



History of hematopoietic cell transplantation: challenges and progress

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ABSTRACT

After more than 60 years of research in allogeneic hematopoietic cell transplantation (HCT), this therapy has advanced from one that was declared dead in the 1960s to a standard treatment of otherwise fatal malignant and non-malignant blood diseases. To date, close to 1.5 million hematopoietic cell transplants have been performed in more than 1,500 transplantation centers worldwide. This review will highlight the enormous efforts by numerous investigators throughout the world who have brought the experimental field of HCT to clinical reality, examine ongoing challenges, and provide insights for the future.

The beginnings

The late 1940s saw major research efforts directed at repairing or preventing radiation damage to organs in response to observations made on survivors of the atomic bomb explosions in Japan. A pivotal report by Jacobson *et al.* in 1949 demonstrated protection of mice from lethal total body irradiation (TBI) damage to the bone marrow when shielding their spleens or femora with lead.^{1,2} Two years later, Lorenz *et al.* saw similar protection when mice were given an intravenous infusion of syngeneic marrow following TBI.³ Of note, Jacobson⁴ and others attributed the radiation protection to some humoral factor present in spleen or bone marrow, the “humoral hypothesis”, a supposition that was controversial and not shared by others who thought the ‘rescue’ of the irradiated mice had cellular origins. It was not until the mid-1950s that several laboratories unequivocally documented, with the help of blood genetic markers, that the radioprotection was due to repopulation of the irradiated marrow spaces by transplanted donor cells, thereby validating the “cellular hypothesis”.^{5,6} Much of that early work has been comprehensively described in the 1967 book “Radiation Chimeras” written by van Bekkum and de Vries.⁷

The unequivocal validation of the cellular hypothesis was greeted enthusiastically by immunologists, radiation biologists, and clinicians because of its implications for cell biology and because it promised clinical translation for treating patients with life-threatening blood disorders. Investigators thought that high doses of chemoradiation therapy could be used both to destroy diseased marrow and suppress the host immune system, thereby preventing rejection of an infused marrow graft from a healthy donor. Already one year after the studies in rodents were published, Thomas *et al.* reported in 1957 in *The New England Journal of Medicine* that marrow could be infused into irradiated leukemia patients and then engraft, even though, in the end, the patients were not cured of their leukemia.⁸ In 1965, Mathé *et al.* described a patient with acute leukemia who was given TBI followed by a marrow infusion from each of six relatives.⁹ The marrow of one of the relatives engrafted. While the patient eventually succumbed to an immunologic complication, initially called secondary disease and now known as graft-versus-host disease (GvHD), his leukemia remained in remission. With this observation, Mathé *et al.* corroborated a previous report by Barnes and Loutit from 1956 in mice showing that GvHD could lead to eradication of leukemic cells.¹⁰ In order to describe this phenomenon, Mathé coined the term “graft-versus-leukemia” effect.

Unfortunately, all human allogeneic marrow grafts in these early years failed, as meticulously documented in a paper from 1970 by Bortin.¹¹ Of the 200 patients reported between 1957 and 1967, 73 were transplanted for aplastic anemia, 115 for advanced and refractory hematologic malignancies, and 12 for immunodeficiency diseases. In the end, all 200 patients died, 125 with graft failure, 47 with GvHD,

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and others with infections or recurrence of their underlying malignancies.

These early human transplants were performed before a full understanding of conditioning regimens and GvHD prevention was achieved, and before the discovery of the importance of histocompatibility matching for the outcome of marrow transplantation. The early transplants were based on observations in inbred mice, for which major histocompatibility complex (MHC) matching was not an absolute requirement. As a result of the complete failure of translating findings from mice to humans, most investigators abandoned the idea that allogeneic HCT could ever become a valuable asset in clinical medicine, and prominent immunologists doubted that the immunological barrier from one human to another could ever be crossed.

Back to the laboratory

Discouraged by the disastrous clinical results, most investigators left the field, declaring it a dead end. However, a few small laboratories in Europe and the United States persisted in systematic efforts to understand and overcome the perceived “insurmountable” obstacles encountered in early human marrow transplantation. Much of the work was carried out in large animals, including monkeys and dogs. An important paper published in 1968 showed that canine littermates matched for the MHC antigens by *in vitro* tissue typing had far better HCT outcomes than MHC-mismatched recipients.¹² *In vitro* typing for the MHC, called human leukocyte antigen (HLA) region in humans, H2 in mice, and DLA in dogs, was very primitive at the time and, moreover, the complexity of the MHC was not yet understood. Typing consisted of serologic measurements using multi-specific antibodies collected from parous women or transfusion recipients in trypan blue exclusion or leuko-agglutination assays,¹³⁻¹⁶ combined with testing of donor and recipient lymphocytes for reactivity in a mixed leukocyte culture.¹⁷ While trail-blazing at the time, these primitive testing techniques are now history, and typing is accomplished by genetic sequencing of up to 14 HLA-alleles.

The second, completely unexpected observation made in the original canine experiment was that GvHD, either in acute, subacute or chronic form, developed in MHC-matched littermates, even though significantly later than in mismatched littermates.¹⁸ This finding was surprising since it had not been encountered in mice that were mismatched with their donors for non-H2 antigens. It pointed out the need for investigating methods to prevent and control GvHD even in well-matched human donor-recipient combinations. Consequently, studies of numerous immunosuppressive agents were conducted in a canine model that eventually led to identifying the antimetabolite methotrexate as the best drug for GvHD prevention.¹⁹ By balancing the drug's toxicities against its efficacy, a regimen of intermittent methotrexate was established, with administration of the drug 1, 3, 6, and 11 days after transplantation and then weekly for at least 3 months. This regimen entered the clinic in 1969 and was used until the early 1980s.

Other research efforts focused on effective and tolerable conditioning regimens. In the beginning, single-dose TBI up to 10 Gray (Gy) was utilized. However, extensive stud-

ies in canines revealed that delivering TBI in multiple fractions of 2 Gy each reduced damage to slow-responding tissues, such as liver, lung and others, while barely diminishing radiation effects on marrow and lymphoid tissues. Based on these studies, fractionating TBI has remained the standard.²⁰ Additionally, effective drug-based conditioning regimens were developed. Among those, cyclophosphamide has become the standard for patients with aplastic anemia since the drug had outstanding immunosuppressive qualities. However, cyclophosphamide spared stem cells and was not myeloablative,²¹ and so was not deemed suitable for conditioning patients with leukemia. In contrast, another alkylating agent, busulfan, proved to be highly myeloablative but lacked the immunosuppressive qualities of cyclophosphamide or TBI. Prospective, randomized trials showed that busulfan was better tolerated than TBI and had equivalent efficacy to TBI for conditioning patients with myeloid malignancies;²² however, in order to ensure hematopoietic engraftment, busulfan needed to be combined with immunosuppressive drugs such as cyclophosphamide²³ or fludarabine.

Other studies addressed transfusion-induced sensitization to minor histocompatibility antigens, which often resulted in marrow graft rejection among HLA-identical recipients with aplastic anemia. Rejection rates in early transplants for aplastic anemia ranged from 36% to 60%.^{24,25} In order to surmount this major problem, methods were identified that minimized the risk of sensitization from transfusions. Also, a more immunosuppressive conditioning regimen was developed that combined antithymocyte globulin (ATG) with cyclophosphamide.^{26,27} This regimen has become standard practice for aplastic anemia patients with HLA-identical sibling donors. Other studies showed that, unlike in solid organ transplantation, post-HCT immunosuppression was not required for the remainder of the patients' life but could often be discontinued after 6 months. After 6 months, donor-derived regulatory T cells (then called “suppressor T cells”) were found in the peripheral blood, which were thought to enable and maintain a state of graft-*versus*-host tolerance; of note, these cells were absent in patients with chronic GvHD.²⁸ It was also shown that successful grafts could be accomplished using hematopoietic cells derived from the peripheral blood in mice, dogs and baboons.²⁹ In later years, it was found that large numbers of these cells could be “mobilized” from the marrow into the peripheral blood (peripheral blood stem cells or PBSC) with granulocyte-colony stimulating factor (G-CSF).^{30,31}

Finally, since dogs share spontaneous blood disorders with humans, preclinical exploration of treating such diseases by allogeneic HCT was possible. For example, dogs with severe combined immunodeficiency (SCID) were cured by marrow transplants, as were dogs with severe hemolytic anemia due to pyruvate kinase deficiency. The latter dogs had massive iron deposits in their inner organs from the severe hemolysis.³² Long-term follow-up of transplanted dogs showed impressive resolution of iron deposits in the liver over time. This finding encouraged the first successful transplantation for multiply transfused human patients with thalassemia major.³³ Dogs with spontaneous non-Hodgkin lymphoma (NHL) served to establish the value of autologous HCT in the treatment of this disease. Moreover, comparisons with results of allogeneic HCT confirmed the presence of graft-*versus*-lymphoma effects in dogs.

Return to the clinic: 1968 to 1980

By 1968, the progress made in preclinical transplantation and the advances in the understanding of HLA set the stage for clinical trials to resume. In 1968/1969, three publications reported the first successful marrow grafts for patients with primary immune deficiency disorders.³⁴⁻³⁶ However, during the subsequent years, most clinical transplants were performed in patients with advanced hematologic malignancies and severe aplastic anemia.^{37,38} These early trials posed serious challenges not only in the field of transplantation biology but also in aspects of supportive care, especially infections and transfusion support. Therefore, these trials stimulated incredible progress in infectious disease and transfusion research.

Even though donors and recipients in nearly all early trials were HLA-identical siblings, and despite prophylaxis with methotrexate, GvHD occurred in almost half of the patients. Major advances in GvHD prevention and, consequently, improvement in overall patient survival were accomplished when, based on preclinical canine studies, methotrexate was combined with calcineurin inhibitors such as cyclosporine or tacrolimus.³⁹⁻⁴¹ These synergistic drug combinations have remained among the most widely used methods for GvHD prevention to date. The first grading system for acute GvHD was described in 1974,⁴² and the first effective treatment of acute GvHD with anti-thymocyte globulin (ATG) was reported in the same year.⁴³ In those early years, ATG was not commercially available and the drug was produced in our laboratory by immunizing rabbits with human thymocytes.

Early results in patients with aplastic anemia conditioned with cyclophosphamide showed 45% long-term survival.^{44,45} One reason for the disappointing findings was fatal GvHD. However, as predicted from canine studies, the most serious fatal complication was graft rejection due to sensitization through transfusions to minor histocompatibility antigens for which donors and recipients were disparate. Preclinical studies transformed how clinical transfusions and transplants were conducted and paved the way for better transplantation outcomes. Changing transfusion support to leukocyte-depleted, *in vitro* irradiated platelet and red blood cell products reduced the risk of sensitization to minor antigens and, with it, the risk of graft rejection not only for patients with aplastic anemia but also those with hemoglobinopathies. In addition, the newly developed cyclophosphamide/ATG regimen more effectively suppressed recipient immunity thereby enabling almost uniform marrow engraftment. The cumulative effects of these changes have resulted in survivals for patients with aplastic anemia given HLA-identical sibling marrow grafts ranging from 64% to 100%.^{39,46-55}

All early transplantations for acute leukemia were performed in patients who were in refractory relapse. As a result, in addition to fatalities from GvHD, many patients died from post-transplantation relapse. A decision in the mid-1970s to transplant patients earlier in the course of their disease, while the leukemia burden was low, reduced the relapse risk and led to a significant improvement in survival among patients with acute leukemias.^{37,38} Two pivotal publications from 1979 and 1981 in *The New England Journal of Medicine* described powerful graft-versus-leukemia effects associated with acute and chronic GvHD.^{56,57} This work provided the rationale for the subsequent introduction of donor lymphocyte infusions in the 1990s to prevent or combat relapse after HCT.^{58,59}

Some transplant centers focused on removing T cells from the marrow in order to reduce the risk of GvHD. However, initial studies showed unacceptably high incidences of mortality from graft rejection, disease relapse and infections.⁶⁰ When T-cell depletion was combined with high-intensity conditioning regimens before and careful monitoring after transplantation for recurrence of acute leukemia and prompt treatment by donor lymphocyte infusions, outcomes were improved. This approach has remained an acceptable procedure in patients with acute leukemia.⁶¹

In the late 1980s, G-CSF-mobilized PBSC were introduced for allogeneic transplants. Randomized, prospective trials showed marrow and PBSC to be equivalent as far as engraftment and overall survival were concerned (Table 1). However, PBSC caused more chronic GvHD than marrow; because of this, marrow has remained the preferred source of stem cells for patients with non-malignant diseases such as aplastic anemia or hemoglobinopathies. However, PBSC continue to be the predominant graft source for patients with hematologic malignancies, in part due to donor preference.

One limitation in early allogeneic HCT was that only approximately 35% of patients had HLA-identical siblings who could serve as marrow donors. In order to get around that limitation, and assisted by an increasing understanding of the genetics of the HLA region, along with improved HLA-typing techniques,⁶²⁻⁶⁴ registries were established in the 1980s that collected HLA data from unrelated volunteer donors, first in the UK with the Anthony Nolan Foundation, in the United States with the National Marrow Donor Registry, and then other national registries (Table 1). Early canine studies had already indicated the feasibility of “matched”, unrelated HCT,^{65,66} and the first successful human transplant from an HLA-matched unrelated donor was carried out in 1979 for a patient with acute lymphoblastic leukemia.⁶⁷ Currently, HLA data from more than 36 million unrelated volunteers are accessible in the various national registries. For Caucasian patients, the likelihood of finding an HLA-matched unrelated donor is approximately 80%; however, this percentage declines dramatically for patients from ethnic groups.⁶⁸⁻⁷¹ In order to provide potentially curative HCT for these otherwise unserved patients, transplant methods have been developed that use grafts either from unrelated umbilical cord blood (UCB) or from HLA-haploidentical relatives (see below). This way donors can be found for 95% of transplant candidates regardless of age and ethnic background.

Moving forward: the 1990s

Over the past 25 years, more and more transplant centers have been established worldwide. In order to collect and analyze outcome data from the ever-increasing numbers of transplants, data registries have been set up, such as the European Bone Marrow Transplant Registry (EBMT) and the Center for International Bone Marrow Transplant Research (CIBMTR). To date, information on close to 1.5 million HCT has been collected.^{72,73} Large and mostly retrospective data analyses have generated information aimed at providing recommendations for the best HCT approaches for the various diseases and donor-recipient combinations.

The 1990s saw many changes in the way transplantations have been carried out. Major advances in infectious disease prevention and treatment were made, including using acyclovir to prevent herpes simplex and varicella zoster virus reactivation, monitoring for cytomegalovirus (CMV) reactivation and, once reactivation occurred, preventing CMV disease with ganciclovir or foscarnet, preventing *Pneumocystis Jirovecii* infections with a synthetic antibacterial combination of sulfamethoxazole and trimethoprim, and introducing more effective anti-fungal agents and antibiotics.⁷⁴⁻⁷⁹ Conditioning regimens were intensified to the upper limit of tolerability in order to optimize tumor cell kill; however, investigators began realizing that these intensive, myeloablative regimens, including cyclophosphamide/TBI or busulfan/cyclophosphamide were too toxic for elderly patients or for those with comorbid conditions. This was especially unfortunate since most hematologic malignancies happen to occur in older patients. The problem was obvious when comparing the median ages of patients transplanted in those years at Fred Hutch (related grafts 40 years, and unrelated grafts 35 years) to the median patient age at diagnosis of the underlying hematologic malignancies (68 years).⁸⁰ In short, most affected patients were excluded from transplantation.

In order to address this serious problem, and extend allogeneic HCT to include older or medically infirm patients, less-intensive conditioning regimens were introduced. These regimens shifted the burden of tumor kill from high-dose chemo-irradiation therapy toward graft-*versus*-tumor effects. The regimens were facilitated by the development of a then new immunosuppressive agent, mycophenolate mofetil (MMF), that blocked the *de novo* purine pathway needed for lymphocyte replication and worked in synergy with calcineurin inhibitors. This synergistic drug combination was not only effective in preventing GvHD but, importantly, also enhanced hematopoietic engraftment.^{81,82} MMF also was synergistic with another agent, sirolimus, which reduced the sensitivity of T cells to interleukin-2 through mTor inhibition.⁸³⁻⁸⁶ Combinations of these agents are now commonly used after allogeneic HCT, leading to relatively low and acceptable risk of non-relapse mortality (NRM).

The 21st century

The early years of the 21st century saw tremendous growth in allogeneic HCT, in part because of non-myeloablative or reduced-intensity conditioning regimens, which enabled extending allogeneic HCT to include older patients, and, in part, the growth was due to increased use of grafts from alternative donors, including unrelated cord blood (UCB) and HLA-haploidentical relatives.

Additionally, progress has been made in GvHD prevention among unrelated recipients. For example, a recently published randomized, prospective phase III trial compared a commonly used drug combination of MMF and cyclosporine to a triple-drug regimen of MMF, cyclosporine, and sirolimus.⁸⁴ Patients on the triple drug arm had a significant reduction in overall acute GvHD, and acute grade III-IV GvHD was seen in only 2% of patients. This resulted in a significant improvement in overall survival. Another recent development has been the US Food and Drug Administration approval of ruxolitinib,

a JAK2 inhibitor for the treatment of steroid-refractory acute GvHD. The approval was prompted by the favorable outcome of the single-arm, phase II REACH 1 (Research Evaluation and Commercialization Hub) study.⁸⁷ Extracorporeal photopheresis (ECP) has been used as an off-label second-line treatment for cutaneous manifestations of steroid-refractory acute and chronic GvHD since the early 2000s, with variable success.⁸⁸ The introduction of the HCT comorbidity index (HCT-CI) in 2005 facilitated comparisons of results between centers worldwide, and has served as an important decision-making tool for choosing appropriate transplant regimens.⁸⁹ Serum biomarkers derived from the gastrointestinal tract, specifically ST2 and REG-3 α , have emerged as an additional method of predicting acute GvHD severity, as presented in a recent Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial.⁹⁰ The application of this tool may enable tailored GvHD treatment and prediction of NRM.

Results with minimal-intensity or reduced-intensity conditioning regimens have been summarized in numerous scientific publications. One publication from 2013 reported outcomes in nearly 1,100 elderly or medically infirm patients with advanced hematologic malignancies who were given HLA-matched related or unrelated grafts after minimal-intensity conditioning with fludarabine and low-dose (2-3 Gy) TBI.⁹¹ The oldest patients in that trial were 75 years of age. Half of the patients had serious comorbidities with HCT Comorbidity Index scores ≥ 3 . These transplants were designed as an outpatient procedure. In fact, nearly half of the patients were never hospitalized while the remaining half had a median hospital stay of only 6 days.⁹² Living at home or in a private apartment and being able to move around freely were appreciated by patients and caregivers. At a median follow-up of 5 years, depending on the relapse risk of the underlying malignancies and on the comorbidity score, lasting remissions were seen in 45-75% of patients and 5-year survivals ranged from 25% to 60%. Overall 5-year NRM was 24%, for the most part associated with concurrent or preceding GvHD, and the overall relapse mortality was 34.5%. With the introduction of the triple-drug regimen of MMF, cyclosporine and sirolimus, the NRM has significantly declined among unrelated recipients. As a result, relapses have remained the major obstacle toward better outcome. Most relapses occurred within the first 2 years after HCT. When analyzing relapse risk per patient year, both disease and disease burden turned out to be major predictors of relapse.⁹³ For example, the risk was 0.19 for multiple myeloma (MM) in remission and as high as 0.32 for patients not in remission. Comparable numbers for acute myeloid leukemia were 0.33 for patients in remission 1-3 and 0.65 for those with relapsed disease.⁹¹ These findings delineated the limitations of graft-*versus*-tumor effects and bore out the adverse impact of high tumor burden. They have encouraged future efforts to reduce relapse through both enhancing graft-*versus*-tumor effects and more effectively reducing the tumor burden before HCT.

A more recent study⁹⁴ reported remarkable improvements in allogeneic HCT outcomes among 1,720 patients with hematologic malignancies who received non-myeloablative conditioning over the past twenty years (Figure 1). These improvements were accomplished even though more recent patients were older (56% >60 years old in 2010-2017 vs. 27% in 1997-2003), had more comorbidities

(45% with HCTCI scores equal to or >3 in 2010-2017 vs. 25% in 1997-2003), and had more frequently unrelated grafts (65% in 2010-2017 vs. 34% in 1997-2003). Explanations for the gradual improvements of outcome include use of ursodeoxycholic acid to prevent cholestasis and hyperbilirubinemia and reduce the incidence of liver GvHD,⁹⁵ improved GvHD prevention, use of topically active oral glucocorticoids for gut GvHD,⁹⁶ more judicious use of systemic glucocorticoid dosing for treatment of GvHD,⁹⁷ and improved antibiotics and anti-fungal agents. As for the latter, a randomized, double-blinded trial showed that posaconazole and fluconazole were similarly effective in preventing overall fungal infections and reducing overall mortality among 600 patients with acute GvHD; however, posaconazole was superior to fluconazole in preventing invasive aspergillosis.⁹⁸

Results from other transplant centers and from CIBMTR and EBMT analyses have shown similar outcomes with a variety of reduced-intensity or minimal-intensity conditioning regimens. Regimens included fludarabine and varying doses of melphalan with or without low-dose TBI, fludarabine and reduced doses of busulfan, reduced busulfan, cyclophosphamide and thiotepa and others. A 2016 review in the journal *Haematologica* summarized the findings with these regimens.⁹⁹ Moreover, researchers at Johns Hopkins utilized the backbone of the

fludarabine/low-dose TBI regimen and added two small doses of pre-transplant cyclophosphamide, followed by two higher doses of cyclophosphamide on days 3 and 4 after HCT plus MMF and tacrolimus to enable engraftment of HLA-haploidentical related marrow or PBSC and minimize acute and chronic GvHD.¹⁰⁰ This regimen has been surprisingly effective, although, owing in part to the reduction in acute and chronic GvHD, relapse has remained a prominent problem.

The use of UCB as an innovative, alternative source of stem cells was introduced in the 1990s. Cord blood cells are immunologically naïve and allow for greater HLA disparity with a given recipient. This feature enabled transplantation for patients who lacked HLA-matched donors. An EBMT report showed promising outcomes among 143 UCB transplantations performed in 45 centers.¹⁰¹ An observational study by Brunstein *et al.* in 2010 suggested that outcome after transplantation of two partially HLA-matched unrelated UCB units was comparable to those of HLA-matched related and unrelated HCT.¹⁰² A prospective, randomized trial comparing double-unit UCB to single-unit UCB transplantation among 224 patients with hematologic malignancies showed equivalent 1-year survivals of 65% versus 73%.¹⁰³ Moreover, patients given single-unit UCB experienced more rapid platelet recovery and less grade 3-4 acute GvHD. Others have experiment-

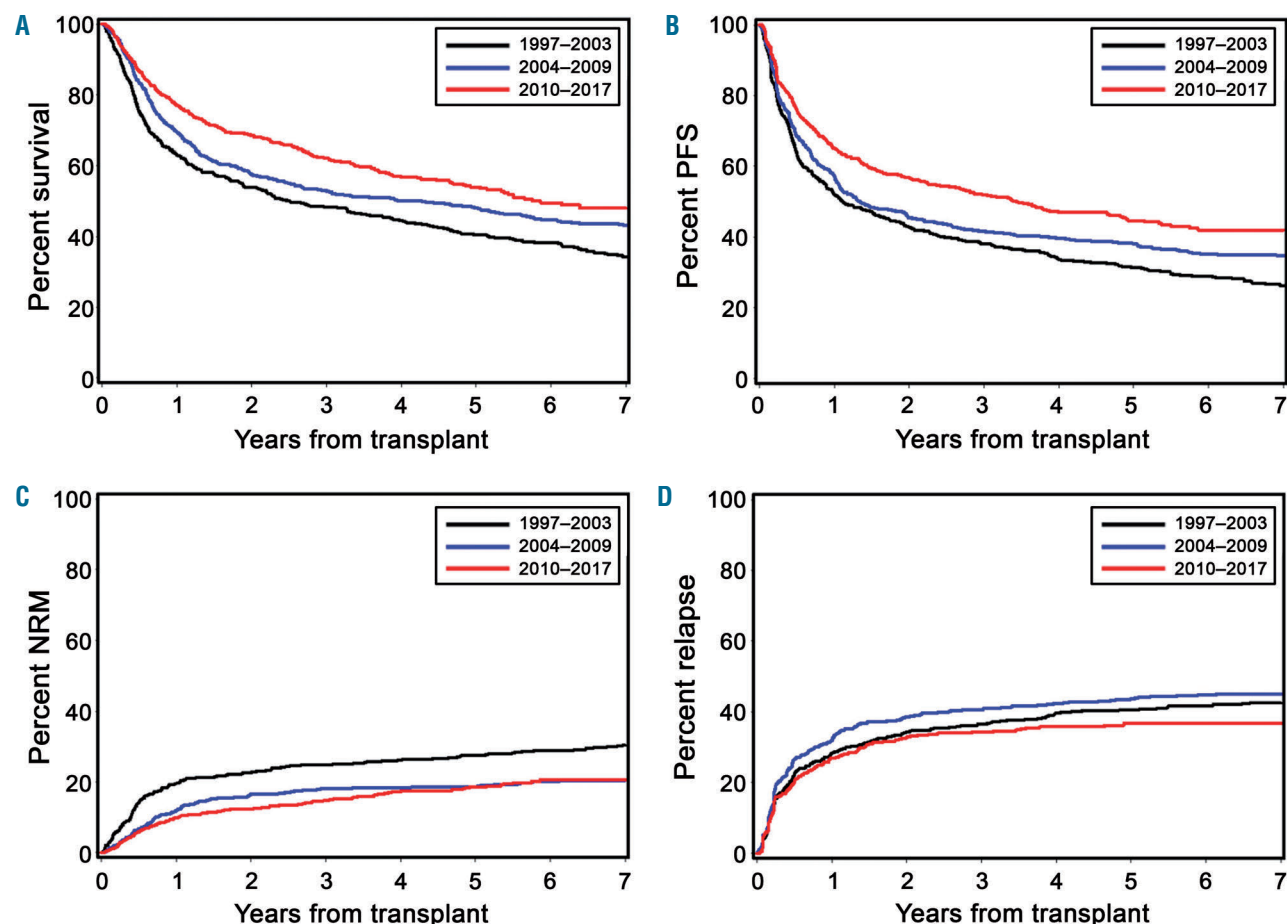


Figure 1. Improved outcomes of allogeneic hematopoietic cell transplantation with non-myeloablative conditioning for older and medically infirm patients with hematologic malignancies over two decades at Fred Hutchinson Cancer Research Center (WA, USA).⁹⁴ Overall survival (A), progression-free survival (PFS) (B), non-relapse mortality (NRM) (C), and incidence of relapse (D) by time period of transplant: 1997-2003 (black line), 2004-2009 (blue line), and 2010-2017 (red line) (from Cooper *et al.*,⁹⁴ with permission).

ed with *ex vivo* UCB expansion methods which may have led to higher engraftment rates.^{104,105} Additional potential advantages of UCB transplantation included the lack of risk to the donor, rapid availability, and ease of scheduling of transplantation.

In 2001, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) was established through funding from the National Institutes of Health as a collaborative effort of the CIBMTR, the NMDP/Be The Match and the Emmes Company, together with 20 Core Transplant Centers. The BMT CTN has opened more than 30 multi-institutional clinical trials involving more than 100 transplant centers.

Current trends

While early HCT involved grafts from HLA-identical sibling donors, from 2006 on unrelated donors became the most frequently used graft source in the USA with almost 4,500 transplants in 2018 alone (Figure 2A¹⁰⁶). This increase could be attributed to: (i) the ever-larger number of unrelated, HLA-typed volunteers in the registries; (ii) advances in HLA-typing including the recognition of the importance of HLA-DPB1 expression for the development of GVHD;¹⁰⁷ and (iii) increasing age of patients whose siblings were also older and often unfit to donate because of comorbidities. A rise in the use of UCB during the early 2000s has been offset and reversed by the remarkable increase in HLA-haploidentical, related grafts after the introduction of post-transplant cyclophosphamide for GVHD prevention. Post-HCT cyclophosphamide served to cause *in vivo* depletion of both donor-*versus*-host reactive T cells (GVHD prevention) and host-*versus*-donor T cells and natural killer (NK) cells (prevention of graft rejection).¹⁰⁸ An alternative regimen for HLA-haploidentical grafts has been reported by Chinese investigators.¹⁰⁹ They conditioned patients by busulfan, cyclophosphamide, ME-CCNU and ATG and combined cyclosporine, MMF and a short course of methotrexate for GVHD prevention and reported favorable outcomes. A very recent review summarized the various conditioning regimens used for HLA-haploidentical HCT.¹¹⁰

Retrospective comparisons of results from different centers have suggested comparable outcomes with HLA-haploidentical related *versus* UCB grafts. In contrast, two recent prospective, randomized trials indicated better outcomes with HLA-haploidentical grafts compared to UCB transplants.^{111,112} However, relapse has remained a major complication, as half of the patients relapsed two years after transplant in both studies, regardless of conditioning regimen intensity. Additional controlled comparisons of the two donor sources may be needed to validate the superiority of HLA-haploidentical over UCB grafts. Unfortunately, accrual to such trials may be challenging since a patient, when given the choice between the two modalities, might prefer the related donor over an UCB graft.

Figure 2B shows trends in disease indications for HCT in North America for the past 18 years. Most notable has been a linear increase in acute myeloid leukemia, from 1,000 patients in 2000 to 3,500 in 2018. This increase was largely due to extending allogeneic HCT to include older patients in whom chemotherapy, as a rule, fails to maintain long-term remissions. For the same reason, increases,

although at lower levels, were also seen for patients with acute lymphoblastic leukemia and myelodysplastic syndromes (MDS). In contrast, allogeneic HCT for chronic myeloid leukemia, chronic lymphocytic leukemia (CLL), and MM have either remained at very low levels or declined. These trends were influenced by the introduction of alternative therapies for these diseases, including tyrosine kinase inhibitors, a BCL-2 antagonist, Bruton tyrosine kinase inhibitors, bi-specific or mono-specific monoclonal antibodies, proteasome inhibitors and chimeric antigen receptor (CAR) T cells, among others. However, these therapies including CART-T cells could also be used as a 'bridge' to allogeneic HCT, for example, in order to consolidate remissions in acute lymphoblastic leukemia (ALL) patients. Allogeneic HCT might also serve as a salvage treatment in NHL and CLL patients who relapsed after CAR-T cell treatment. A recent study reviewed our center's experience with allogeneic HCT after CAR-T cell therapy in 32 ALL, NHL and CLL patients and found no additional risk for infections and GvHD.¹¹³ In addition, recipients of allogeneic HCT after CAR-T cell therapy had longer event-free survival compared to patients given CAR-T cell therapy alone ($P=0.014$). A recently published Chinese study concurred with these results in ALL patients (1-year OS: 79.1% vs. 32.0%; leukemia-free survival: 76.9% vs. 11.6%; $P<0.0001$),¹¹⁴ while an earlier Memorial Sloan Kettering Cancer Center trial, also in ALL patients, showed no significant advantage with allogeneic HCT after CAR-T cell therapy compared to CAR-T cell therapy alone ($P=0.89$, $P=0.64$, respectively).¹¹⁵ In the aggregate, most reports recommended CAR-T cell therapy as a bridging treatment to allogeneic HCT in patients with high-risk B-cell malignancies.

While allogeneic HCT has remained the only curative therapy for CLL, it is currently used mainly for patients in whom all other therapies failed and who are often in poor general condition. Given its curative potential, allogeneic HCT should be considered earlier in the disease course, for example, in patients with poor-risk CLL and no or few comorbidities, in whom the risk of HCT-associated NRM is very low.

Because of novel alternative therapies, allogeneic HCT for NHL has declined from >1,000 cases in 2013 to approximately 600 in 2018. A recent retrospective CIBMTR analysis of allogeneic HCT showed that fludarabine/2 Gy TBI conditioning gave better results than a fludarabine/4 Gy TBI regimen, largely because of lower NRM and better overall 5-year survival (51% vs. 31%) with the former regimen while relapse rates at 5 years were comparable; this result was a testimony to powerful graft-*versus*-lymphoma effects.¹¹⁶ Allogeneic HCT can be considered as salvage therapy in select high-risk MM patients in the setting of a clinical trial, and has been reviewed in detail by a number of investigators.^{117,118}

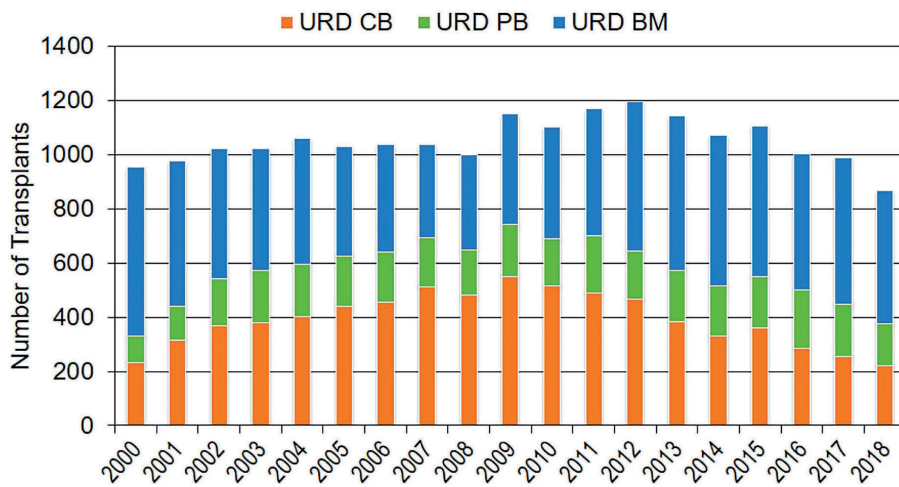
Allogeneic HCT has remained the therapy of choice for disorders such as congenital immunodeficiencies or autoimmune and immune dysregulation disorders. Given the rarity of these diseases, a better understanding of post-transplant complications and long-term outcome is only now emerging.^{119,120} Better timing of transplants, improved screening methods, lasting immune reconstitution post transplant, and reduced toxicity conditioning regimens have contributed to better outcomes for all immunodeficiencies. Allogeneic HCT has also remained standard of

care for other non-malignant diseases such as severe aplastic anemia (AA), sickle cell disease, and thalassemia major. For AA, this is not only true for HLA-identical sibling marrow grafts, but increasingly also for unrelated HLA-matched marrow transplants, where survivals close to or of 100% have been reported.⁵⁴ The most frequently used unrelated HCT regimens for AA patients, either fludarabine, ATG, cyclophosphamide and 2 Gy TBI or fludarabine combined with Campath antibody, appeared to produce similar results, including for older patients.^{121,122} Moreover, recent papers reported outstanding survival figures for AA patients given HLA-haploidentical grafts.^{123,124} Taken together, these findings suggested that upfront marrow transplantation should be considered for all patients with AA who have a suitable donor rather than waiting until failure of immunosuppressive therapy.

ATG has also been widely used as a form of *in vivo* T-cell depletion in conditioning regimens for patients with hematologic malignancies. Kumar *et al.* recently reported a systematic review of prospective, randomized trials comparing ATG to no ATG.¹²⁵ They concluded that, while ATG reduced the incidence of acute and chronic GvHD, there was no statistically significant difference in NRM or overall survival. They suggested designing future studies with improved methodological quality to conclusively establish the role of ATG in allogeneic HCT.

CMV positivity before HCT has remained an adverse risk factor despite monitoring for CMV reactivation and pre-emptive therapy in case of reactivation. Therefore, the results of a recent phase III double-blind trial by Marty *et al.* comparing prophylactic letermovir to placebo in CMV-seropositive patients were encouraging.¹²⁶ In that study,

A Unrelated Donor Allogeneic HCT in Patients <18 Years



B Selected Disease Trends for Allogeneic HCT in the US

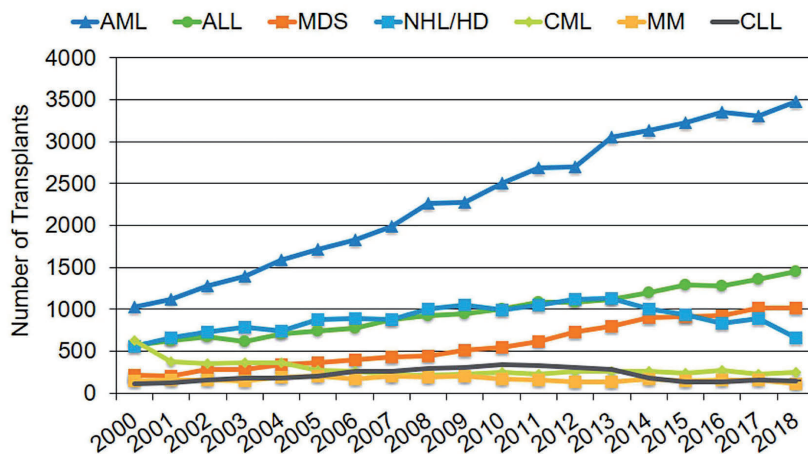


Figure 2. Trends in allogeneic hematopoietic cell transplantation (HCT) over two decades in North America. Donor source (A), transplant indications (B). 2019 data from the Center for International Blood and Marrow Transplant Research (CIBMTR).¹⁰⁶ ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CLL: chronic lymphocytic leukemia; CML: chronic myelogenous leukemia; MDS: myelodysplastic syndrome; MM: multiple myeloma; NHL/HL: non-Hodgkin lymphoma/ Hodgkin disease; URD-CB: unrelated donor cord blood; URD-PB: unrelated donor peripheral blood; URD-BM: unrelated donor bone marrow.

patients randomized to letermovir showed a significant reduction in clinically significant CMV infection after HCT without encountering hematologic toxicities. A

promising option for management of resistant and refractory CMV infection includes maribavir, which is currently being investigated in a phase III trial.¹²⁷ These newer treat-

Table 1. Timeline of list of notable events throughout the years.

Year	Event
1949-1955	Evidence of hematopoietic cell recovery after exposure to lethal radiation ^{2,6}
1956	Bone marrow transplant induces graft-versus-host immune response (GvHD) ¹⁰
1957	First human bone marrow transplantation ^{8,153}
1958	Major histocompatibility complex discovered: human leukocyte antigen (HLA) ^{13,15,16,154,155}
1958-1969	Major preparative regimens developed: total body irradiation (TBI), cyclophosphamide, busulfan ¹⁵⁶⁻¹⁶⁰
1958-1970	Methotrexate for control GvHD in animal models ^{19,161-163}
1968	First allogeneic transplants for primary immunodeficiencies ³⁴⁻³⁶
1971	First successful transplant for end-stage leukemia ¹⁶⁴
1972-1974	First allogeneic transplants for aplastic anemia, PNH and Fanconi anemia ^{44,45}
1973	GvHD and graft-versus-leukemia effects are separate reactions ^{9,165}
1974	Acute grading system and first effective treatment of acute GvHD ^{62,43}
1974	The first bone marrow donor registry was established by the Anthony Nolan Foundation
1975	Transplantation earlier in the course of leukemia ⁴⁷
1979-1981	Establishing graft-versus-leukemia effect in human patients ^{56,57}
1980	First successful unrelated HLA-matched transplant in acute leukemia patient ⁶⁷
1981	Establishment of conditioning regimen for non-malignant diseases leading to successful full immune reconstitution ¹⁶⁶
1981	First successful treatment of chronic GvHD with immunosuppression combination ¹⁶⁷
1981	Introduction of the concept of fractionated total body irradiation ²⁰
1981	Introduction of acyclovir for HSV and VZV prophylaxis ⁷⁹
1982	First successful transplant for thalassemia major ³³
1983	Busulfan-cyclophosphamide conditioning for acute myeloid leukemia ²³
1986	Establishment of the National Marrow Donor Program in the USA
1986	More effective acute GvHD prophylaxis with a combination of methotrexate and cyclosporine or tacrolimus ⁴⁰
1987-1993	HLA class I and HLA class II structures are defined, and HLA-typing transitions from cellular to DNA based ^{62,64}
1988	Standard treatment of chronic GvHD established; prednisone, cyclosporine ^{168,169}
1991	Early treatment with ganciclovir after allogeneic HCT to prevent CMV disease ⁷⁷
1995	Use of peripheral blood stem cells mobilized with granulocyte colony stimulating factor (G-CSF) ^{30,31,170}
1995	Donor lymphocyte infusions for disease relapse ^{38,59}
1997	Umbilical cord blood as an alternative source of hematopoietic cells ¹⁰¹
1998	Impact of matching for class II HLA-DRB1, HLA-DQB1 and class I HLA-C ¹⁷¹
1997-2001	Less toxic conditioning regimens expand allogeneic transplant for older patients ¹⁷²⁻¹⁷⁶
1998	CMV monitoring assays ¹⁷⁷
1983-2005	HLA-haploidentical related grafts for severe combined immunodeficiency and leukemia patients ¹⁷⁸⁻¹⁸¹
2001	BMT CTN established
2002	Dramatic reduction in liver GvHD with ursodeoxycholic acid ¹⁶⁵
2005-2012	Novel antibacterial and antifungals improve transplantation outcomes ^{74,76,78}
2008	Improved outcomes of HLA-haploidentical transplants with post-transplant cyclophosphamide ¹⁰⁰
2009	More judicious dosing of systemic glucocorticoids for treatment of acute GvHD ^{96,97}
2012	Same outcomes with PBSC versus bone marrow from unrelated donors, and less chronic GvHD with bone marrow ¹⁸²
2014	Addition of sirolimus for control of GvHD ^{43,45}
2015	Introduction of novel therapies ^{149,150}
2017	Novel CMV prophylaxis with letermovir ¹²⁶
2018	Ruxolitinib for treatment of steroid-refractory acute GvHD ⁹⁷
2019-2020	Improved outcomes of aplastic anemia patients with HLA-haploidentical transplants ^{123,124}
2018-2020	CAR-T cell therapy as a 'bridge' to allogeneic HCT ¹¹³⁻¹¹⁵

BMT CTN: The Blood and Marrow Transplant Clinical Trials Network; CAR T-cell: chimeric antigen receptor T-cell; CMV: cytomegalovirus; G-CSF: granulocyte-colony stimulating factor; GvHD: graft-versus-host disease; HCT: hematopoietic cell transplantation; HSV: herpes simplex virus; PBSC: peripheral blood stem cell; PNH: paroxysmal nocturnal hemoglobinuria; VZV: varicella zoster virus.

ments have been recently reviewed by Einsele *et al.*¹²⁸ Another approach is adoptive CMV-specific T-cell therapy.¹²⁹ Adoptive T-cell therapy has been effective not only for CMV, but also for Epstein-Barr virus-associated lymphoproliferative syndrome.¹³⁰

Future directions

For allogeneic HCT to become an even more relevant treatment modality, advances must be made in mitigating three major interrelated problems: regimen-related toxicities, post-HCT relapse, and chronic GvHD.

As for the first, younger patients have traditionally received systemic, high-intensity conditioning regimens for maximal tumor cell kill before HCT and reducing the risk of relapse after HCT. Regimen intensity seems to be especially important for patients with AML. A prospective, randomized trial in younger patients with AML in morphologic remission published in 1990¹³¹ showed that conditioning with cyclophosphamide and 1,575 cGy TBI resulted in a significantly lower relapse rate than conditioning with cyclophosphamide and 1,200 cGy TBI, even though this benefit was offset by an increase in NRM. The importance of regimen intensity for controlling relapse was underscored by a recent randomized BMT-CTN-sponsored trial in patients with AML or MDS.¹³² That trial compared conditioning with various high-intensity regimens to that with a number of reduced-intensity or non-myeloablative regimens. The less-intense regimens showed lower NRM, but higher relapse mortality compared to myeloablative regimens, resulting in a statistically significantly lower relapse-free survival (though not overall survival). A recent, retrospective analysis of outcomes for patients with AML showed a clear advantage of myeloablative regimens in patients without measurable residual disease over reduced-intensity or non-myeloablative regimens both with respect to relapse and survival.¹³³ Counterintuitively, this benefit was not seen in patients with measurable residual disease.

However, it has to be considered that high-intensity regimens not only target the malignant tumor cells but also affect every other cell in the body. As a result, transplanted patients experience numerous short- and long-term toxicities. These include mucositis, gastrointestinal damage, veno-occlusive disease of the liver, adverse effects on growth and development, sterility, endocrine imbalance, cataracts, subsequent neoplasms, and others. For example, a recent, retrospective analysis of 4,905 patients transplanted at one center found a cumulative incidence of subsequent malignancies of 22% at 30 years.¹³⁴ The magnitude of the tumor incidence was associated with regimen intensity. This observation coupled with the remarkable graft-versus-tumor effects following the newer reduced or minimal-intensity regimens seen in older patients raises the possibility of using such regimens more broadly, including in younger patients. This would be especially desirable for children and young adults given their longer life expectancy after HCT. Minimizing the systemic regimen intensity would markedly reduce the risks of short- and long-term toxicities, including secondary cancers. For this to become reality, the problem of post-HCT relapse needs to be harnessed. This could be accomplished by: (i) increasing graft-versus-tumor effects after HCT; (ii) reducing the tumor burden before HCT through adding target-

ed radioimmunotherapy (RIT) with few off-target effects to low-intensity conditioning regimens; and (iii) administering maintenance therapy after HCT.

In order to design approaches to increase graft-versus-tumor effects, a better understanding of polymorphic minor histocompatibility antigens specific for hematopoietic cells and distinct from those expressed on other tissue cells will be required. Such understanding might result in the generation of vaccines or of activated T cells that would selectively target hematopoietic antigens and enable exclusive destruction of tumor cells, rather than causing general GvHD.^{135,136}

Another promising approach has been reducing the pre-transplant tumor burden through targeted RIT. Most often RIT have included monoclonal antibodies to the hematopoietic cell surface antigen, CD45, or the B-cell antigen CD20, which are coupled to a radioactive isotope, and then added to a minimal-intensity conditioning regimen. Such targeted RIT, while adding intensity, do not add significant toxicity. First encouraging trials have used β -emitting radionuclides for this purpose including iodine-131, rhenium-188 or yttrium-90.¹³⁷⁻¹⁴⁰ However, while somewhat effective in patients transplanted for myeloid and lymphoid malignancies, these isotopes have the disadvantages of long half-lives, relatively low dose rates, relatively low energy, and long path lengths. More recent, extensive preclinical work has led to the introduction of an α -emitting radionuclide, astatine-211 (²¹¹At), that has several major advantages over the heretofore used β -emitters.¹⁴¹ First, it emits much higher energy in its decay, second, its half-life is a mere 7.2 hours, and finally, its path length is only 60 μ m. The high energy of this radioisotope leads to complete destruction of targeted cells, without the possibility of DNA repair. The short pathlength results in few off-target effects. ²¹¹At decays as a pure alpha, and therefore no isolation of patients is required. Phase I-II, first-in-human clinical trials are ongoing in patients with advanced myeloid malignancies receiving HCT from HLA-matched and unrelated donors, and from HLA-haploidentical related donors. Also, other target antigens are being explored in patients with MM, e.g., CD 38 and B-cell maturation antigen.^{142,143} Furthermore, trials have begun using ²¹¹At-based RIT in order to reduce the intensity of conventional, systemic conditioning for patients with non-malignant blood disorders, which would result in fewer short- and long-term toxicities following HCT.

Encouraging results with maintenance therapy after HCT have been reported in patients with FLT3-ITD AML. A randomized, prospective trial in 204 patients conditioned with busulfan/cyclophosphamide showed significantly less relapse with post-HCT sorafenib compared to controls (1-year relapse 7% vs. 24.5%) and improved leukemia-free and overall survival.¹⁴⁴ Early results of the Routine Antenatal Diagnostic Imaging with Ultrasound (RADIUS) study showed that midostaurin reduced post-HCT relapse in FLT3-mutated AML patients but the difference was as yet not statistically significant.¹⁴⁵ Results with post-HCT azacytidine have been equivocal. Bortezomib maintenance after HCT was beneficial in patients with high-risk MM,¹⁴⁶ while rituximab maintenance has been equivocal in patients with CLL¹⁴⁷ or ineffective in patients with NHL.¹⁴⁸

Apart from relapse, chronic GvHD has remained the most challenging complication of allogeneic HCT. While

there are significant, beneficial graft-*versus*-tumor effects associated with chronic GvHD, these have been offset by morbidity and mortality from this immune complication. The conundrum of preventing chronic GvHD while not sacrificing graft-*versus*-tumor effects has, as yet, not been satisfactorily resolved. Many current approaches, for example, global *in vivo* T-cell depletion with ATG or *in vitro* depletion of naïve T cells from the graft, have used high-intensity, myeloablative conditioning regimens to control post-HCT relapse, but this comes at the cost of regimen-related sequelae. Emerging approaches in preventing GvHD have been achieved through understanding of immunologic pathways of chronic GvHD. These include therapies targeting alloreactive T cells, alloreactive and autoreactive B cells through direct depletion from stem cell grafts (e.g., post-transplantation cyclophosphamide, CD34 selection, IL-2 and IL-17 therapy), *in vivo* depletion (e.g., rituximab, ofatumumab, obinutuzumab), and signal inhibition (e.g., ITK, JAK 1/2, ROCK-II, BTK, SYK inhibition); such studies were recently reviewed in depth by Cutler *et al.*¹⁴⁹ and MacDonald *et al.*¹⁵⁰ The multitude of approaches is an indication that no single method was found to be unequivocally effective.

In addition, novel therapies focus on adoptive transfer and expansion of regulatory T cells (Tregs) to prevent and treat chronic GvHD through administration of low-dose IL-2 and T Tregs sparing therapy. Most recently, removal of naïve T cells from the graft has shown encouraging results for GvHD prevention in younger patients with high-risk leukemia.¹⁵¹ These patients were conditioned with a very intensive conditioning regimen consisting of fludarabine, thiotepa and 13.2 Gy TBI. This approach reduced rates of chronic GvHD (9% at 2 years) while preserving immune reconstitution, without increasing relapse or NRM, though observation periods are still short. Also, the intensity of the conditioning regimen, the TBI dose in particular, places patients at high risk for short- and long-term complications such as secondary cancer.

Researchers are also looking for ways to avoid GvHD without compromising graft-*versus*-leukemia effects in

HLA-haploidentical transplants by co-infusion of donor-derived Tregs and conventional T cells, and infusion of NK cells after transplantation. Another approach has been selective depletion of B cells and T cells by removal of CD45RA⁺ or α/β^+ cells from the graft. In a recent multicenter clinical trial, 80 pediatric acute leukemia patients were transplanted with α/β^+ T- and B-cell depleted HLA-haploidentical grafts, and no additional post-transplantation GvHD prophylaxis.¹⁵² This study resulted in 5-year probability of chronic GvHD-free, relapse-free survival of 71%.

In conclusion, most current methods of preventing chronic GvHD have adversely impacted graft-*versus*-tumor effects thereby increasing the risk of relapse. In order to get around this problem, systemic, myeloablative conditioning regimens have been intensified for better tumor cell kill. However, this has increased the risk of short- and long-term toxicities. Also, high-intensity regimens cannot be tolerated in older patients. It remains to be seen whether in the future, high-dose systemic conditioning can be replaced by RIT that specifically destroy the malignant hematopoietic cells but spare normal tissues. In addition, vaccines to hematopoietic antigens or use of *in vitro* generated T cells that are cytotoxic for hematopoietic cells but not for target tissues involved in GvHD, might generate powerful graft-*versus*-tumor effects and reduce the risk of post-transplantation relapse.

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