The number of allogeneic haemopoietic-cell transplantations (HCT) continues to rise, with more than 25,000 procedures undertaken annually. Several changes in our transplantation practice have contributed to decreased severity of GVHD and organ toxicity, which resulted in improvement in patient outcomes. These changes include the use of reduced intensity conditioning, less toxic conditioning/immunosuppressive agents such as fludarabine, ursodiol, high-resolution HLA matching methods for related and unrelated donors, reduced dose prednisone in GVHD treatment, more effective anti-infective agents, continuous viral monitorization, improved supportive care measures, and giving more emphasis on GVL effect (1-13). In this review, recent findings from select manuscripts were summarized.

Reduced Mortality after Allogeneic HCT

Standard transplant outcomes including overall and non-relapse mortality were compared between 1418 patients who received their first allogeneic transplants at Fred Hutchinson Cancer Research Center in Seattle between 1993 through 1997 and 1148 patients transplanted between 2003 through 2007 (14). As compared with the earlier period, a significant decreases in non-relapse mortality was observed, both at day 200 (by 60%) and overall (by 52%), the rate of relapse or progression of a malignant condition (by 21%), and overall mortality (by 41%), after adjustment for components of the Pretransplant Assessment of Mortality score. The results were similar when the analyses were limited to patients who received myeloablative conditioning. The risk of severe GVHD; disease caused by viral, bacterial, and fungal infections; and damage to the liver, kidneys, and lungs were also decreased in the later period. In brief, there was a substantial reduction in the hazard of death related to allogeneic HCT, as well as increased long-term survival, over the past decade. Improved outcomes appear to be related to reductions in organ damage, infection, and severe acute GVHD.

Another long-term follow-up study of 953 HCT between 1992 and 2009 at Karolinska University Hospital, Stockholm, has demonstrated significant improvements over time in overall survival and transplant-related mortality (TRM), including a 100-day TRM of 5.5% in the most recent time period (2006-2009). The researchers noted that these improvements over time came despite HCT being currently used to treat older patients with more advanced disease. However, the problem of relapse was still the major cause of transplant failure because the study found that the incidence of relapse had not changed since 1992, ranging from 22% to 25% (15).

Stem Cell Source

A large randomized BMT-CTN trial recently presented at the ASH meeting in 2011 showed that PBSC from unrelated donors was associated with higher rates of chronic GVHD compared to BM, although rates of acute GVHD, relapse, non-relapse mortality and overall survival were similar (16).
In a non-randomized (2 parallel) multicenter phase 2 trials conducted by Blood and Marrow Transplant Clinical Trials Network (BMT-CTN), patients with leukemia or lymphoma and no suitable related donor received reduced intensity conditioning (RIC) followed by either unrelated double umbilical cord blood (dUCB) or HLA-haploidentical related donor bone marrow (Haplo-marrow) transplantation (17). For both trials, the transplantation conditioning regimen incorporated cyclophosphamide, fludarabine, and 200 cGy of total body irradiation. Patients in the haplo-marrow group received two doses of post-transplant cyclophosphamide on day 3+ and day 4+ as GVHD prophylaxis. Median follow-up was short at the time of reporting the data. The 1-year probabilities of overall and progression-free survival were 54% and 46%, respectively, after dUCB transplantation (n = 50) and 62% and 48%, respectively, after Haplo-marrow transplantation (n = 50). The day +56 cumulative incidence of neutrophil recovery was 94% after dUCB and 96% after Haplo-marrow transplantation. The 100-day cumulative incidence of grade II-IV acute GVHD was 40% after dUCB and 32% after Haplo-marrow transplantation. The 1-year cumulative incidences of non-relapse mortality and relapse were 24% and 31%, respectively, after dUCB transplantation and 7% and 45%, respectively, after Haplo-marrow transplantation. It was concluded that UCB cell dose had no impact on time to hematopoietic recovery. It was concluded that UCB selection can prioritize matching rather than cell dose in the setting of combined haplo-cord transplant (18).

Non-Myeloablative/Reduced Intensity Conditioning (RIC)

A recent prospective sibling donor versus no-donor comparison demonstrated that adult patients with standard-risk ALL in first complete remission have significantly better outcomes after allogeneic HCT than after autologous HCT and other treatments (19). In this study, 91 patients underwent HCT with a sibling donor and were compared to 161 patients without a sibling donor, the majority of whom underwent autologous transplantation (n=123) or allogeneic transplantation with an unrelated donor (n=29). Five-year disease-free survival was significantly better in the allogeneic transplantation than in the no sibling donor group: 60% vs. 42%, respectively (p<0.01).

A Pediatric Blood and Marrow Transplant Consortium study of 47 high-risk pediatric patients with relapsed hematological malignancies ineligible for second myeloablative transplantation suggested that reduced-intensity conditioning transplantation was associated with low TRM to patients relapsing after a first myeloablative regimen who obtain a second remission. Patients were conditioned with IV busulfan, fludarabine and ATG, and received marrow (n=18), peripheral blood stem cells (n=17) or single cord blood units (n=12). At a median follow-up of 24 months, 2-year event-free survival, overall survival, transplant-related mortality (TRM), and relapse were 40%, 45%, 11%, and 43%, respectively (20).

A multi-center study of 103 adults with myelofibrosis transplanted between 2002-2007 using a reduced-intensity conditioning regimen resulted in a five-year event-free and overall survival of 51% and 67%, respectively (21). Patients were a median age of 55 years (range 32-68) and received a busulfan- and fludarabine-based reduced-intensity regimen. Transplants used related (n=33) or unrelated donor (n=70) grafts. Grade II-IV acute GVHD and chronic GVHD occurred in 27% and 43% of patients, respectively. One-year non-relapse mortality was 16% and was significantly lower for patients with a completely matched donor: 12% vs. 38% (p=0.003).
Non-myeloablative allogeneic HCT is a curative treatment approach in the majority of patients with follicular NHL. In a study from MD Anderson Cancer Center, overall survival and progression-free survival were 85% and 83%, respectively, with a median follow-up of 5 years (range, 19-94 months). Incidence of severe II-IV acute GVHD after nonmyeloablative stem cell transplantation is 11% (22).

In a prospective trial of 162 consecutive patients with newly diagnosed multiple myeloma who were 65 years of age or younger were treated with VAD induction followed by melphalan and autologous stem-cell rescue. Patients with an HLA-identical sibling (n=80) then received non-myeloablative allogeneic HCT. Patients without an HLA-identical sibling received two consecutive myeloablative doses of melphalan, each of which was followed by autologous stem-cell rescue. After a median follow-up of 45 months (range, 21 to 90), the median overall survival and event-free survival were longer in the allo-HCT group (80 months vs. 54 months, P = 0.01; and 35 months vs. 29 months, P = 0.02, respectively). Among patients who completed their assigned treatment protocols, treatment-related mortality was not different significantly between the double-autologous-transplant group (46 patients) and the autograft–allograft group (58 patients, P = 0.09), but disease-related mortality was significantly higher in the double-autologous-transplant group (43% vs. 7%, P>0.001). Overall, 21 of 58 patients (36%) were in complete remission after a median follow-up of 38 months (range, 10 to 72) after allografting. Of the 46 patients who received two autografts, 25 (54%) died (23).

A long-term, multi-center study has shown that non-myeloablative HCT in older patients with advanced hematologic malignancies can lead to a 5-year overall survival of 35%. Median age of patients was 64.1 years (range: 60.1-75.1), and pre-transplant conditioning was low-dose total body irradiation and/or fludarabine at 90mg/m2. Graft sources were related (n=184) and unrelated (n=188) donors. In multivariate analyses, higher HCT-specific comorbidity index scores were significantly associated with worse outcomes, but there was no association between increasing age and organ toxicities, or acute or chronic GVHD (24).

**Anti-HLA Antibody and Graft Failure**

Pre-transplant blood component transfusion may cause development of allo-sensitization against HLA antigens. A new report has found that donor-specific anti-HLA antibodies (DSA) can lower outcomes in double cord blood transplants (CBT). In a study of 73 patients who underwent double CBT between 2004 and 2008, DSA were detected in 18 patients: 11 patients had DSA directed against the first or second infused cord blood unit, and 7 patients had DSA directed against both units. Three-year overall survival was significantly lower in patients with DSA against both cord blood units compared to those without DSA: 0% vs. 45.0%, respectively; (p=0.04) (25).

Donor-specific anti-HLA antibodies (DSA) have also been reported to be associated with graft failure in mismatched HCT as well as matched unrelated donor (MUD) transplantation. In a recent study, the presence of anti-HLA antibodies pre-transplant was studied prospectively in 592 MUD transplant recipients using mixed screen beads in a solid phase solid-phase fluorescent assay. DSA identification was performed using single antigen beads containing the corresponding donor’s HLA mismatched antigens. Anti-HLA antibodies were detected in 116 patients (19.6%), including 20 patients (3.4%) with anti-DPB1 antibodies. Overall, graft failure occurred in 19 of 592 transplants (3.2%). This event was found in 16/584 (2.7%) patients without anti-HLA antibodies, compared to 3/8 (37.5%) patients with DSA (p=0.0014). In multivariate analysis, DSA was the only factor highly associated with graft failure (p=0.0001, OR 21.3). Anti-HLA allosensitization was higher in females than males (30.8% versus 12.1%, p<0.0001), and greater in women with one (p=0.008) and 2 or more pregnancies (p=0.0003), versus males (26).

**Allogeneic Transplant for Adult Sickle Cell Disease**

In this pioneering study, 10 adults (age range, 16 to 45 years) with severe SSD underwent non-myeloablative transplantation with G-CSF-mobilized CD34+ peripheral-blood stem cells from HLA-matched siblings. The conditioning regimen was 300 cGy of total-body irradiation plus alemtuzumab and sirolimus was given for GVHD prophylaxis. No death occurred at a median follow-up of 30 months after transplantation (range, 15 to 54). Nine patients had long-term, stable donor lymphohematopoietic engraftment at levels that sufficed to reverse the sickle cell disease phenotype. Mean (±SE) donor–recipient chimerism for T cells (CD3+) and myeloid cells (CD14+15+) was 53.3±8.6% and 83.3±10.3%, respectively, in the nine patients whose grafts were
successful. Hemoglobin values before transplantation and at the last follow-up assessment were 9.0±0.3 and 12.6±0.5 g per deciliter, respectively. Serious adverse events included the narcotic-withdrawal syndrome and sirolimus-associated pneumonitis and arthralgia. Neither acute nor chronic GVHD developed in any patient (27).

**Pediatric Hodgkin**

A study of 91 children and adolescents with relapsed or refractory Hodgkin's lymphoma (HL) has shown that allogeneic transplantation can benefit these patients. This study of the European registry of pediatric HL transplants from 1987-2005 found 2- and 5-year overall survival (OS) of 54% and 45%, respectively. Patients with good performance status and treatment-sensitive disease transplanted since 2001 had a 3-year OS of 83% and progression-free survival of 60% (28).

**GVHD and Transplant Biomarkers**

In a recent study of 46 chronic GVHD patients, early measurement of serum B-cell activating factor (BAFF) level during photopheresis (ECP) was found to be a potentially useful biomarker in prediction of treatment outcome. BAFF level at 1 month of ECP predicted 3- and 6-month skin disease response, with BAFF less than 4 ng/mL associated with significant skin improvement and complete resolution in 11 of 20 patients (29). High BAFF at 1-month ECP associated with a worsening median 6-month skin score and resolution in 1 of 10 patients. BAFF level at 3 months also predicted the likelihood of maintaining skin disease improvement at 6 months. BAFF level was not correlated directly with extracutaneous cGVHD response, although full cutaneous responders exhibited improved extracutaneous organ response rates compared with skin nonresponders (65% vs 35%).

Another biomarker, TNF receptor 1 (TNFR1), was measured as a surrogate marker for TNF-alpha in 438 recipients of myeloablative HCT before and at day 7 after transplantation. Day 7 TNFR1 ratio correlated with cumulative incidence of GVHD and OS. Patients with TNFR1 ratio more than or equal to 2.5 baseline experienced increased incidence of GVHD grades II to IV compared with those with a ratio less than 2.5 (58% vs 32%, P < .001) and with treatment-related mortality (39% vs 17%, P < .001). In a multivariate analysis including age, degree of HLA match, donor type, recipient and donor sex, disease, and status at HCT, the increase in TNFR1 level at day 7 remained a significant predictor for outcome (30). The specificity of a day 7 TNFR1 ratio > 2.5 for predicting GVHD was 83%. However, the sensitivity of a TNFR1 ratio > 2.5 to predict GVHD was only 38% because the majority of patients who developed grades II to IV GVHD had a TNFR1 ratio < 2.5. Nevertheless, in patients with a TNFR1 ratio > 2.5, the likelihood of developing significant GVHD is sufficiently high (58%) to justify the study of preemptive treatment strategies. A recent study has shown that patients with GVHD who were treated with the TNF-alpha inhibitor (etanercept) in addition to standard, high-dose steroids experience higher complete response rates than patients treated with steroids alone (31) One logical strategy to treat patients at high risk for GVHD might be to initiate preemptive TNF-alpha blockade in patients with high day 7 TNFR1 ratios in an attempt to prevent the occurrence of GVHD in high-risk group.

Most recently, another plasma protein, regenerating islet-derived 3-alpha (REG3α), was identified as a biomarker of lower gastrointestinal (LGI) GVHD. REG3α discerned GI GVHD from non-GVHD diarrhea better than hepatocyte growth factor and cytokeratin fragment 18. Although all three biomarkers predicted non-response to therapy at day 28 in LGI GVHD patients, only REG3α and HGF concentrations predicted 1-year non-relapse mortality (p=0.01 and 0.02). All three biomarkers were elevated in liver GVHD but did not distinguish GVHD from other causes of hyperbilirubinemia (32).

**GVHD Wound Care**

Platelet (PLT) gel has been successfully used in tissue regeneration of diabetic/surgical wounds through the releasing of growth factors such as basic fibroblast growth factor and PLT-derived growth factor. Allogeneic blood components were used to obtain PLT gel with an automated system for the on-site preparation and application of patient (autologous) or healthy blood donor (allogeneic)-derived fibrin sealant or PLT-rich fibrin (Vivostat system, Vivostat A/S). Six patients with multiple lesions involving dermis (Grade I, n = 2), subcutaneous (Grade II, n = 4), or oral mucosa and related to GVHD underwent PLT gel as local therapy. After the second PLT gel application, the pain disappeared in all cases and the granulation tissue was observed in the four patients with Grade II lesions. After a median of eight PLT gel applications (range, 4-10), five of six patients showed a
complete response, while one patient with a partial response died early from multiorgan failure. No side effects were documented (33).

**Management of Post-Transplant Relapse**

In a study of 59 patients transplanted for CD34+ MDS or AML, 20 had minimal residual disease (MRD) defined as a CD34+ donor chimerism of <80%. At a median of 169 days post-transplant, all 20 MRD patients received four cycles of preemptive azacitidine to prevent imminent relapse. Sixteen of the 20 patients (80%) responded with either increasing CD34+ donor chimerism to ≥80% (n=10) or stabilization (n=6) without relapsing (34).

Pediatric HCT patients who have mixed chimerism (MC) after transplant are at higher relapse risk. In a recent study of 71 children transplanted for AML, 20 showed signs of MC, and 13 patients were immediately taken off immunosuppressive drugs and/or received donor leukocyte infusions. Six of the 13 MC patients achieved continuous complete chimerism and long-term remission, leading to a 46% event-free survival. The researchers concluded that MC is a prognostic factor for impending relapse, and that “preemptive immunotherapy may improve the outcome in defined high-risk patients after transplantation” (35).

**Blockade of the CTLA4 molecule can effectively augment antitumor immunity mediated by autologous effector T cells. Ipilimumab is a neutralizing, human anti-CTLA4 monoclonal antibody, which may stimulate the GVL effect after allo-HCT. Twenty-nine patients with malignancies that was recurrent or progressive after allo-HCT, received ipilimumab as a single infusion at dose cohorts between 0.1 and 3.0 mg/kg. Dose-limiting toxicity was not encountered, and ipilimumab did not induce GVHD or graft rejection. Three patients with lymphoid malignancy developed objective disease responses following ipilimumab: 2 CR and 1 PR (36).**

**Cure of HIV Infection with Allogeneic Transplant**

Long-term control of HIV infection was achieved after allogeneic HCT in a 40-year-old HIV+ patient with AML. The graft used came from a donor specifically selected for having a 32-bp deletion in the CCR5 allele, which is known to provide resistance against HIV-1 acquisition. The researchers tested 61 HLA-matched donors before finding one with the CCR5 deletion. The patient has discontinued antiretroviral therapy and has had no detectable proviral HIV DNA in tissue specimens at 20 months post-transplant (37).

**References**


