Are we making progress in GVHD prophylaxis and treatment?

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Allogeneic hematopoietic stem cell transplantation (allo-HCT) is an effective immunotherapy for human cancer. More than 20 000 allo-HCTs are performed each year worldwide, primarily for the treatment of hematologic malignancies. Several technical innovations implemented in allo-HCT over past 2 decades have reduced NRM by 50% and improved overall survival. The allo-HCT practice has changed with the introduction of peripheral blood, cord blood, and haploidentical transplantations and reduced-intensity conditioning, and the patient population is also different regarding age and diagnosis. However, both acute and chronic GVHD remain serious barriers to successful allo-HCT and it is not clear that a major improvement has occurred in our ability to prevent or treat GVHD. Nevertheless, there is an increasing knowledge of the biology and clinical manifestations and the field is getting better organized. These advances will almost certainly lead to major progress in the near future. As the long list of new potential targets and respective drugs are developed, systems need to be developed for rapid testing of them in clinical practice. The current reality is that no single agent has yet to be approved by the US Food and Drug Administration for GVHD prevention or therapy. Although a primary goal of these efforts is to develop better therapies for GVHD, the ultimate goal is to develop treatments that lead to effective prevention or preemption of life-threatening and disabling GVHD manifestations while harnessing the desirable graft-versus-tumor effects.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is an effective immunotherapy for human cancer.[1] More than 20 000 allo-HCTs are performed each year worldwide, primarily for the treatment of hematologic malignancies. Several technical innovations implemented in the past 2 decades have reduced nonrelapse mortality (NRM) by 50% and improved the overall survival (OS) after allo-HCT.[2] Observed decreases in mortality could be due to better methods for the prevention and treatment of GVHD, but to many other advances, including: better treatment of infection, less toxic conditioning regimens, and better HLA matching of unrelated donors (URDs). Allo-HCT clinical practice has also changed over last 20 years and has departed from the uniform use of HLA-matched sibling donor BM transplantations and myeloablative conditioning to a much more complex field. The introduction of peripheral blood, cord blood, and haploidentical transplantations and reduced-intensity conditioning (RIC) regimens, an older patient population, and different diagnoses have modified and made it more difficult to study factors that affect the risks and incidence of GVHD in today's era.[3] Nevertheless, acute GVHD (aGVHD) and chronic GVHD (cGVHD) remain a major contributor to transplantation-related deaths and the most significant barrier to the success of allo-HCT.[4-6] Despite prophylactic treatments with immunosuppressive agents, approximately 50% of transplantation recipients develop GVHD. Most GVH reactions are undesirable and affect multiple organs; however, GVH reactions against hematopoietic tissue targets are desirable and critical for the cure of hematologic malignancies (ie, the graft-versus-tumor effect [GVT]) and for donor immune-hematopoietic system engraftment. These disparate effects of GVH reactions are difficult to separate and any strategies directed against GVHD may adversely affect survival by increasing malignancy relapse or infections. This chapter examines the progress made in GVHD prevention and therapy. Other areas of progress, such as GVHD's impact on health-related quality of life and functional status and advances in basic research or trial designs, will also be discussed.

Who gets GVHD and how is it diagnosed?

GVHD is an immunological complication of allo-HCT caused by donor T cells recognizing the genetically disparate recipient who is unable to reject the donor graft.[6] cGVHD is additionally complicated by disturbances in pathways of immunological reconstitution and failure to acquire immunological tolerance, thereby resulting in both alloimmune and autoimmune attacks on multiple host tissues.[7]

aGVHD diagnosis should be confirmed by biopsy of an affected organ if possible; in addition, other non-GVHD complications involving the skin, liver, and GI tract should be ruled out.[8] Although diagnostic biopsies are highly specific if current histopathology criteria are used, the sensitivity of these biopsies is only approximately 60%; therefore, the ultimate aGVHD diagnosis and decision to treat systemically is based on careful integration of all available clinical information.[9] There is clearly an unmet need for developing more accurate diagnostic tests for aGVHD.[10] The severity of aGVHD is graded according to the Keystone 1994 consensus criteria (grades I-IV) or, less commonly, by the Center for International Blood and Marrow Transplant Research (CIBMTR) criteria (grades A-D).[11,12] The diagnosis of cGVHD is also primarily clinical and requires at least one *diagnostic* sign in a target organ per National Institutes of Health (NIH) criteria (ie, a sign found only in cGVHD) or at least one *distinctive* sign (ie, a sign highly suggestive of cGVHD) in combination with some other laboratory, biopsy, or other test confirmation in the same or another organ.[7] Due to the frequent presence of typical clinical manifestations, biopsies are less commonly done for cGVHD diagnosis and are more often used to rule out other diagnoses such as infection, drug reactions, or cancer.

The incidence of GVHD described in the available literature must be interpreted in light of new classifications that view GVHD as a

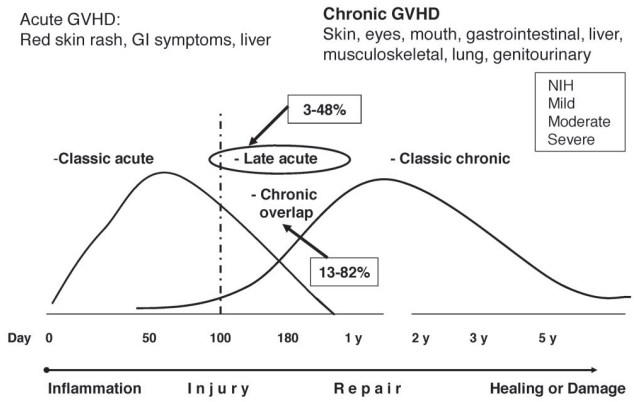

Figure 1. GVHD classification after the NIH consensus conference. The current consensus is that clinical manifestations and not the time after transplantation determine whether the clinical syndrome is considered aGVHD or cGVHD. Retrospective and prospective studies reported wide ranges in the incidences of "late aGVHD" (3%-48%) and "cGVHD overlap" (13%-82%); more prospective cohort studies are needed.

continuum process rather than as a strict separation of aGVHD and cGVHD by the previously used day-100 posttransplantation cutoff. (Figure 1) The current consensus is that clinical manifestations rather than time after transplantation should determine whether the clinical GVHD syndrome is considered acute or chronic.[7] Some signs and symptoms are common to both aGVHD and cGVHD (ie, erythema, macular-papular rash, nausea, vomiting or diarrhea, and elevated liver function tests) and thus cannot be used to distinguish the two. Two main categories of GVHD are now recognized, each with 2 subcategories. The broad category of aGVHD includes: (1) *classic* aGVHD (ie, macular-papular erythematous rash, gastrointestinal symptoms, or cholestatic hepatitis), occurring within 100 days after transplantation or donor leukocyte infusion and (2) *persistent, recurrent, or late* aGVHD, occurring beyond 100 days after transplantation or donor leukocyte infusion. To facilitate reporting in clinical trials, the arbitrary day-100 distinction is retained for the purpose of separating of these 2 aGVHD categories. Both aGVHD subentities occur without the presence of diagnostic or distinctive cGVHD manifestations. A second broad category is cGVHD, which encompasses: (1) *classic* cGVHD, which consists only of manifestations that can be ascribed to cGVHD; and (2) *aGVHD and chronic overlap syndrome*, in which features of both aGVHD and cGVHD appear together. With appropriate stratification, patients with persistent, recurrent, or late aGVHD or overlap syndrome can be included in clinical trials with patients who have cGVHD. The newly defined entities of "late-onset" aGVHD and overlap syndrome subset have been associated with poor survival in some studies but not in others.[13-16] It remains to be determined whether the type or duration of immunosuppressive therapy should differ in patients with "classic" versus "late" aGVHD or "overlap cGVHD."

Historically, cGVHD severity was staged as "limited" (ie, localized skin involvement and/or liver dysfunction) or "extensive" (ie, generalized skin involvement, liver histology showing aggressive hepatitis, or involvement of any other target organ).[17] This classification is relatively poorly reproducible across investigators and does not provide information about the number and extent of the organs involved or the severity of organ function impairments.[18] A new cGVHD clinical staging system is now recommended for scoring of individual organs (scale, 0-3) that describes the severity for each affected organ/site at any given time and also measures functional impact.[7] A global staging of severity (ie, mild, moderate, or severe) is derived by combining organ-specific scores, thereby replacing the "limited-extensive" nomenclature.[7,17] The feasibility of using the NIH staging scale and the distribution of the individual organ scores and global severity stages has now been established in several large prospective studies.[16,19,20] In the largest study of 298 cGVHD patients enrolled into the cGVHD consortium, it was determined that 10%, 59%, and 31% of patients had mild, moderate, or severe cGVHD, respectively.[19] This new and practical scoring system enhances the quality and level of detail of cGVHD data recording and can be used in clinical practice or investigational trials (Figure 2).

Historically, several factors have been identified that predict the onset of aGVHD or cGVHD. However, in previous studies, aGVHD

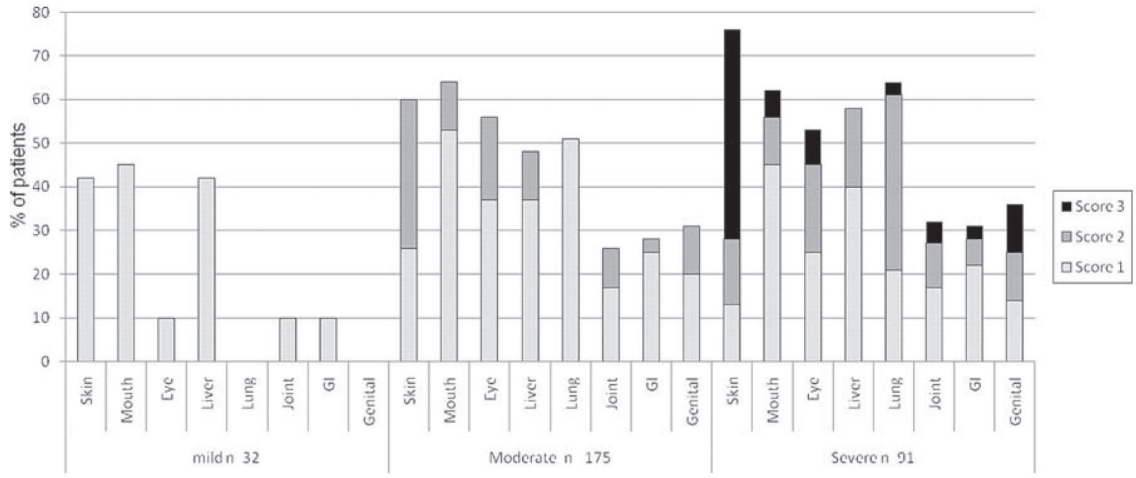

Figure 2. Distribution of individual organ severity scores of cGVHD within global severity mild-moderate-severe staging categories. Data were obtained from the prospective study of the US cGVHD consortium (N = 298). The severity score accounts for both the magnitude of clinical manifestations and the degree of functional impairment. Reprinted with permission from Arai et al.[19]

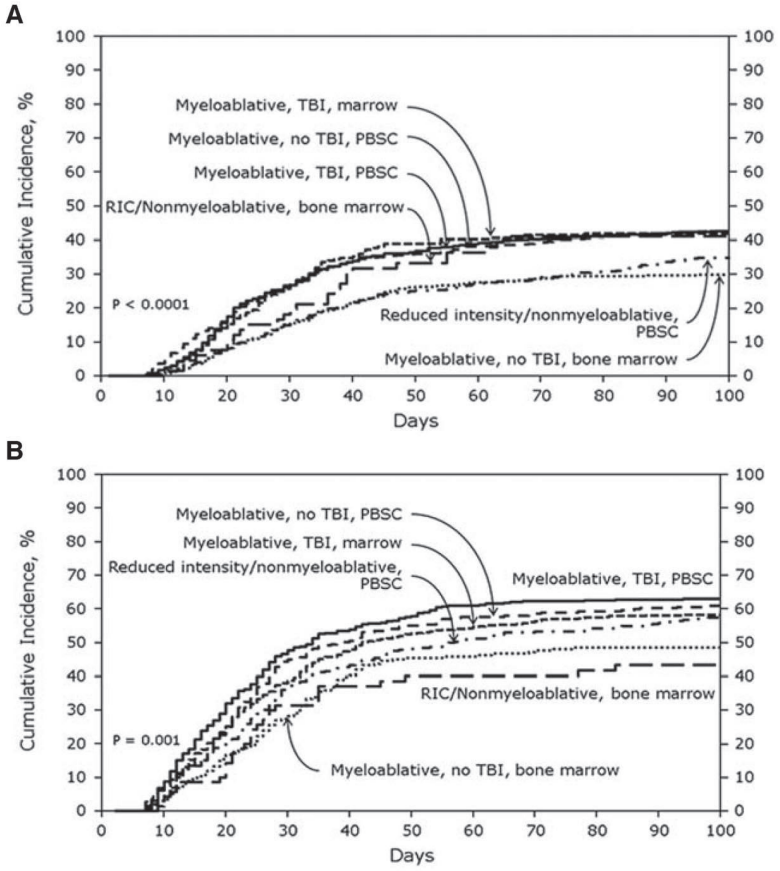

Figure 3. Cumulative incidence of aGVHD grade B-D in related donors (A; n = 3191) and URDs (B; n = 2370) stratified by treatment category. The analysis was performed through the CIBMTR. PBSC indicates peripheral blood stem cell. Reprinted with permission from Jagasia et al.[4]

and cGVHD were generally referred to as disease that occurred within the first 100 days or after 100 days after transplantation. A recent large retrospective study of 2941 patients transplanted after myeloablative conditioning at the Fred Hutchinson Cancer Research Center evaluated risk factors for aGVHD and cGVHD using patients reclassified according to new NIH criteria.[21] Risk factors for aGVHD grades II-IV included transplantation from HLA-matched unrelated donor (MUD) or a mismatched related or URD, use of total body irradiation (TBI) in the conditioning, and use of a female donor for a male recipient. Factors associated with lower risk of aGVHD were the use of rabbit antithymocyte globulin (ATG) in pretransplantation conditioning and chronic myeloid leukemia diagnosis. Grafting with growth-factor mobilized blood cells and patient/donor age were not associated with increased risk of grades II-IV aGVHD classified according to the NIH criteria. Risk factors for cGVHD scored by NIH criteria were similar to the aGVHD risk factors, with the exception of TBI in the conditioning. The use of growth factor–mobilized blood cells and donor or recipient age were also associated with cGVHD, suggesting that aGVHD and cGVHD are not entirely congruent processes. In a separate subanalysis, prior aGVHD grades III-IV were also associated with higher risk of cGVHD according to NIH guidelines.

Compared with these extensive data in the myeloablative setting, there is a relative paucity of data in patients receiving RIC. However, a recent study from the CIBMTR analyzed risk factors for classic aGVHD (within 100 days after transplantation) in a cohort of 5561 adult patients receiving transplantations between 1999 and 2005 (approximately 20% received allo-HCT after a RIC regimen).[4] In the sibling donor cohort (n = 3191), the cumulative incidences of CIBMTR grades B-D and C-D aGVHD were 39% and 16%, respectively. In the URD cohort (n = 2370), the cumulative incidences of grades B-D and C-D aGVHD were 59% and 32%, respectively. Certainly, these data illustrate the magnitude of the aGVHD problem in a contemporary community–based cohort of patients. In an innovative way, this study analyzed the impact of the most common treatment packages currently used in transplantation protocols, because it took into account stem cell source, use of TBI, and conditioning intensity (Figure 3). A recent prospective study in 206 patients with cGVHD enrolled in an NIH natural history study identified TBI, especially in the RIC setting, as a significant prognostic factor for sclerotic-type cGVHD of the skin (Figure 4).[22] Nevertheless, our current ability to predict aGVHD or cGVHD remains insufficiently reliable; however, it is possible that improved predictive criteria may be developed through integration of clinical and emerging biological markers.[10,23]

Prognostic factors for outcomes in patients with GVHD

The most established prognostic factors for poor survival and mortality in patients who develop aGVHD are grade III-IV severity and refractory disease.[24-27] The characteristics most consistently associated with an increased risk of NRM among patients with cGVHD have been thrombocytopenia ($< 100 \times 10^9$/L) and progressive onset of cGVHD from aGVHD. Several other factors associated with increased NRM in patients with cGVHD include: elevated

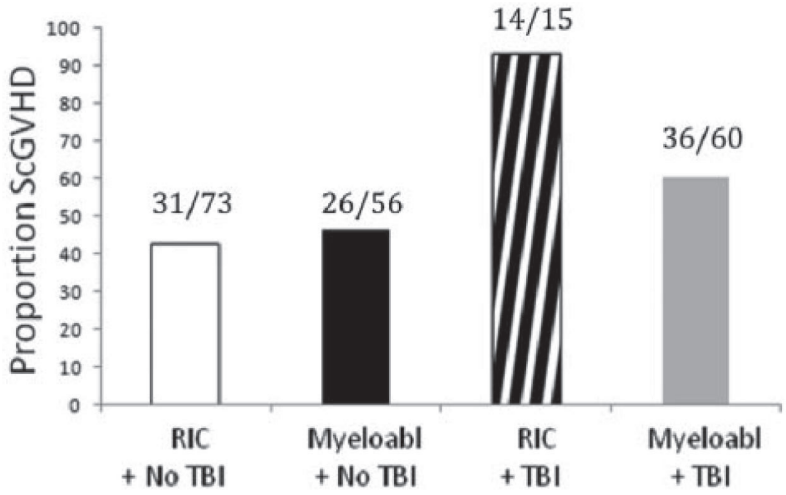

Figure 4. TBI is associated with an increased risk of development of sclerotic-type cGVHD. The association between TBI and sclerotic cGVHD was demonstrated most strongly among patients treated with RIC ($P = .0114$). Data are from the NIH study group prospective cohort. Reprinted with permission from Martires et al.[22]

bilirubin, poor Karnofsky performance status, steroid therapy at the time of onset, diarrhea, weight loss, GI involvement, HLA mismatch, increased patient age, prior aGVHD, and lack of therapeutic response to cGVHD treatment.[18,28-33] Recently, a prognostic score has been developed for cGVHD that is defined by traditional criteria derived from a large cohort of 5343 patients reported to the CIBMTR between 1995 and 2004. The study cohort included patients of all ages treated by all graft sources, donor sources, and both myeloablative and RIC regimens. This analysis showed an OS for the whole cohort of 72% at 1 year and 55% at 5 years.[5] The cumulative incidence of NRM was 21% at 1 year and 31% at 5 years; 6 risk groups were identified that had OS ranging from 15% to 90%.

It is important to emphasize that most studies evaluating prognostic factors for NRM and survival in GVHD are retrospective, from various treatment eras, include heterogeneous patient populations, and did not use contemporary diagnosis and staging criteria. However, in a positive vein, prospective data are now emerging in newly diagnosed and advanced patients due largely to the efforts of the cGVHD consortium in the United States and some single-center studies.[19,34] These studies confirmed the significance of some previously recognized prognostic factors, such as low platelet count, progressive disease onset, and Karnofsky performance status, and also identified new prognostic factors such as NIH global severity stage (mild vs moderate vs severe), overlap syndrome, NIH lung score, and lymphopenia (Figure 5).[15,16,19,20] Recent studies established the association between NIH mild-moderate-severe global stages and health-related quality of life.[35] It is also expected that integration of established clinical prognostic factors and emerging biomarkers will assist in better individualization of GVHD therapy depending on the risk stratification.[36,37]

GVHD prophylaxis

aGVHD

The original aGVHD prophylaxis regimens developed during the 1970s used the folate antagonist methotrexate (MTX) due to its

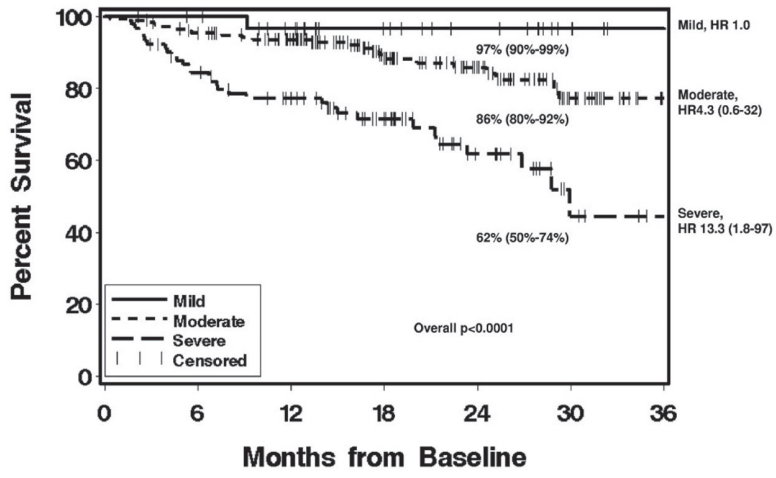

Figure 5. Cumulative incidence of OS according to NIH global severity at enrollment. Graph shows 2-year survival estimates, 95% confidence intervals (in parentheses), and hazard ratios (HR). Data are from the prospective study of the US cGVHD consortium (N = 298). Reprinted with permission from Arai et al.[19]

ability to delete proliferating donor lymphocytes. The initial MTX dosing regimen of days 1, 3, 6, and 11 and then once weekly through day 102 yielded an incidence of grades III-IV aGVHD of approximately 25%.[38] Cyclosporine (CSA) entered clinical trials of GVHD prophylaxis in the late 1970s and showed equivalency with MTX in prospective studies.[39] True progress in GVHD prevention occurred with combination regimens containing CSA and a short course of IV MTX (15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6, and 11), which showed synergism and a survival benefit in BM transplantation from matched siblings and remains a commonly used regimen.[4,40,41] No improvements in cGVHD incidence were seen with these regimens, again suggesting divergent pathogenic mechanisms. Attempts to improve outcomes by adding prednisone to the MTX/CSA combination did not yield positive results.[42,43] During the 1990s, another calcineurin inhibitor, tacrolimus (TAC) used in combination with short-course MTX was tested in 2 large North-American phase 3 clinical trials after related and URD BM transplantation.[44,45] Both trials showed reductions in overall aGVHD incidence (but not cGVHD) among patients receiving TAC/MTX relative to recipients of CSA/MTX; however, OS was not different. These studies prompted some centers to more frequently use the TAC combination, particularly in URD transplantations.

Mycophenolate mofetil (MMF), via its metabolite mycophenolic acid, inhibits proliferation of lymphocytes and is synergistic with calcineurin inhibitors in preventing GVHD. MMF also facilitates donor engraftment and is now widely used in RIC transplantations from related or URDs.[38] Although GVHD prevention does not seem to be improved by use of MMF rather than MTX in calcineurin inhibitor–based regimens, there is a significant decrease in incidence and severity or oropharyngeal mucositis with the use of MMF.[46,47]

Although the combinations of calcineurin inhibitors and MTX or MMF have resulted in satisfactory rates of aGVHD and survival outcomes, these regimens are not uniformly effective and many patients are still dying from GVHD and related complications.[4] Therefore, substantial efforts have been invested in attempts to improve on these calcineurin-inhibitor–based combinations. Anti–T-cell Abs have been explored as part of preparative regimens since the earliest days of allo-HCT; in uncontrolled studies, such Abs prevented GVHD but also increased risk of leukemia relapse, infections, non-relapse-related complications, and engraftment failures.[48] Interpretation of these data is complicated by the huge variability in the studies, particularly in regard to the form of Ab used (at least 4 different forms have been used), source of the stem cell, type of donor, and conditioning regimen intensity. The best evidence for in vivo Ab efficacy is for ATG in URD BM transplantation after myeloablative conditioning.[49] In a large randomized trial, patients who underwent allo-HCT from 8/8 MUDs (approximately 80% received peripheral blood stem cells) were randomly assigned to receive CSA/MTX with or without anti-Jurkat rabbit ATG. ATG recipients had significant reduction of grade II-IV and grade III-IV aGVHD from 51%-33% and from 24.5%-11.7%, respectively. ATG recipients also had a reduced 3-year incidence of extensive cGVHD (45.0% vs 12.2%).[50] There was no statistically significant difference in relapse, NRM, mortality from infectious disease, or OS between groups. A smaller and older randomized study originally performed in the late 1990s showed similar short-term results.[51] In addition, long-term follow-up showed reduced late pulmonary disease in the ATG arm, suggesting a potential long-term impact of in vivo ATG on health-related quality of life.[52] Randomized trials to address the role of ATG, especially in cGVHD prevention, are progressing in the United States and Canada (www.clinicaltrials.gov identifiers NCT01295710 and NCT01217723, respectively). The role of ATG in RIC allo-HCT has not been formally tested because the success of these transplantations in terms of controlling relapse is more dependent on intact GVT reactions. A large retrospective CIBMTR study involving > 1400 patients confirm these concerns, because ATG recipients after RIC had increased risk of malignancy relapse, more NRM, more EBV lymphoproliferative disease, and lower OS and disease-free survival.[53] Prospective randomized trials are needed to define the role of optimal dose and timing of ATG administration in the RIC allo-HCT setting.[54,55] In a related approach, potent and practical techniques for ex vivo T-cell depletion strategies have been evaluated to prevent GVHD. Recently, a phase 2 study in acute myeloid leukemia patients in remission (mostly in in first complete remission [CR1]) demonstrated feasibility of such an approach in related donor transplantations using myeloablative conditioning devoid of posttransplantation systemic immunosuppression.[56] In that study, the incidences of aGVHD and cGVHD were low and relapse did not appear to be increased; however, survival rates were not different from historical controls.

Another pharmacological approach to preventing GVHD has been developed by investigators at the Dana-Farber Cancer Institute through the use of sirolimus, an mTOR inhibitor, as an addition to TAC and MTX.[57] In addition to effector T-cell inhibition, sirolimus can preserve regulatory T cells after transplantation, thereby adding to GVHD control. In a single-arm phase 2 study, the substitution of sirolimus for MTX in combination with TAC after myeloablative conditioning resulted in grade II-IV aGVHD of 20.5% and grade III-IV of 4.8%; no differences in outcomes were observed between recipients of related or URDs.[58] This approach has been extended into the RIC setting, with results indicating that the addition of MTX to sirolimus and TAC is not necessary.[59,60] These data support the utility of sirolimus as a second agent with TAC in GVHD prophylaxis. However, due to an increased risk of veno-occlusive disease, sirolimus should not be used with myeloablative doses of busulfan or in the TBI-based myeloablative regimens if combined with MTX.[61]

Because long-term administration of calcineurin inhibitors has toxicities and impairs T-cell development, Johns Hopkins University investigators are testing the use of high-dose posttransplantation cyclophosphamide (Cy) as sole prophylaxis for GVHD after HLA-matched related and URD T cell–replete BM transplantation.[62] Cy, when given early after transplantation, acts similarly to MTX in terms of deleting rapidly dividing alloreactive T cells. Hematopoietic stem cells contain high levels of aldehyde dehydrogenase, which converts 4-hydroxycyclophosphamide into a nonalkylating metabolite, thus sparing stem cells from the antiproliferative activity of this agent. Cy was given at a dose of 50 mg/kg on days 3 and 4 after transplantation with myeloablative Bu-Cy conditioning without addition of any other systemic immunosuppression.[62] The median time to neutrophil engraftment was 23 and 25 days in matched related donor (MRD) and URD patients, respectively, without use of exogenous colony stimulating factors; in addition, there was a relatively low treatment-related mortality of 13% and 21% at 2 years for MRD and MUD, respectively. Grade II-IV aGVHD incidence was 42% (MRD) and 46% (URD), with grade III and IV occurring in 12% and 8% of patients, respectively. Perhaps the most impressive clinical result of the Cy regimen was the low cumulative incidence of cGVHD, which was 10%. The potential advantage of this approach is selective elimination of host-reactive

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