieved in 22 patients, and NRM was only 14%.[20] Interestingly, infusion of the engineered T cells was associated with an increase in serum concentrations of IL-7 and recovery of thymic function with the production of new T cells.[21] A randomized phase 3 trial of haplo-SCT with or without add back of HSV-TK donor lymphocytes for patients with high-risk acute leukemia is under way (www.clinicaltrials.gov number NCT00914628).

Investigators at the Baylor College of Medicine in Houston devised an inducible T-cell safety switch based on the fusion of human caspase 9 to a modified human FK-binding protein, allowing conditional dimerization and cell suicide after administration of the small molecule–dimerizing drug AP1903. Five leukemia patients received transplantations with HLA-haploidentical, CD34-selected hematopoietic stem cells, followed by infusion of the genetically modified T cells. Four patients developed GVHD and were treated with AP1903; 90% of the modified T cells were eliminated within 30 minutes and the GVHD was terminated without recurrence.[22]

Ex vivo photodepletion of alloreactive donor T cells

Photodepletion using dibromorhodamine (TH9402) eliminates alloreactive T cells from healthy donors responding to recipient alloantigens ex vivo[23] while potentially sparing regulatory T cells (Tregs).[24] In a phase 1 clinical trial, allodepleted cells were infused back into 19 leukemic recipients of T cell–depleted haplo-SCT. The depletion technique eliminated greater than 90% of activated ($CD25^+CD44^+$) $CD4^+$ and $CD8^+$ T cells, as well as > 90% of antihost cytotoxic T-lymphocyte precursors. Grade II acute GVHD developed in 4 patients and extensive chronic GVHD developed in 5 patients. The highest T-cell doses were associated with the earliest reconstitution of $CD3^+$, $CD4^+$, and $CD8^+$ T cells and lower incidences of infection and NRM.[25]

Regulatory T cells

An additional method for augmenting immune reconstitution after haplo-SCT involves the sequential infusion of $CD4^+CD25^+$ Tregs, followed by conventional ($CD4^+CD25^-$) T cells. In mouse models of mismatched SCT, the adoptive transfer of donor strain Tregs suppressed GVHD without suppressing GVL effects,[26-29] permitting effective immune reconstitution from conventional T cells.[30] This latter finding prompted a clinical trial in which 28 leukemia patients were conditioned from days −10 to −6 with 8 Gy of TBI, fludarabine, thiotepa, and cyclophosphamide before haploidentical donor Treg infusion on day −4 and transplantation of purified $CD34^+$ stem cells plus conventional T cells on day 0. No pharmacologic immunosuppression was administered after SCT. Twenty-six of the 28 patients achieved full donor engraftment and grade II-IV GVHD occurred in only 2 patients. Recipients of Tregs appeared to have improved lymphoid reconstitution and immunity to opportunistic pathogens without loss of a GVL effect. Nevertheless, 13 of the 26 evaluable patients died from nonrelapse causes, including 8 from infection with or without GVHD.[31] More recently, alemtuzumab on day −22 has been substituted for cyclophosphamide, with only 1 relapse in 18 patients and a reduction in NRM to 17% (3 of 18).[32] These results

demonstrate the feasibility of enhancing immune reconstitution and decreasing NRM by infusing donor Tregs before haplo-SCT.

Selective allodepletion in the context of T cell–replete haplo-SCT

Ex vivo anergy induction by costimulation blockade

The 2-signal model of T-cell activation[33] postulates that resting T cells must see antigen (signal 1) in the context of a costimulatory signal (signal 2) for efficient activation, and that antigen recognition in the absence of a costimulatory signal results in antigen-specific T-cell tolerance. Perhaps the best-studied costimulatory interaction involves ligation of the CD28 costimulatory receptor on T cells by B7-1 (CD80) or B7-2 (CD86) on APCs. Abatacept (CTLA-4Ig) is a recombinant fusion protein that promotes the induction of T-cell tolerance, or anergy, by binding B7 molecules with high affinity and preventing their interaction with CD28, effectively blocking the delivery of signal 2. Guinan et al treated 11 patients with haplo-SCT using donor BM that had been incubated with irradiated recipient cells in the presence of CTLA-4Ig.[34] This treatment resulted in a 1- to 4-log reduction in recipient-reactive helper T cells without affecting the frequency of helper cells reactive to third-party allogeneic stimulators. Clinically, all 11 patients engrafted, and GVHD developed in only 3 patients. Belatacept (Nulojix) is a second-generation CTLA-4Ig approved for prevention of acute rejection in kidney transplantation recipients. Ex vivo anergization with belatacept induces a greater reduction in alloreactivity than does abatacept; further, reexposure of the anergized T cells to alloantigen in the absence of belatacept results in an expansion of Tregs with enhanced alloantigen-specific suppressive function.[35] It will be of interest to determine whether belatacept can be administered to prevent GVHD after haplo-SCT.

Selective depletion of T cells ex vivo

T cells can be removed from a BM or peripheral blood graft using negative selection or positive selection of $CD34^+$ cells. CD34 selection results in a > 4-log depletion of T cells and effectively abrogates GVHD after haplo-SCT, but is associated with poor immune reconstitution because of the depletion of other populations, including natural killer (NK) cells, monocytes, and dendritic cells. Grafts depleted of $CD3^+$ and $CD19^+$ cells retain such cells, but would be expected to cause less GVHD and fewer occurrences of B-cell lymphoproliferative disorders than with unmanipulated products. In a recent study, 61 adults with high-risk hematologic malignancies were treated with reduced intensity conditioning and transplantation of CD3/CD19-depleted grafts from HLA-haploidentical donors.[36] All but 5 patients engrafted, with a median time to 500 neutrophils/μL of 12 days and a median time to 20 000 platelets/μL of 11 days. The cumulative incidences of grades II-IV acute GVHD and chronic GVHD were 46% and 18%, respectively. NRM was 23% at 100 days and 42% at 2 years. The 2-year incidence of relapse was 31% and overall survival (OS) was 28%.

Gamma delta (γδ) T cells are a population of cells that do not cause GVHD but may have potent antileukemia effects.[37] These cells can be preserved in a stem cell graft by negatively selecting only T cells that express an alpha beta (αβ) T-cell receptor. Twenty-three children with advanced hematologic malignancies received transplantations after reduced-intensity (n = 10) or myeloablative conditioning (n = 13) with haploidentical peripheral blood stem cells depleted of $TcR\alpha\beta^+$ and $CD19^+$ cells using the CliniMACS (Miltenyi Biotec) magnetic cell separation system.[38] All patients engrafted promptly, and grade II GVHD occurred in only 4 patients. With a median follow-up of 4-5 months, 17 of 23 patients were alive in remission, 5 patients relapsed, and 1 patient died from pulmonary aspergillosis.

High-dose posttransplantation cyclophosphamide

High-dose cyclophosphamide (Cy), when administered in a narrow window after transplantation (posttransplantation Cy [PT/Cy]), depletes alloreactive T cells from the donor and host and can inhibit both GVHD and graft rejection. As a form of drug-induced immunologic tolerance, the high-dose PT/Cy strategy takes advantage of the heightened cytotoxic sensitivity of proliferating, alloreactive T cells over nonalloreactive, resting T cells to being killed by a DNA-damaging agent. Among 210 hematologic malignancy patients treated at Johns Hopkins with reduced-intensity conditioning and HLA-haploidentical BMT with high-dose PT/Cy, the cumulative incidences of acute grades II-IV, grades III-IV, and chronic GVHD were 27%, 5%, and 13%, respectively. The 2-year cumulative incidences of relapse and NRM were 51% and 15%, respectively, and event-free survival at 2 years was 34%.[39] Relapse of the underlying the malignancy was the cause of death in 79 patients. In contrast, only 15 patients died from opportunistic infections and 5 patients died from complications of GVHD.

Ciurea et al compared outcomes of T cell–replete BMT with PT/Cy versus T cell– depleted peripheral blood SCT from HLA-haploidentical donors in 65 consecutive patients treated with the same conditioning regimen: fludarabine (40 mg/m^2/d × 4), melphalan (140 mg/m^2), and thiotepa (10 mg/kg).[40] Primary engraftment was achieved in 94% of the T cell–replete group and in 81% of the T cell–depleted group (P = .1). NRM at 1 year was 16% for the T cell–replete group versus 42% for the T cell–depleted group (P = .03). The cumulative incidences of grade II-IV aGVHD were 27% versus 11% (P = .5) and cGVHD were 8% versus 18%, in the T cell–replete and T cell– depleted groups, respectively (P = .03). OS and PFS at 1 year after transplantation were 66% versus 30% (P = .02) and 45% versus 21% (P = .03), respectively. Improved NRM in the T cell–replete group was associated with better immunologic reconstitution of T-cell subsets. In another study, immune reconstitution after haplo-SCT with PT/Cy was superior to recovery after MUD adult donor or cord blood transplantation, and even approached the immunologic recovery seen after transplantation from MSDs.[41] The low infectious mortality may be explained by rapid recovery of T cells specific for pathogens such as human CMV,[42] which suggests that PT/Cy spares resting memory T cells responsible for reconstitution of immunity to infection.

Bashey et al in Atlanta, GA, compared the outcomes of haplo-SCT with PT/Cy (27 reduced intensity, 18 myeloablative) with contemporaneous first allografts from matched related donors (MRDs; n = 115) and MUDs (n = 99).[43] Median follow-up for surviving patients was 36 months (range, 9-74.5). The adjusted OS was not significantly different between the 3 types of transplantation at 36 months (71%, 58%, and 58% for MRD, MUD, and haplo-SCT, respectively; P = nonsignificant [NS]). The adjusted disease-free-survival at 36 months was 47%, 46%, and 55%, respectively (P = NS). The estimated cumulative incidence of relapse at 36 months was 35%, 38%, and 36%, respectively, for MRD, MUD, and haplo-SCT (P = NS). These results indicate comparable outcomes of haplo-SCT compared with MRD or MUD SCT, and suggest that partially mismatched related donors (PMRDs) are a viable donor option for patients lacking an HLA-matched donor. Depending on the clinical situation, myeloablative conditioning[44,45] and/or transplanting filgrastim-mobilized peripheral blood stem cells[44,46] may be considered in conjunction with PT/Cy.

Considerations in the selection of an HLA-haploidentical donor

Antidonor HLA Abs

Three assays are available for measuring the presence of Abs against donor HLA molecules: (1) lymphocytotoxic cross-matching, (2) flow cytometric cross-matching, and 3) solid-phase immuno-assay (SPI) using fluorochrome-conjugated beads coated with single HLA molecules. The presence of antidonor HLA Ab by either cross-matching technique is

considered an absolute contraindication to the use of that donor because of an increased risk of graft failure.[47] The SPI is the most sensitive test for antidonor HLA Ab, and we generally exclude donors when the SPI is positive for Ab against donor HLA with a mean fluorescence intensity > 1000. An occasional patient, usually a multiparous female, has Abs against all potential related donors. As long as the crossmatch tests are negative, it may be possible to desensitize such patients with a combination of plasmapheresis, CMV Ig, tacrolimus, and mycophenolate mofetil. This protocol was first developed for allosensitized kidney graft recipients,[48] but has been applied successfully to secure donor cell engraftment in at least 4 of 6 sensitized hematologic malignancy patients undergoing haplo-SCT.[1]

Role of HLA mismatching: does increasing HLA disparity worsen outcome?

Early studies of T cell–replete haplo-SCT demonstrated worse outcomes with increasing HLA mismatch between donor and recipient.[6,7] Although mismatching was associated with a decreased risk of relapse,[49] this beneficial effect was outweighed by a substantially increased GVHD and NRM. With improvements in pharmacologic immunosuppression and prophylaxis and treatment of infection, the relationship between mismatching and outcome deserves reexamination. Huo et al examined the impact of HLA mismatching on the outcomes of 481 patients undergoing myeloablative conditioning with ara-C, busulfan, cyclophosphamide, semustine, and rabbit ATG, followed by transplantation of filgrastim-mobilized BM plus peripheral blood from PMRD.[50] GVHD prophylaxis comprised cyclosporine A, short-course methotrexate, and mycophenolate mofetil. In a multivariable analysis, mismatching at HLA-B increased the risk of acute GVHD and NRM, but was not associated with a significant decrease in OS or leukemia-free survival. Further, multiple HLA mismatches did not have a synergistic detrimental effect on outcomes. Kasamon et al examined the impact of HLA mismatching on the outcomes of 185 hematologic malignancy patients treated with nonmyeloablative, HLA-haploidentical BMT and high-dose PT/Cy.[51] No significant association was found between the number of HLA mismatches in the graft-versus-host direction (HLA-A, HLA-B, HLA-Cw, and HLA-DRB1 combined) and risk of acute grade II-IV GVHD (hazard ratio [HR] = 0.89; P = .68 for 3-4 compared with fewer antigen mismatches). Interestingly, increased HLA class I antigen mismatching and HLA-DRB1 antigen mismatch in the graft-versus-host direction were both associated with *improved* event-free survival, possibly due to a reduction of relapse without a corresponding increase in NRM. Together with the study by Huo et al, these results suggest that modern regimens of pharmacologic immunosuppression are mitigating the detrimental impact of HLA disparity on outcome, and raise the possibility that donors can be selected based upon characteristics other than HLA.

NK cell alloreactivity

Were the philosopher William James alive today and practicing SCT, he would be tempted to characterize the literature on NK cells as "one great blooming, buzzing confusion."[52] There is a general consensus that NK cells can mediate a GVL effect after haplo-SCT,[53] but the consensus pretty much ends there. A critical question regarding donor selection is whether donor genes, especially HLA and killer immunoglobulin receptor (KIR) genes, influence NK cell alloreactivity. The "missing self" model of NK cell alloreactivity predicts that HLA genes in the donor and in the recipient influence outcome, whereas the "missing ligand" model predicts that only HLA genes of the recipient have an effect. Early studies from Perugia strongly support a benefit of "missing self," or KIR ligand incompatibility, on the outcome of myeloablative, T cell–depleted PMRD SCT.[53] In contrast, more recent studies of haplo-SCT after reduced-intensity conditioning suggest a role for "missing ligand,"[54,55] and thus no effect of donor HLA on NK alloreactivity. These divergent outcomes regarding the role of donor HLA on NK cell effects may be ascribed to differences in the intensity of conditioning, presence or absence of T cells in the graft, and prophylaxis

of GVHD. Other studies point to a beneficial role of activating KIR genes such as KIR2DS1[56] or KIR2DS2[54] or the KIR "B" haplotype,[57] which contains most activating KIR genes, on the outcome of PMRD SCT. Further studies will be required to determine whether the outcome of haplo-SCT can be improved by selecting donors for enhanced NK cell alloreactivity.

Nonengrafting haploidentical cell therapy

Despite conclusive evidence that alloreactive T cells mediate potent antitumor effects against hematologic malignancies,[49] fewer than 10% of patients diagnosed with a blood cancer are treated with allo-SCT. Most patients are simply considered to be too old or too sick to be treated with SCT, or their diseases do not respond well enough to chemotherapy to proceed to transplantation. Fortunately, observations in animals and in human clinical trials suggest that allogeneic lymphocytes do not need to engraft durably for an antitumor effect to occur.[58-60] Based upon these observations, several groups have conducted clinical trials of HLA-haploidentical lymphocyte[61,62] or purified NK cell infusions[63-65] in minimally conditioned recipients. In many cases, remissions of refractory hematologic malignancies were obtained in elderly patients despite the lack of sustained engraftment of donor cells. Transiently engrafting HLA-mismatched lymphocyte infusions holds promise as an effective therapy for patients with otherwise refractory hematologic malignancies, and may eventually be used as a bridge to SCT from a different donor.

How does haplo-SCT compare to transplantations from MSDs, MUDs, or UCB?

Transplantation of stem cells from MSDs still produces the best outcomes, but the performance gap among MSDs, MUDs, umbilical cord blood (UCB), and HLA-haploidentical donors is narrowing. For children with very-high-risk leukemia, the results of transplantation have improved over time for all graft sources, but perhaps most for haplo-SCT. The 5-year survival for children receiving transplantations from MSDs has increased from 24% to 70%, from MUDs has increased from 37% to 61%, and from haploidentical donors has improved from 19% to 88%. These improvements are attributable to fewer infections, regimen-related toxicities, and leukemia-related deaths.[66]

A recent study from China compared the historical outcomes of 117 consecutive high-risk acute leukemia patients undergoing T cell–replete SCT from either HLA-haploidentical donors (n = 81) or MSDs (n = 36).[67] The cumulative incidence of acute grades II-IV GVHD was higher among recipients of haploidentical compared with MSD grafts (49% vs 24%; P = .014) and the 2-year incidence of relapse was significantly lower (26% vs 49%; P = .008). Because NRM did not differ significantly between recipients of haploidentical versus MSD grafts (34% vs 38%; P = .85), the 3-year probability of OS was actually higher among recipients of haploidentical grafts as opposed to MSD grafts (42% vs 20%; P = .048). Although this study confirms the stronger antileukemic effect of haploidentical transplantation, it also points out that haplo-SCT is becoming a highly feasible alternative for patients who lack MSDs or MUDs.

A small study in Korea compared the outcomes of 23 patients undergoing reduced-intensity, haplo-SCT for high-risk acute myeloid leukemia with those of 33 patients treated with well-matched UD transplantation and 13 patients undergoing partially mismatched UD transplantation for the same indication.[68] After a median follow-up of 28 months, OS, disease-free survival, relapse, and NRM were 83%, 74%, 20%, and 7% for well-matched UD transplantation; 51%, 51%, 31%, and 18% for partially mismatched UD transplantation; and 66%, 64%, 26%, and 10% for haplo-SCT, respectively. This study revealed a trend for

improved survival with well-matched UDs over haploidentical donors and for haploidentical donors over partially mismatched UDs.

Finally, the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) in the United States recently completed two parallel phase 2 trials of reduced-intensity conditioning and either HLA-haploidentical related donor BMT with high-dose PT/Cy or double-unrelated donor UCB (dUCB) transplantation for patients with leukemia or lymphoma.[69] Eligibility criteria and end points were identical for the 2 trials. For both trials, the transplantation conditioning regimen incorporated cyclophosphamide, fludarabine, and 200 cGy of TBI. The 1-year probabilities of OS and progression-free survival were 54% and 46%, respectively, after dUCB transplantation and 62% and 48%, respectively, after haplo-BMT (n = 50). The day 56 cumulative incidence of neutrophil recovery was 94% after dUCB and 96% after haplo-BMT. The 100-day cumulative incidence of grade II-IV acute GVHD was 40% after dUCB and 32% after haplo-BMT. The 1-year cumulative incidences of NRM and relapse after dUCB transplantation were 24% and 31%, respectively, with corresponding results of 7% and 45%, respectively, after haplo-BMT. These 2 trials set the stage for BMT-CTN 1101, a multicenter, phase 3, randomized trial of reduced intensity conditioning and transplantation of dUCB versus HLA-haploidentical related BM for patients with hematologic malignancies. The primary objective is to compare progression-free-survival at 2 years after randomization between the 2 different graft sources. The trial will also capture important information on the patient's quality of life after transplantation, which may differ according to graft source, even if OS and/or progression-free survival do not.

Summary

Outcomes of haplo-SCT have improved markedly over the past decade to the point that it is an acceptable procedure for patients lacking an HLA-matched donor. Haplo-SCT offers the advantages of rapid and near universal donor availability, and may be associated with a more potent graft-versus-tumor effect than is induced by an HLA-matched graft. With improved pharmacologic immunosuppression, the incidences of severe GVHD and NRM are acceptably low. Selection among several potential donors is a unique challenge of haplo-SCT and may be influenced by donor HLA and KIR alleles. Mismatched lymphocytes may exert an antitumor effect against hematologic malignancies even in the absence of sustained donor cell engraftment. The stage is now set for comparisons of mismatched related, unrelated UCB, and unrelated adult donor stem cells to determine the best stem cell source to use when an MSD is unavailable.

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