Published in final edited form as:

Expert Rev Hematol. 2010 June ; 3(3): 285–299. doi:10.1586/ehm.10.21.

Allogeneic hematopoietic cell transplantation: the state of the art

Boglarka Gyurkocza^{†,1}, Andrew Rezvani¹, and Rainer F Storb¹

¹Fred Hutchinson Cancer Research, Center and the University of Washington School of Medicine, Seattle, WA, USA

Abstract

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative procedure for a variety of hematologic malignancies. The field has evolved substantially over the past decade, with advances in patient and donor selection, stem cell sources, supportive care, prevention of complications and reduced-toxicity preparative regimens. As a result, the indications for HCT and the pool of eligible patients have expanded significantly. In this article, we provide an overview of the major aspects of allogeneic HCT, and focus specifically on areas of active research and on novel approaches to challenges in the field. Specifically, we will discuss approaches to reduce the toxicity of the preparative regimen, with the goal of increasing the safety and applicability of HCT. The availability of suitable donors may be an obstacle to wider application of HCT. We review three major approaches to broadening the donor pool: the use of HLA-mismatched unrelated donors, umbilical cord blood and HLA-haploidentical family donors. Graft-versus-host disease remains a major cause of morbidity and mortality after HCT. We review recent advances in the understanding of this phenomenon, and novel prophylactic and therapeutic approaches that hold the promise of further improving the safety of the procedure. We conclude with a speculative outline of the next 5 years of research in the field of HCT.

Keywords

bone marrow transplantation; graft-versus-host disease; hematopoietic cell transplantation

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative procedure for a variety of malignant and non-malignant conditions. When developed initially, allogeneic HCT was considered an approach to rescue patients from the toxic side effects of supralethal doses of radiation and chemotherapy used to treat various underlying diseases by transplanting hematopoietic stem cells, which had the ability to reconstitute hematopoiesis. However, it soon became evident that much of the effectiveness of HCT in malignant diseases stemmed from the immunologic reactions of donor cells against malignant host cells.

With this recognition, the use of allogeneic HCT has expanded rapidly over the past decades and its role will continue to evolve as advances in conditioning, supportive care, management of complications and expanding stem cell sources further widen its applicability.

© 2010 Expert Reviews Ltd

[†]Author for correspondence: Tel.: +1 206 667 4961, Fax: +1 206 667 6124, bgyurkoc@fhcrc.org.

Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

The field of HCT is extremely broad and incorporates elements of immunology, radiobiology, infectious disease and oncology. In this article, we provide an overview of the most salient aspects of HCT, with a special focus on areas of active research and novel therapies.

Recent trends in the use of allogeneic HCT

In the early era of bone marrow transplantation, allogeneic HCT was mostly performed for patients with late-stage leukemia or aplastic anemia after failure of all conventional treatments [1]. Owing to advances in donor selection, HLA typing, conditioning regimens and supportive care, the indications for allogeneic HCT have grown dramatically since this time. Box 1 lists diseases for which allogeneic HCT may represent a treatment option at present.

Currently, an estimated 55,000–60,000 HCTs are performed worldwide every year [2]. Figure 1 shows the most frequent indications for HCT in North America in 2005. The diseases most commonly treated by allogeneic HCT were acute and chronic leukemias and myelodysplastic and myeloproliferative syndromes, accounting for approximately 70% of allogeneic HCTs in North America. Approximately 15% were for other malignant diseases, such as non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, multiple myeloma and other types of cancers. The remainder were performed for aplastic anemia, immunodeficiencies and other diverse nonmalignant disorders.

In addition to the constantly expanding list of indications, there has been a trend towards performing allogeneic HCT earlier in the course of the disease rather than employing this approach as a rescue attempt in the late or end stages of disease progression. This shift in practice was based on studies that revealed that transplant outcomes are highly dependent upon timing. In a retrospective analysis of the US National Marrow Donor Program (NMDP) data from 3857 unrelated-donor transplantations (performed for acute myeloid leukemia [AML], acute lymphoblastic leukemia [ALL], chronic myelogenous leukemia [CML] and myelodysplastic syndrome [MDS]), intermediate- rather than early-stage disease was associated with a 38% greater risk of mortality, while advanced-stage patients had approximately double the mortality risk of patients with early-stage disease in a multivariate analysis [3]. In another study involving 127 patients with poor-risk ALL who underwent HCT from HLA-matched unrelated donors, disease-free survival (DFS) was significantly better when allogeneic HCT was performed in first complete remission [4]. In the same multivariate analysis, shorter interval from diagnosis to HCT was independently associated with increased DFS. Similar conclusions were made in a study involving patients with CML: an analysis of NMDP data from 1423 CML patients undergoing bone marrow transplantation from unrelated donors demonstrated improved DFS for patients in chronic phase who were transplanted within 1 year of diagnosis [5].

Early rather than late allogeneic HCT was not only associated with better outcomes but also a decrease in the likelihood of complications that preclude HCT (e.g., refractory disease, infections and organ toxicities).

While the mentioned trends all resulted in increasing the use of allogeneic HCT in recent years, the largest contribution can probably be attributed to the introduction of reduced-intensity and nonmyeloablative-conditioning regimens. Reduced-intensity and nonmyeloablative-conditioning regimens were associated with decreased regimen-related morbidity and mortality when compared with myeloablative regimens, and made allogeneic HCT available for older and medically infirm patients (Figure 2). This is especially important, as the diseases for which allogeneic HCT is most frequently applied are often more prevalent in the elderly.

Donor selection/alternative donors

The preferred donor for an HCT patient has been HLA-identical sibling. Given dominant inheritance patterns, there is a 25% chance that a given sibling will be HLA-identical with a patient. Overall, approximately 15–30% of patients referred for allogeneic HCT have suitable HLA-identical sibling donors. For patients without sibling donors, a search for an HLA-matched unrelated donor may be undertaken. Donor registries have grown rapidly over the past 20 years (Figure 3); the NMDP currently maintains a database of more than 7.4 million potential donors and 90,000 umbilical cord blood units, and similar (although smaller) registries exist in Europe. The likelihood of identifying an HLA-matched unrelated donor varies with the patient's specific HLA alleles and ethnicity, which influences HLA diversity and the number of registered potential donors. For patients in whom HCT is indicated but who lack suitable HLA-matched unrelated donors, three alternative stem cell sources are potentially available: HLA-mismatched unrelated donors, umbilical cord blood and HLA-haploidentical family members.

Currently, HLA typing is performed using intermediate- or high-resolution DNA-based methods with sequencing of MHC class II genes and sequence-specific oligonucleotide probes for MHC class I alleles. Patients are generally typed at five HLA loci: HLA-A, -B, -C, -DRB1 and -DQB1. Thus, an ideal match carries alleles identical to those of the recipient at each of these loci. However, unrelated donors mismatched at a single HLA allele have been utilized successfully in allogeneic HCT. Some evidence suggests that certain alleles may be more 'permissive' – that is, disparities at these alleles may present less of a barrier to successful transplantation. The acceptable degree and sites of HLA mismatch are matters of evolving evidence and a topic of debate. Lee *et al.* found that allelic disparities at HLA-B or HLA-C may be better tolerated than those at HLA-A or HLA-DRB1, while HLA-DQB1 disparities appeared to confer no additional risk at all [3]. Thus, the NMDP currently recommends matching at HLA-A, -B, -C, and -DRB1, but does not consider HLA-DQB1 matching essential [6]. Disease type and the number of HLA mismatches may play a contributing role; for example, HLA-C disparities have a detrimental impact in low-risk disease (e.g., early CML), which disappears in patients with higher-risk disease. In addition, HLA-DQB1 may be detrimental only when combined with other allele-level mismatches [7]. Current research has focused on the question of whether alloreactivity can be mapped to specific amino-acid residues within an HLA gene. This line of research was stimulated by a 2001 report from Ferrara *et al.* linking a specific amino-acid substitution in the class I HLA heavy chain with higher rates of acute graft-versus-host disease (GVHD) and mortality [8], and expanded by a recent analysis of the Japan Marrow Donor Program data identifying six specific class I amino acid substitutions responsible for provoking severe acute GVHD [9]. These advances in the understanding of HLA-mismatched unrelated-donor HCT were recently reviewed by Petersdorf and Hansen [10].

Umbilical cord blood can be collected safely from newborns and banked. Cord blood contains a significant proportion of hematopoietic stem cells (HSCs) and, thus, is capable of reconstituting the hematopoietic system after allogeneic infusion. Given the relative naivety of the newborn immune system, umbilical cord blood can be transplanted across significant HLA barriers; full HLA matching is not required. Thus, suitable cord blood units (with no more than two mismatches at the HLA-A, -B and -DR loci) can be located for more than 95% of HCT candidates, representing an important option for patients otherwise lacking stem cell donors. Additional potential advantages of cord blood use over other stem sources include the lack of risk to the donor, rapid availability, and ease of rescheduling if transplantation is delayed. On the other hand, it is impossible to collect additional cells from a cord blood donor for administration to treat relapsed malignancy or graft failure, which is a possible disadvantage when compared with other donor options. Cord blood units typically provide approximately a

tenth of the number of CD34⁺ HSCs found in a bone marrow graft [11]. Thus, the initial use of cord blood in the adult setting was hampered by the relatively small size and low stem cell content of cord blood units, which led to high rates of non-engraftment and graft rejection. The most common approach to this problem at present is the infusion of two units of cord blood into a single recipient (so-called double-cord HCT), which appears to result in higher rates of engraftment without an increase in GVHD [12]. Other attempts to improve engraftment after cord blood transplantation have included *ex vivo* expansion of cord blood units [13] and coinfusion of peripheral blood mononuclear cells or mesenchymal stem cells [14-16]. In a pilot study, the administration of cord blood directly into the bone marrow of the recipient, in place of intravenous infusion, also reportedly overcame the problem of umbilical cord blood graft failure [17]. Despite these approaches, prolonged time to engraftment and a potentially higher risk of opportunistic infection remain concerns associated with umbilical cord blood transplantation.

The number of cord blood transplants performed has increased steadily over the past decade. No randomized, controlled trials directly compare outcomes with cord blood to those seen with other stem cell sources and all comparisons have been retrospective. Several groups have reported lower rates of acute GVHD with the use of umbilical cord blood compared with marrow or granulocyte colony-stimulating factor-mobilized PBMC(G-PBMC) grafts [18-20]. The observed lower rates of acute GVHD have been attributed to the relative immunologic naivety of cord blood cells, as manifested by a less 'inflammatory' cytokine profile with less TNF- α and IFN- γ production [21]. Other comparative studies have failed to find a difference in acute GVHD rates with cord blood [22]. The impact of cord blood on chronic GVHD risk is less clear, although it appears that cord blood is probably associated with a similar or somewhat lower risk of chronic GVHD compared with marrow or G-PBMC allografts [23-25]. Several groups have reported survival and disease-control rates with umbilical cord blood comparable to those seen with marrow or G-PBMC; such studies were recently reviewed in depth by Sauter and Barker [26]. Some authors have reported that use of umbilical cord blood as a stem cell source significantly increases the cost of HCT. For example, in 2007, a Canadian group estimated the cost of a single bone marrow transplant at approximately US \$57,000, while an umbilical cord blood transplant was estimated to cost US\$81,000, although the authors emphasized that both approaches yielded a cost per life-year gained within widely accepted ranges, and acknowledged the difficulty of summarizing the cost of a complex multi-disciplinary intervention such as HCT [27].

The third source of stem cells for patients lacking HLA-matched donors is HLA-haploidentical transplantation, typically from a parent, sibling or child. Many patients have such a donor available. Given the profound HLA disparity involved, early attempts at HLA-haploidentical HCT were unsuccessful, owing to severe and often fatal hyperacute GVHD, as well as immunologic graft rejection [28]. Thus, current approaches to haploidentical HCT rely on T-cell depletion from the allograft to ameliorate these reactions and surmount the HLA disparity. With advances in positive selection of CD34⁺ cells, encouraging rates of engraftment and disease control with acceptable rates of GVHD have been reported [29]. The Johns Hopkins group has taken an alternate approach to T-cell depletion in HLA-haploidentical HCT, administering the lymphotoxic agent cyclophosphamide in one or two doses several days after stem cell infusion, with the goal of selectively depleting activated alloreactive donor lymphocytes *in vivo*. This approach has resulted in stable engraftment with acceptable, and even possibly improved, rates of GVHD. However, disease relapse and opportunistic infection remain significant problems, possibly because of the inadvertent depletion of donor lymphocytes necessary for graft-versus-tumor (GVT) effects and for effective immune reconstitution [30]. HLA-haploidentical HCT may be most effective in lymphoid diseases. For example, a recent report suggested that nonmyeloablative haploidentical HCT was associated with superior outcomes in Hodgkin lymphoma compared with HLA-matched related or

unrelated donors [31]. Given the vigorous T-cell depletion necessary for successful HLA-haploidentical HCT, GVT effects are thought to be mediated largely by natural killer (NK) cells in this setting [32]. NK cells are not HLA restricted, and identify their targets through a complex system of stimulatory and inhibitory signals that are, as yet, incompletely characterized. The best-understood regulator of NK function is the inhibitory killer cell immunoglobulin-like receptor (KIR), which interacts with host MHC class I epitopes to prevent NK cells from damaging host tissue. Thus, the effects of donor/recipient KIR-ligand mismatching (which would be expected to provoke greater NK cell activity after HCT) have been explored by several groups. Ruggeri *et al.* reported that KIR ligand-mismatched recipients of HLA-haploidentical HCT had superior engraftment and overall survival with a lower risk of relapse [33]. However, KIR ligand mismatching does not appear to confer clinical benefit in the setting of T-cell-replete HCT from HLA-matched unrelated donors [34].

Overall, advances in alternative-donor transplantation have widened the availability of HCT substantially. By incorporating acceptably HLA-mismatched unrelated donors, umbilical cord blood units, and HLA-haploidentical donors, a stem cell source can be identified for the vast majority of patients eligible for HCT. While good outcomes have been reported in uncontrolled studies, the precise comparative risks and benefits of the various alternative-donor sources remain to be elucidated. Disease-specific niches for these approaches may exist, as the results with HLA-haploidentical HCT in Hodgkin lymphoma suggest [31]. Additionally, each approach brings a set of challenges with it that are the subject of active research. In the case of HLA-mismatched unrelated-donor HCT, GVHD remains a major issue, and some protocols have studied more intensive prophylaxis in these patients. HLA-haploidentical transplantation with post-transplant cyclophosphamide is an intriguing approach; however, the long-term consequences for immune reconstitution remain to be examined, and relapse rates in aggressive diseases (e.g., AML) have been substantial [30]. Umbilical cord blood has unique properties of immunologic naivety, but work continues on overcoming the barriers presented by small unit size, slow engraftment and substantial rates of opportunistic infection; the most promising approaches at present involve the use of double-cord HCT and *ex vivo* expansion of progenitor cells to augment the cord blood cell dose.

Conditioning regimens

Myeloablative conditioning

Historically, marrow-ablative doses of chemotherapy and total-body irradiation (TBI) were thought to be necessary to eradicate the underlying malignancy, to provide immunosuppression to the recipient, which would allow engraftment of donor hematopoietic cells and to create 'marrow space'. These regimens are considered myeloablative, meaning that without transfusion of donor hematopoietic cells, patients would almost invariably die of marrow failure. High-dose regimens are still used for a large number of patients, particularly those with aggressive malignant diseases where there is a need for strong anti-leukemia or anti-tumor effect. The combinations of cyclophosphamide and TBI or busulfan are established myeloablative regimens [35] but other combinations, such as busulfan and fludarabine are being used increasingly [36]. While this approach has been successful in providing long-term survival for some patients with otherwise incurable diseases, its usage has been restricted to patients younger than 50–55 years of age owing to associated toxicity and high nonrelapse mortality rates. Patients with pre-existing comorbidities, or those who underwent previous extensive chemotherapy or radiation treatment were at particularly high risk for developing serious, potentially fatal regimen-related toxicities, such as sinusoidal obstruction syndrome (also known as veno-occlusive disease of the liver) or idiopathic interstitial pneumonia.

Reduced intensity & nonmyeloablative regimens

The observation that patients with acute or chronic GVHD after allogeneic HCT had decreased relapse rates led to the recognition that allogeneic hematopoietic cells not only rescue myeloablated patients by restoring hematopoiesis but also impose a durable graft-versus-leukemia (GVL) or GVT effect, leading to subsequent cure [37-39]. The hypothesis that GVL/GVT effects alone have the potential to eradicate malignant diseases led to the development of several reduced-intensity conditioning regimens since the early 1990s. Initial studies at the MD Anderson Cancer Center in Houston (TX, USA), used purine nucleoside analogue-based regimens for the treatment of hematologic malignancies [40,41]. Slavin *et al.*, at Hadassah University (Israel), used a regimen that consisted of fludarabine, busulfan and antithymocyte globulin (ATG) in a younger group of patients with both hematologic malignancies and genetic diseases [42]. Investigators at the Massachusetts General Hospital (MA, USA) evaluated the use of cyclophosphamide, ATG and thymic irradiation in patients undergoing bone marrow transplantation from HLA-matched donors [43].

One barrier to reduced-intensity conditioning was the concern that decreasing the intensity of the conditioning regimen would likely increase the risk of allograft rejection (host-versus-graft [HVG] effect). In the MHC-identical setting, both HVG and GVH reactions are mediated primarily by T cells. Therefore, it was postulated that intensified postgrafting immunosuppression would simultaneously modulate HVG reactions, facilitate engraftment and prevent GVHD. This hypothesis was tested with the preclinical canine model in which intensive pre-HCT-conditioning regimens were replaced with post-transplantation immunosuppression in a stepwise manner. TBI has been an integral part of the majority of conditioning regimens used in the preclinical canine model and in patients. The T lymphocytes, responsible for both HVG and GVH reactions are radiation sensitive. To determine the minimal TBI dose necessary for successful engraftment, a series of experiments were completed using dog leukocyte antigen (DLA)-identical dog pairs. TBI with 9.2 Gy was sufficient for stable engraftment in 95% of the recipients without additional immunosuppression [44,45]. At the TBI dose of 4.5 Gy, the addition of cyclosporine (CSP) was necessary to achieve sustained engraftment in all recipient dogs [46]. When the TBI dose was further lowered to the sublethal dose of 2 Gy, post-grafting immunosuppression with CSP alone was ineffective, and all dogs rejected their allografts but survived with autologous hematopoietic recovery [47]. In this scenario, the combination of methotrexate and CSP minimally improved the sustained allograft engraftment rate. By contrast, the addition of mycophenolate mofetil (MMF), an antimetabolite drug, in combination with CSP, was successful in promoting long-term engraftment after conditioning with TBI of 2 Gy; four out of five dogs had sustained engraftment, without evidence of GVHD [47]. Similar observations were made when rapamycin was substituted for MMF [48]. Only transient engraftment was observed with additional reduction of the TBI dose to 1 Gy, identifying a threshold at which eventual graft rejection was the rule. In the subsequent observation that irradiation of cervical, thoracic and upper abdominal lymph nodes could be substituted for 2 Gy TBI in this model to promote sustained allograft engraftment, it was established that creating empty marrow space was not necessary for engraftment, and that allogeneic hematopoietic cell grafts could create their own space.

Based on the aforementioned studies utilizing the canine model of allogeneic HCT, a low-dose TBI-based conditioning regimen was developed at the Fred Hutchinson Cancer Research Center (FHCRC; WA, USA) [49]. To prevent graft rejection and increase pretransplantation host T-cell immunosuppression, administration of fludarabine at 30 mg/m² was added to the conditioning regimen of 2 Gy TBI (Figure 4) [50]. Postgrafting immunosuppression consisted of CSP and MMF. This nonmyeloablative conditioning regimen was associated with shorter in-patient hospital stays, reduced need for transfusions [51] and a shorter duration of neutropenia with fewer bacterial infections [52-54]. An ongoing prospective Phase III trial will

randomize patients with MDS or AML to HCT with either myeloablative or nonmyeloablative conditioning to better characterize the differences in disease- and regimen-related outcomes.

A variety of reduced-intensity conditioning regimens have been studied. Most of these regimens are based on fludarabine and an alkylating agent (e.g., melphalan, cyclophosphamide or busulfan), with or without the addition of anti-T-lymphocyte antibodies, such as ATG or the anti-CD52 antibody, alemtuzumab. Alemtuzumab appears to be highly effective in preventing GVHD [55], however, its activity against donor T cells delays immune reconstitution and may inhibit GVT reactions. One fundamental difference between the various forms of anti-T-lymphocyte antibodies and TBI was that, while the former provided different degrees of *in vivo* depletion affecting both host and donor T lymphocytes, TBI only impacted the host immune system, leaving the incoming donor lymphocytes intact. TBI, therefore, allowed donor T cells to exert the desired GVH effect, both for overcoming engraftment barriers and control of underlying malignancies.

The spectrum of intensity of commonly used regimens is shown in Figure 5. At present no prospective comparisons of the various reduced intensity and nonmyeloablative regimens have been published.

The adoption of less toxic conditioning regimens has expanded the number of patients eligible to undergo HCT to include patients who previously have been excluded due to age or comorbidities. Currently, patients in their mid-to-late 70s can be considered for allogeneic HCT.

In addition, some transplant centers are performing autologous HCTs followed by nonmyeloablative allogeneic transplantation. This strategy combines the tumor cytorreduction of a high-dose autologous transplant with the lowered treatment-related mortality (TRM) of a nonmyeloablative conditioning regimen. This approach has been particularly promising in treating patients with multiple myeloma [56-58].

Graft-versus-host disease

Graft-versus-host disease is one of the major complications of allogeneic HCT. GVHD is an immunologic process wherein donor T cells attack host tissue that they recognize as foreign. This process was observed and recognized in some of the earliest mouse models of HCT, leading Billingham to propose the classical requirements for the development of GVHD [59]:

- The graft must contain immunologically active cells (now understood to be T cells)
- The recipient must express antigens not present in the donor
- The recipient must be unable to mount an immune response capable of eliminating the transplanted cells

While the most potent graft-versus-host reactions are seen in HLA-mismatched HCT, GVHD frequently develops even in transplants from HLA-identical sibling donors. This phenomenon is mediated by minor histocompatibility antigens (mHA) – peptides presented in conjunction with MHC on the cell surface capable of inducing a T-cell response. GVHD is typically divided into acute and chronic forms, each affecting specific organ systems and possessing distinctive clinical and histologic manifestations.

Acute GVHD

Acute GVHD occurs most frequently in the first 100 days after HCT, although particularly with nonmyeloablative conditioning, a syndrome of ‘late’ acute GVHD has been recognized. The major targets of alloreactivity in acute GVHD are the skin, the GI tract and (less frequently)

the liver. All patients undergoing T-cell-replete HCT receive immunosuppressive prophylaxis against GVHD; without such prophylaxis, the incidence and severity of GVHD would be prohibitive, even in the HLA-identical setting. The pathophysiology and treatment of acute GVHD was recently reviewed in detail by Ferrara *et al.* [60].

The most widely used prophylactic regimens for acute GVHD combine a calcineurin inhibitor (CSP or tacrolimus) with several doses of post-transplant methotrexate [61,62]. Tacrolimus may be more effective than CSP in preventing acute GVHD, although a survival advantage has not been apparent [63]. After nonmyeloablative HCT, CSP has been combined with MMF, which preferentially inhibits activated lymphocytes by blocking the *de novo* purine synthetic pathway [49,64]. Other approaches to the prevention of acute GVHD include the use of T-cell depletion. Nonspecific T-cell depletion has been associated with high rates of graft rejection, relapse and infection; thus, several groups have explored more specific means of selectively depleting alloreactive T cells. The alkylating agent, cyclophosphamide, administered several days after HCT when alloreactive T cells have been stimulated, has been explored in the HLA-haploidentical setting [30]. This approach appears effective in preventing acute GVHD, although the long-term effect on GVT alloreactivity and immune reconstitution remains unclear. Selective *ex vivo* depletion of alloreactive T cells has also been studied; donor cells are exposed to recipient antigens *ex vivo* and then treated with an anti-CD25 antibody to purge activated T cells before stem cell infusion [65].

Other immunomodulatory agents have been explored; the Boston group has reported encouraging results with sirolimus [66], although other centers have had less positive results [67]. KGF was effective in preventing acute GVHD in animal models but a Phase I/II trial failed to confirm its utility in humans [68]. In rodent models, the histone deacetylase inhibitor suberoylanilide hydroxamic acid (SAHA) is effective in preventing acute GVHD, as is the proteasome inhibitor bortezomib [69,70]. However, as yet, there is no published evidence of effectiveness against acute GVHD in humans. One novel approach to the prevention of acute GVHD involves the modulation of T-cell costimulatory signals. These signals are essential for T-cell activation in response to antigen; in the absence of such costimulatory signals, T cells may become anergic and tolerant. By exposing the donor cells to recipient antigen while blocking costimulatory signals, specific tolerance against host antigens could be induced, thus preventing GVHD [71]. Similarly, exposure of donor cells to recipient antigens *ex vivo* in the presence of costimulatory blockade could induce recipient tolerance and facilitate engraftment, thus reducing or eliminating the need for immunosuppressive conditioning. Described costimulatory pathways include CD28, HVEM, ICOS, OX40 and PD-1. The role of costimulatory signals in acute GVHD was recently reviewed in more depth by Welniak *et al.* [72]. Preliminary reports of the effectiveness of mesenchymal stem cells (MSCs) in treating refractory acute GVHD have generated a great deal of interest in this approach. MSCs from the stem cell donor or from a third party have been suggested to possess immunomodulatory and immunosuppressive effects, although the exact mechanism of these effects remains controversial [73]. Early reports indicated that infusion of MSCs was safe and could enhance engraftment and treat refractory acute GVHD after HCT [74,75]. MSCs, in combination with steroids, are currently being studied as upfront treatment of acute GVHD; initial uncontrolled results have suggested a high response rate [76], and randomized controlled trials are ongoing.

Chronic GVHD

In comparison with acute GVHD, chronic GVHD is much more poorly characterized and understood. One of the major barriers has been the lack of a suitable and logistically feasible animal model. While large strides have been made in the prevention and treatment of acute GVHD, the incidence and impact of chronic GVHD have remained largely unchanged over the past 25 years. If anything, chronic GVHD may be increasingly prevalent because of better

overall survival (that is, more at-risk patients) and the increasing use of G-PBMCs as a stem cell source, which may be associated with a higher risk of chronic GVHD [77]. In addition to its role as a major cause of long-term morbidity and mortality in survivors of HCT, chronic GVHD is the most significant determinant of post-transplant quality of life [78]. However, chronic GVHD exemplifies the double-edged sword of alloreactivity, as the development of chronic GVHD is associated with lower relapse rates and better control of underlying malignancies [79,80]. The course of chronic GVHD is highly variable; many patients have eventual resolution of chronic GVHD and are able to discontinue all immunosuppressive treatment as tolerance develops [81], while others have severe and treatment-refractory manifestations. The current understanding of chronic GVHD and recent advances in therapy are reviewed in depth elsewhere [82,83].

The manifestations of chronic GVHD differ significantly from those of acute GVHD; recent consensus guidelines from the NIH have attempted to standardize the distinction between these two entities on clinical and histologic grounds [84]. Chronic GVHD can affect nearly any organ system and its manifestations typically resemble those of classical autoimmune diseases, such as lupus, Sjogren syndrome and systemic sclerosis. First-line treatment for chronic GVHD typically includes a corticosteroid. For steroid-refractory patients, numerous approaches have been described as beneficial in single-arm, uncontrolled studies. However, there are few head-to-head trials of these agents, and there is no clear second-line agent of choice in steroid-refractory chronic GVHD. One recent randomized, controlled trial explored the addition of MMF, one of the most popular second-line agents, to corticosteroids in upfront treatment of chronic GVHD. The trial was terminated early because of a lack of benefit from MMF, and a suggestion of increased mortality in the MMF arm [85].

Chronic GVHD, similar to acute GVHD, is generally understood as a T-cell-mediated phenomenon. However, the description of autoantibodies in chronic GVHD, directed against targets, such as PDGF receptor and various minor histocompatibility antigens, has stimulated interest in a possible complementary role of B cells in chronic GVHD [86,87]. Subsequently, several groups have reported that the anti-B-cell agent rituximab is effective in treating some manifestations of chronic GVHD [88,89]. Additionally, elevated levels of the B-cell growth factor BlyS have been correlated with chronic GVHD, leading to speculation that dysregulated B-cell homeostasis may be associated with the development and persistence of chronic GVHD [90,91].

Outcomes in specific diseases

Allogeneic HCT has been applied to a variety of hematologic diseases. We will summarize recent results for some of the most common indications for allogeneic HCT in the following sections.

Allogeneic HCT in AML

Approximately 65–70% of adult patients with *de novo* AML achieve complete remissions when treated with induction therapy. These remissions, however, are often not durable and additional therapy is needed to provide long-term relapse-free survival. Since the mid-1990s, based on a study from the Cancer and Leukemia Group B (CALGB) [92], multiple cycles of high-dose cytarabine therapy have become the standard consolidation for patients with favorable, and some patients with intermediate cytogenetic risk under the age of 60 years. In this study, the 4-year DFS rate for patients under the age of 60 years, receiving cytarabine 3 g/m² was 44%, irrespective of karyotype. Similar results were reported by the Southwest Oncology Group (SWOG) [93], with a 4-year estimated survival on the high-dose treatment arm of 32% for those younger than 50 years of age, however, this was only 13% for patients aged 50–64 years.

Allogeneic HCT following myeloablative conditioning represents a treatment option with curative potential for younger patients in first complete remission (CR1); however, treatment-related morbidity and mortality remain concerning.

A large number of prospective trials attempted to compare the outcomes of HCT and nontransplant approaches. In general, these studies enrolled newly diagnosed patients who achieved CR after induction therapy and assigned those with HLA-identical sibling donors to allogeneic HCT in CR1, while those without such donors were treated with chemotherapy or autologous HCT, or were randomized between the two. A recent meta-analysis compared outcomes of allogeneic HCT following myeloablative conditioning versus non-allogeneic treatments from 24 trials that included 6007 patients with AML in CR1, who were younger than 40–60 years [94]. This meta-analysis found that, compared with nonallogeneic therapies, allogeneic HCT had statistically significant better relapse-free and overall survivals for AML with intermediate or unfavorable cytogenetic risks, but not for those with favorable-risk AML.

The development of nonmyeloablative and reduced-intensity conditioning regimens (detailed later) has enabled older and medically infirm patients with myeloid malignancies to undergo allogeneic HCT. A number of studies of reduced-intensity conditioning followed by allogeneic HCT from HLA-identical siblings or HLA-matched unrelated donors have been published [95–99]. Among the largest studies is that from the Seattle Consortium, which included 274 patients with a median age of 60 years who had *de novo* and secondary AML, and underwent HCT with nonmyeloablative conditioning (fludarabine 30 mg/m²/day for 3 days and 2 Gy of TBI) from HLA-identical siblings, HLA-matched or HLA-mismatched unrelated donors [100]. The estimated 5-year overall survival was 33%, with 5-year relapse and nonrelapse mortalities of 42 and 26%, respectively. Of note, patients in first and second CR had similar outcomes (5-year overall survival of 37 and 34%, respectively), which were significantly better than that of patients with more-advanced disease (5-year estimated overall survival of 18%).

Allogeneic HCT in myelodysplastic syndrome

For patients with myelodysplastic syndrome (MDS), allogeneic HCT represents the only treatment modality with curative potential.

A decision analysis published by Cutler *et al.* in patients with MDS showed that the International Prognostic Scoring System (IPSS) could be used to determine the timing of HCT for those with an HLA-identical sibling donor [101]. This study showed that patients in the intermediate-2- and high-risk groups benefited from early HCT, while patients in the low-risk group had the best life expectancy when HCT was delayed until evidence of disease progression. A recent study from our institution, the Fred Hutchinson Cancer Research Center, reported the experience with allogeneic HCT using targeted busulfan and cyclophosphamide in MDS patients (median age: 46 years; range: 6–66 years) [102]. The estimated 3-year relapse-free survival was 56% for related recipients and 59% for unrelated recipients. Nonrelapse mortality at 3 years was 28% for related recipients and 30% for unrelated recipients. Factors that significantly correlated with relapse were advanced French–American–British classification and IPSS score, poor-risk cytogenetics and treatment-related etiology. None of the factors examined were statistically significant for nonrelapse mortality. Patient age and donor type had no significant impact on outcomes.

The success rates with HCT declined as the prognosis by WHO or the IPSS criteria worsened, especially with increasing bone marrow myeloblast counts and the presence of high-risk cytogenetics, owing to progressively increasing relapse rates. The most advanced stages of MDS are usually categorized and analyzed together with AML. Since MDS disproportionately affects older patients, nonmyeloablative conditioning has been explored in this setting. A retrospective analysis from our Center compared outcomes of myeloablative and

nonmyeloablative conditioning in patients with MDS and secondary AML undergoing HCT from HLA-identical related or HLA-matched unrelated donors [103]. Patients receiving nonmyeloablative conditioning were older, had higher IPSS and comorbidity scores and had more durable responses to pre-HCT chemotherapy. The 3-year overall survival, progression-free survival and nonrelapse mortality did not differ significantly between patients receiving myeloablative and nonmyeloblastic conditioning.

Allogeneic HCT in ALL

More than 80% of adult patients with newly diagnosed ALL achieve complete remission with intensive induction therapy. Without additional therapy aimed at eliminating minimal residual disease, however, virtually all patients would relapse within a few months. The intensity of post-remission therapy is selected based on a risk-adapted approach, offering more intensive therapy for patients with higher risk of relapse. The major adverse prognostic factors for achieving durable CR and long-term survival are advanced age and Philadelphia chromosome-positive (Ph+) ALL. Additional adverse prognostic factors include leukocytosis at presentation (white blood cell count >30,000 cells/ μ l at the time of diagnosis) and late achievement of complete remission (>3–4 weeks). Currently, there is no consensus on the optimal post-remission therapy for standard risk ALL patients. Multiagent post-remission chemotherapy regimens result in 40–60% longterm (5–7-year) survival rates [104–106], and allogeneic HCT in CR1 has been mostly reserved for patients who present with poor-risk features. In a recent prospective trial, however, better disease control was achieved in patients younger than 50 years of age with no additional poor-risk characteristics with early allogeneic HCT [107], (presumably with myeloablative conditioning). In the same study, however, the transplantation-related mortality for high-risk older patients was unacceptably high and negated the reduction in relapse risk. Similar findings were reported by the Dutch–Belgian Hemato–Oncology Cooperative Group (HOVON): patients with standard-risk ALL in CR1 undergoing HCT from an HLA-identical sibling donor had significantly better DFS than those undergoing autologous HCT due to lack of such donors (5-year DFS of 60 and 42%, respectively) [108].

Historically, allogeneic HCT in CR1 has been reserved for patients with high-risk disease, such as those with Ph+ ALL. In general, patients with Ph+ ALL undergoing allogeneic HCT in CR1 have superior outcomes than those transplanted in CR2 or at more-advanced disease stage (10-year overall survival: 54 and 29%, respectively) [109]. The introduction of imatinib and other tyrosine kinase inhibitors for the treatment of hematopoietic malignancies harboring the *BCR–ABL* fusion gene has changed the induction treatment strategy, and probably affects the outcome after HCT. In a recent study, the risk of relapse was significantly reduced in patients who received imatinib before allogeneic HCT compared with historical controls (3.8 vs 45.7% at 3 years; $p < 0.001$) [110].

Although traditionally myeloablative doses of chemoradiation were thought to be required for improved long-term relapse-free survival, recent small studies reported promising results with reduced-intensity conditioning, particularly in older patients [111,112]. In a retrospective analysis from the European Group for Blood and Marrow Transplantation (EBMT) the 2-year overall survival was $31 \pm 5\%$, with significantly better outcomes for patients transplanted in CR1 ($52 \pm 9\%$ 2-year overall survival) compared with those transplanted in a more-advanced phase (2-year overall survival $27 \pm 8\%$ for patients in CR2 and CR3 and $20 \pm 7\%$ for those with more-advanced disease) [113].

Allogeneic HCT in lymphoma

Allogeneic HCT has been widely applied as a salvage therapy in both NHL and Hodgkin lymphoma. As high rates of transplant-related mortality have generally been reported in

myeloablative allogeneic HCT for lymphoma, most transplants for these diseases currently utilize reduced-intensity conditioning [114], although myeloablative conditioning is occasionally proposed for selected younger and healthier patients [115]. Reported outcomes have varied depending on disease histology and grade [116], and have been reviewed in detail by Wrench and Gribben [117]. The most promising results have generally been reported with indolent NHL, where progression-free survivals at 3–5 years after HCT have ranged from 43 to 85% depending on patient selection, timing of HCT and other factors [118–121]. Results in aggressive NHL are generally somewhat poorer owing to a higher relapse rate, although success has been reported in selected patients with chemosensitive disease [122]. Excellent results with long-term DFS have been reported with reduced-intensity or nonmyeloablative HCT in mantle cell lymphoma [123,124]. Several large studies have recently provided evidence that allogeneic HCT is an effective treatment for poor-risk or fludarabine-refractory chronic lymphocytic leukemia (CLL), with rates of progression-free survival at 3–5 years of 37–39% in this very high-risk patient population [125,126]. A recent large study reported a superior progression-free survival of 51% at 5 years with the use of unrelated donors, suggesting that the more intense alloreactivity seen in unrelated-donor HCT may be clinically beneficial in CLL [126]. Allogeneic HCT has been employed as salvage therapy in patients with Hodgkin lymphoma who relapse after autologous HCT; however, the graft-versus-lymphoma effect seems more tenuous in Hodgkin lymphoma than in CLL or NHL, and relapse has been a major limitation [127,128]. Interestingly, a recent retrospective analysis suggested that HCT from an HLA-haploidentical donor (see ‘Donor selection’) may be associated with superior disease control in Hodgkin lymphoma compared with HLA-matched related- or unrelated-donor HCT [31].

Allogeneic HCT in multiple myeloma

Several large studies have recently examined the role of allogeneic HCT in multiple myeloma. As with lymphoma, myeloablative conditioning in this setting is associated with excessive morbidity and mortality, so reduced-intensity or nonmyeloablative regimens have been the rule. Single or double autologous HCT after suitable induction therapy is the standard of care for newly diagnosed myeloma. Therefore, research has focused on both the integration of allogeneic HCT into such a program, and comparing tandem autologous/allogeneic HCT with double autologous HCT. A randomized trial, published in 2007, reported better results with autologous/allogeneic HCT compared with double-autologous HCT [57]. Subsequent follow-up has confirmed prolonged DFS in myeloma patients after autologous/allogeneic HCT, with a median event-free survival of approximately 3 years [58,129]. However, the survival of patients randomized to the tandem autologous arm was poorer than that seen in previously published, uncontrolled studies, and patients undergoing allogeneic HCT had a significant incidence of chronic GVHD. Therefore, at the current time, tandem autologous/allogeneic HCT for newly diagnosed myeloma patients is generally restricted to clinical trials. Careful patient selection is also important, as this approach may be most suitable for patients with particularly aggressive myeloma and those at high risk of early relapse with tandem autologous HCT. The role of maintenance treatment with agents such as bortezomib or lenalidomide after allogeneic HCT for myeloma is the subject of active research, although few data have been published thus far.

Expert commentary

One of the most significant developments within the past 10 years in hematopoietic cell transplantation has been the development and proliferation of reduced-intensity conditioning regimens. These regimens have been feasible and effective, particularly for older adults. A major challenge for the next decade will be to determine the optimal niches for these regimens and further individualize treatment. Similarly, alternative stem cell sources, such as haploidentical donors and cord blood grafts have demonstrated effectiveness and feasibility,

but further research will be needed to clarify the role of these approaches relative to more established practices. GVHD remains a major challenge; efforts to reduce GVHD while preserving GVT effects remain an ongoing focus of research.

Five-year view

In the next 5 years, additional improvements in conditioning regimens, donor selection and supportive care can be expected. In particular, ongoing research in the field of T-cell costimulatory blockade has raised the possibility that TBI could be safely eliminated from the current nonmyeloablative conditioning regimens. Costimulatory blockade holds the promise of selectively modulating alloreactive T-cell clones of the host, while preserving donor T-cell function necessary for engraftment and GVT reactions. Studies have suggested that the equivalent of 1 Gy TBI could be replaced by costimulatory signal blockade with either CTLA-4 immunoglobulin or a monoclonal antibody directed against CD154 [130,131]. Another area of active investigation is the replacement of TBI with radioimmunotherapy with α -emitting radionuclides and monoclonal antibodies to TCR $\alpha\beta$ and CD45.

In addition, over the next 5 years, we will accrue additional data on the utility and comparative risks and benefits of alternative donor transplantation. These data will enable us to select alternative donors for patients who lack HLA-identical family members or HLA-matched unrelated donors more rationally. In particular, the expansion of the HSC component of cord blood units may reduce the risk of rejection associated with this approach.

Advances in the prevention and treatment of acute GVHD will continue to progress over the next 5 years. Additional randomized controlled trials will provide head-to-head tests of some of the agents that, thus far, have shown intriguing results in uncontrolled Phase II studies. The search for biomarkers and other clinical factors to stratify patient risk, both in terms of pre-transplant comorbidities and post-transplant complications, may help target available therapies more effectively. Chronic GVHD remains a significant problem with fewer promising leads than acute GVHD, but the standardization of diagnostic criteria will enable additional multicenter, randomized trials, which may help clarify the role of the numerous second-line treatments currently in use. Additionally, further research over the next 5 years will explore the role of B cells in chronic GVHD and determine whether they are participants or largely bystanders in the process.

Box 1. Diseases for which allogeneic hematopoietic cell transplantation can be considered

Acquired diseases

- Aplastic anemia
- Paroxysmal nocturnal hemoglobinuria
- Acute myeloid leukemia
- Acute lymphoblastic leukemia
- Myelodysplastic syndrome
- Myeloproliferative disorders
- Chronic myeloid leukemia
- Multiple myeloma and other plasma cell disorders
- Hodgkin lymphoma
- Non-Hodgkin lymphoma

- Chronic lymphocytic leukemia
- Selected autoimmune disorders

Inherited diseases

- Thalassemia
- Sickle cell disease
- Fanconi anemia
- Diamond–Blackfan syndrome
- Dyskeratosis congenita
- Shwachman–Diamond syndrome
- Severe combined immunodeficiency syndrome and other congenital immune deficiencies
- Wiskott–Aldrich syndrome
- Osteopetrosis
- Hemophagocytic lymphohistiocytosis
- Hurler’s syndrome and other inherited metabolic disorders

Key issues

- The list of diseases in which allogeneic hematopoietic cell transplantation (HCT) can be considered continues to expand.
- Reduced-intensity and nonmyeloablative conditioning regimens made allogeneic HCT available for older and medically infirm patients.
- For patients in whom allogeneic HCT is indicated but who lack HLA-matched related or unrelated donors, alternative stem cell sources should be considered, such as HLA-mismatched unrelated donors, umbilical cord blood and HLA-haploidentical family members.
- The most common complications of allogeneic HCT include opportunistic infections, graft-versus-host disease and treatment-related morbidity and mortality.

Acknowledgments

This study was supported by grants AI067770, CA15704, CA18029, CA76930, CA78902 and HL36444, NIH, Bethesda, MD, USA.

References

1. Thomas ED, Storb R, Clift RA, et al. Bone-marrow transplantation. *N. Engl. J. Med* 1975;292(16,17): 832–843. 895–902. [PubMed: 234595]
2. Horowitz, MM. Uses and growth of hematopoietic cell transplantation. In: Appelbaum, FR.; Forman, SJ.; Negrin, RS.; Blume, KG., editors. *Thomas’ Hematopoietic Cell Transplantation*. Wiley-Blackwell; Oxford, UK: 2009. p. 15-21.

3. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood* 2007;110(13):4576–4583. [PubMed: 17785583]
4. Cornelissen JJ, Carston M, Kollman C, et al. Unrelated marrow transplantation for adult patients with poor-risk acute lymphoblastic leukemia: strong graft-versus-leukemia effect and risk factors determining outcome. *Blood* 2001;97(6):1572–1577. [PubMed: 11238093]
5. McGlave PB, Shu XO, Wen W, et al. Unrelated donor marrow transplantation for chronic myelogenous leukemia: 9 years' experience of the National Marrow Donor Program. *Blood* 2000;95(7):2219–2225. [PubMed: 10733488]
6. Kamani N, Spellman S, Hurley CK, et al. State of the art review: HLA matching and outcome of unrelated donor umbilical cord blood transplants. *Biol. Blood Marrow Transplant* 2008;14(1):1–6. [PubMed: 18158954]
7. Petersdorf EW, Anasetti C, Martin PJ, et al. Limits of HLA mismatching in unrelated hematopoietic cell transplantation. *Blood* 2004;104(9):2976–2980. [PubMed: 15251989]
8. Ferrara GB, Bacigalupo A, Lamparelli T, et al. Bone marrow transplantation from unrelated donors: the impact of mismatches with substitutions at position 116 of the human leukocyte antigen class I heavy chain. *Blood* 2001;98(10):3150–3155. [PubMed: 11698304]
9. Kawase T, Morishima Y, Matsuo K, et al. High-risk HLA allele mismatch combinations responsible for severe acute-graft-versus-host disease and implication for its molecular mechanism. *Blood* 2007;110(7):2235–2241. [PubMed: 17554059]
10. Petersdorf E, Hansen JA. New advances in hematopoietic cell transplantation. *Curr. Opin. Hematol* 2008;15:549–554. [PubMed: 18832924]
11. Laughlin MJ, Barker J, Bambach B, et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. *N. Engl. J. Med* 2001;344(24):1815–1822. [PubMed: 11407342]
12. Barker JN, Weisdorf DJ, Defor TE, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. *Blood* 2005;105(3):1343–1347. [PubMed: 15466923]
13. Delaney C, Brashem-Stein C, Voorhies H, et al. Notch-mediated expansion of human cord blood progenitor cells results in rapid myeloid reconstitution *in vivo* following myeloablative cord blood transplantation. *Blood* 2008;112(11):85–86. Abstract 212.
14. Magro E, Regidor C, Cabrera R, et al. Early hematopoietic recovery after single unit unrelated cord blood transplantation in adults supported by co-infusion of mobilized stem cells from a third party donor. *Haematologica* 2006;91(5):640–648. [PubMed: 16670070]
15. Chung NG, Jeong DC, Park SJ, et al. Cotransplantation of marrow stromal cells may prevent lethal graft-versus-host disease in major histocompatibility complex mismatched murine hematopoietic stem cell transplantation. *Int. J. Hematol* 2004;80(4):370–376. [PubMed: 15615264]
16. Martin-Donaire T, Rico M, Bautista G, et al. Immune reconstitution after cord blood transplants supported by coinfusion of mobilized hematopoietic stem cells from a third party donor. *Bone Marrow Transplant*. 2009 doi:10.1038/bmt.2009.15-9999. Epub ahead of print.
17. Frasson F, Gualandi F, Podesta M, et al. Direct intrabone transplant of unrelated cord-blood cells in acute leukaemia: a Phase I/II study. *Lancet Oncol* 2008;9(9):831–839. [PubMed: 18693069]
18. Takahashi S, Ooi J, Tomonari A, et al. Comparative single-institute analysis of cord blood transplantation from unrelated donors with bone marrow or peripheral blood stem-cell transplants from related donors in adult patients with hematologic malignancies after myeloablative conditioning regimen. *Blood* 2007;109(3):1322–1330. [PubMed: 17038536]
19. Rocha V, Wagner JE, Sobocinski KA, et al. Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling. *N. Engl. J. Med* 2000;342(25):1846–1854. [PubMed: 10861319]
20. Rocha V, Cornish J, Sievers EL, et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. *Blood* 2001;97(10):2962–2971. [PubMed: 11342418]
21. Chalmers IM, Janossy G, Contreras M, Navarrete C. Intracellular cytokine profile of cord and adult blood lymphocytes. *Blood* 1998;92(1):11–18. [PubMed: 9639493]

22. Barker JN, Davies SM, DeFor T, Ramsay NK, Weisdorf DJ, Wagner JE. Survival after transplantation of unrelated donor umbilical cord blood is comparable to that of human leukocyte antigen-matched unrelated donor bone marrow: results of a matched-pair analysis. *Blood* 2001;97(10):2957–2961. [PubMed: 11342417]
23. Eapen M, Rubinstein P, Zhang MJ, et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. *Lancet* 2007;369(9577):1947–1954. [PubMed: 17560447]
24. Rocha V, Labopin M, Sanz G, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N. Engl. J. Med* 2004;351(22):2276–2285. [PubMed: 15564544]
25. Hwang WY, Samuel M, Tan D, Koh LP, Lim W, Linn YC. A meta-analysis of unrelated donor umbilical cord blood transplantation versus unrelated donor bone marrow transplantation in adult and pediatric patients. *Biol. Blood Marrow Transplant* 2007;13(4):444–453. [PubMed: 17382250]
26. Sauter C, Barker JN. Unrelated donor umbilical cord blood transplantation for the treatment of hematologic malignancies. *Curr. Opin. Hematol* 2008;15(6):568–575. [PubMed: 18832927]
27. Costa V, McGregor M, Laneuville P, Brophy JM. The cost–effectiveness of stem cell transplantations from unrelated donors in adult patients with acute leukemia. *Value in Health* 2007;10(4):247–255. [PubMed: 17645679]
28. Hansen, JA.; Clift, RA.; Beatty, PG., et al. Marrow transplantation from donors other than HLA genotypically identical siblings. In: Gale, RP., editor. *Recent Advances in Bone Marrow Transplantation*. Alan R Liss Inc.; NY, USA: 1983. p. 739-756.
29. Aversa F, Terenzi A, Tabilio A, et al. Full haplotype-mismatched hematopoietic stem-cell transplantation: a phase II study in patients with acute leukemia at high risk of relapse. *J. Clin. Oncol* 2005;23(15):3447–3454. [PubMed: 15753458]
30. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, post-transplantation cyclophosphamide. *Biol. Blood Marrow Transplant* 2008;14:641–650. [PubMed: 18489989]
31. Burroughs LM, O'Donnell PV, Sandmaier BM, et al. Comparison of outcomes of HLA-matched related, unrelated, or HLA-haploidentical related hematopoietic cell transplantation following nonmyeloablative conditioning for relapsed or refractory Hodgkin lymphoma. *Biol. Blood Marrow Transplant* 2008;14:1279–1287. [PubMed: 18940683]
32. Ruggeri L, Capanni M, Urbani E, et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. *Science* 2002;295(5562):2097–2100. [PubMed: 11896281]
33. Davies SM, Ruggeri L, DeFor T, et al. Evaluation of KIR ligand incompatibility in mismatched unrelated donor hematopoietic transplants. Killer immunoglobulin-like receptor. *Blood* 2002;100(10):3825–3827. [PubMed: 12393440]
34. Farag SS, Bacigalupo A, Eapen M, et al. The effect of KIR ligand incompatibility on the outcome of unrelated donor transplantation: a report from the Center for International Blood and Marrow Transplant Research, the European Blood and Marrow Transplant Registry, and the Dutch Registry. *Biol. Blood Marrow Transplant* 2006;12(8):876–884. [PubMed: 16864058]
35. Kroger N, Zabelina T, Kruger W, et al. Comparison of total body irradiation vs busulfan in combination with cyclophosphamide as conditioning for unrelated stem cell transplantation in CML patients. *Bone Marrow Transplant* 2001;27(4):349–354. [PubMed: 11313663]
36. de Lima M, Couriel D, Thall PF, et al. Once-daily intravenous busulfan and fludarabine: clinical and pharmacokinetic results of a myeloablative, reduced-toxicity conditioning regimen for allogeneic stem cell transplantation in AML and MDS. *Blood* 2004;104(3):857–864. [PubMed: 15073038]
37. Weiden PL, Flournoy N, Thomas ED, et al. Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts. *N. Engl. J. Med* 1979;300:1068–1073. [PubMed: 34792]
38. Weiden PL, Sullivan KM, Flournoy N, Storb R, Thomas ED, the Seattle Marrow Transplant Team. Antileukemic effect of chronic graft-versus-host disease. Contribution to improved survival after allogeneic marrow transplantation. *N. Engl. J. Med* 1981;304:1529–1533. [PubMed: 7015133]
39. Sullivan KM, Weiden PL, Storb R, et al. Influence of acute and chronic graft-versus-host disease on relapse and survival after bone marrow transplantation from HLA-identical siblings as treatment of acute and chronic leukemia. *Blood* 1989;73:1720–1728. [PubMed: 2653460]

40. Giralt S, Estey E, Albitar M, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. *Blood* 1997;89(12):4531–4536. [PubMed: 9192777]
41. Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. *Blood* 2001;97(3):631–637. [PubMed: 11157478]
42. Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. *Blood* 1998;91(3):756–763. [PubMed: 9446633]
43. Spitzer TR, McAfee S, Sackstein R, et al. Intentional induction of mixed chimerism and achievement of antitumor responses after nonmyeloablative conditioning therapy and HLA-matched donor bone marrow transplantation for refractory hematologic malignancies. *Biol. Blood Marrow Transplant* 2000;6(3A):309–320. [PubMed: 10905768]
44. Storb R, Raff RF, Appelbaum FR, et al. What radiation dose for DLA-identical canine marrow grafts? *Blood* 1988;72:1300–1304. [PubMed: 3048439]
45. Storb R, Raff RF, Appelbaum FR, et al. DLA-identical bone marrow grafts after low-dose total body irradiation: the effect of canine recombinant hematopoietic growth factors. *Blood* 1994;84:3558–3566. [PubMed: 7524741]
46. Yu C, Storb R, Mathey B, et al. DLA-identical bone marrow grafts after low-dose total body irradiation: effects of high-dose corticosteroids and cyclosporine on engraftment. *Blood* 1995;86:4376–4381. [PubMed: 7492799]
47. Storb R, Yu C, Wagner JL, et al. Stable mixed hematopoietic chimerism in DLA-identical littermate dogs given sublethal total body irradiation before and pharmacological immunosuppression after marrow transplantation. *Blood* 1997;89(8):3048–3054. [PubMed: 9108426]
48. Hogan WJ, Little M-T, Zellmer E, et al. Postgrafting immunosuppression with sirolimus and cyclosporine facilitates stable mixed hematopoietic chimerism in dogs given sublethal total body irradiation before marrow transplantation from DLA-identical littermates. *Biol. Blood Marrow Transplant* 2003;9:489–495. [PubMed: 12931117]
49. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood* 2001;97(11):3390–3400. [PubMed: 11369628]
50. Niederwieser D, Maris M, Shizuru JA, et al. Low-dose total body irradiation (TBI) and fludarabine followed by hematopoietic cell transplantation (HCT) from HLA-matched or mismatched unrelated donors and postgrafting immunosuppression with cyclosporine and mycophenolate mofetil (MMF) can induce durable complete chimerism and sustained remissions in patients with hematological diseases. *Blood* 2003;101(4):1620–1629. [PubMed: 12393457]
51. Weissinger F, Sandmaier BM, Maloney DG, Bensinger WI, Gooley T, Storb R. Decreased transfusion requirements for patients receiving nonmyeloablative compared with conventional peripheral blood stem cell transplants from HLA-identical siblings. *Blood* 2001;98(13):3584–3588. [PubMed: 11739160]
52. Junghanss C, Marr KA, Carter RA, et al. Incidence and outcome of bacterial and fungal infections following nonmyeloablative compared with myeloablative allogeneic hematopoietic stem cell transplantation: a matched control study. *Biol. Blood Marrow Transplant* 2002;8:512–520. [PubMed: 12374456]
53. Fukuda T, Hackman RC, Guthrie KA, et al. Risks and outcomes of idiopathic pneumonia syndrome after nonmyeloablative and conventional conditioning regimens for allogeneic hematopoietic stem cell transplantation. *Blood* 2003;102(8):2777–2785. [PubMed: 12855568]
54. Hogan WJ, Maris M, Storer B, et al. Hepatic injury after nonmyeloablative conditioning followed by allogeneic hematopoietic cell transplantation: a study of 193 patients. *Blood* 2004;103(1):78–84. [PubMed: 12969980]
55. Chakraverty R, Peggs K, Chopra R, et al. Limiting transplantation-related mortality following unrelated donor stem cell transplantation by using a nonmyeloablative conditioning regimen. *Blood* 2002;99(3):1071–1078. [PubMed: 11807015]

56. Maloney DG, Molina AJ, Sahebi F, et al. Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. *Blood* 2003;102(9):3447–3454. [PubMed: 12855572]
57. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. *N. Engl. J. Med* 2007;356(11):1110–1120. [PubMed: 17360989]
58. Rotta M, Storer BE, Sahebi F, et al. Long-term outcome of patients with multiple myeloma after autologous hematopoietic cell transplantation and nonmyeloablative allografting. *Blood* 2009;113(14):3383–3391. [PubMed: 19015394]
59. Billingham, RE. The Harvey Lectures. Academic Press; NY, USA: 1966. The biology of graft-versus-host reactions; p. 21–78.
60. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet* 2009;373(9674):1550–1561. [PubMed: 19282026]
61. Storb R, Deeg HJ, Whitehead J, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. *N. Engl. J. Med* 1986;314:729–735. [PubMed: 3513012]
62. Storb R, Deeg HJ, Farewell V, et al. Marrow transplantation for severe aplastic anemia: methotrexate alone compared with a combination of methotrexate and cyclosporine for prevention of acute graft-versus-host disease. *Blood* 1986;68:119–125. [PubMed: 3521761]
63. Nash RA, Antin JH, Karanes C, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. *Blood* 2000;96(6):2062–2068. [PubMed: 10979948]
64. Yu C, Seidel K, Nash RA, et al. Synergism between mycophenolate mofetil and cyclosporine in preventing graft-versus-host disease among lethally irradiated dogs given DLA-nonidentical unrelated marrow grafts. *Blood* 1998;91(7):2581–2587. [PubMed: 9516160]
65. Martins SL, St John LS, Champlin RE, et al. Functional assessment and specific depletion of alloreactive human T cells using flow cytometry. *Blood* 2004;104(12):3429–3436. [PubMed: 15284108]
66. Armand P, Gannamaneni S, Kim HT, et al. Improved survival in lymphoma patients receiving sirolimus for graft-versus-host disease prophylaxis after allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning. *J. Clin. Oncol* 2008;26(35):5767–5774. [PubMed: 19001324]
67. Furlong T, Kiem H-P, Appelbaum FR, et al. Sirolimus in combination with cyclosporine or tacrolimus plus methotrexate for prevention of graft-versus-host disease following hematopoietic cell transplantation from unrelated donors. *Biol. Blood Marrow Transplant* 2008;14(5):531–537. [PubMed: 18410895]
68. Blazar BR, Weisdorf DJ, DeFor T, et al. Phase 1/2 randomized, placebo-control trial of palifermin to prevent graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT). *Blood* 2006;108(9):3216–3222. [PubMed: 16835378]
69. Reddy P, Maeda Y, Hotary K, et al. Histone deacetylase inhibitor suberoylanilide hydroxamic acid reduces acute graft-versus-host disease and preserves graft-versus-leukemia effect. *Proc. Natl Acad. Sci. USA* 2004;101(11):3921–3926. [PubMed: 15001702]
70. Sun K, Wilkins DE, Anver MR, et al. Differential effects of proteasome inhibition by bortezomib on murine acute graft-versus-host disease (GVHD), delayed administration of bortezomib results in increased GVHD-dependent gastrointestinal toxicity. *Blood* 2005;106(9):3293–3299. [PubMed: 15961519]
71. Yu C, Linsley P, Seidel K, et al. Cytotoxic T lymphocyte antigen 4-immunoglobulin fusion protein combined with methotrexate/cyclosporine as graft-versus-host disease prevention in a canine dog leukocyte antigen-nonidentical marrow transplant model. *Transplantation* 2000;69(3):450–454. [PubMed: 10706061]
72. Welniak LA, Blazar BR, Murphy WJ. Immunobiology of allogeneic hematopoietic stem cell transplantation (review). *Annu. Rev. Immunol* 2007;25:139–170. [PubMed: 17129175]
73. Toubai T, Paczesny S, Shono Y, et al. Mesenchymal stem cells for treatment and prevention of graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Curr. Stem Cell Res. Ther* 2010;4(4):252–259. [PubMed: 19500066]

74. Le Blanc K, Samuelsson H, Gustafsson B, et al. Transplantation of mesenchymal stem cells to enhance engraftment of hematopoietic stem cells. *Leukemia*. 2007 DOI: 10.1038/sj.leu.2404777-9999. Epub ahead of print.
75. Ringdén O, Uzunel M, Rasmusson I, et al. Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease. *Transplantation* 2006;81(10):1390–1397. [PubMed: 16732175]
76. Kebriaei P, Isola L, Bahceci E, et al. Adult human mesenchymal stem cells added to corticosteroid therapy for the treatment of acute graft-versus-host disease. *Biol. Blood Marrow Transplant* 2009;15(7):804–811. [PubMed: 19539211]
77. Stem Cell Trialists' Collaborative Group. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. *J. Clin. Oncol* 2005;23(22):5074–5087. [PubMed: 16051954]
78. Fraser CJ, Bhatia S, Ness K, et al. Impact of chronic graft-versus-host disease on the health status of hematopoietic cell transplantation survivors: a report from the Bone Marrow Transplant Survivor Study. *Blood* 2006;108(8):2867–2873. [PubMed: 16788100]
79. Weiden PL, Flournoy N, Sanders JE, Sullivan KM, Thomas ED. Antileukemic effect of graft-versus-host disease contributes to improved survival after allogeneic marrow transplantation. *Transplant Proc* 1981;13(1):248–251. [PubMed: 7022833]
80. Baron F, Maris MB, Sandmaier BM, et al. Graft-versus-tumor effects after allogeneic hematopoietic cell transplantation with nonmyeloablative conditioning. *J. Clin. Oncol* 2005;23(9):1993–2003. [PubMed: 15774790]
81. Stewart BL, Storer B, Storek J, et al. Duration of immunosuppressive treatment for chronic graft-versus-host disease. *Blood* 2004;104(12):3501–3506. [PubMed: 15292060]
82. Baird K, Pavletic SZ. Chronic graft versus host disease. *Curr. Opin. Hematol* 2006;13(6):426–435. [PubMed: 17053454]
83. Lee JW, Deeg HJ. Prevention of chronic GVHD. *Best Pract. Res. Clin. Haematol* 2008;21(2):259–270. [PubMed: 18503991]
84. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and Staging Working Group report. *Biol. Blood Marrow Transplant* 2005;11(12):945–956. [PubMed: 16338616]
85. Martin PJ, Storer BE, Rowley SD, et al. Evaluation of mycophenolate mofetil for initial treatment of chronic graft-versus-host disease. *Blood* 2009;113(21):5074–5082. [PubMed: 19270260]
86. Svegliati S, Olivieri A, Campelli N, et al. Stimulatory autoantibodies to PDGF receptor in patients with extensive chronic graft-versus-host disease. *Blood* 2007;110(1):237–241. [PubMed: 17363728]
87. Miklos DB, Kim HT, Miller KH, et al. Antibody responses to H-Y minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission. *Blood* 2005;105(7):2973–2978. [PubMed: 15613541]
88. Cutler C, Miklos D, Kim HT, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. *Blood* 2006;108(2):756–762. [PubMed: 16551963]
89. Zaja F, Bacigalupo A, Patriarca F, et al. Treatment of refractory chronic GVHD with rituximab: a GITMO study. *Bone Marrow Transplant* 2007;40(3):273–277. [PubMed: 17549053]
90. Sarantopoulos S, Stevenson KE, Kim HT, et al. High levels of B-cell activating factor in patients with active chronic graft-versus-host disease. *Clin. Cancer Res* 2007;13(20):6107–6114. [PubMed: 17947475]
91. Sarantopoulos S, Stevenson KE, Kim HT, et al. Altered B cell homeostasis and excess BAFF in human chronic graft versus host disease. *Blood*. 2009 DOI: 10.1182/blood-2008-09-177840-9999. Epub ahead of print.
92. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive post-remission chemotherapy in adults with acute myeloid leukemia. *N. Engl. J. Med* 1994;331:896–903. [PubMed: 8078551]
93. Weick JK, Kopecky KJ, Appelbaum FR, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group Study. *Blood* 1996;88(8):2841–2851. [PubMed: 8874180]

94. Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: a systematic review and meta-analysis of prospective clinical trials. *JAMA* 2009;301(22):2349–2360. [PubMed: 19509382]
95. de Lima M, Anagnostopoulos A, Munsell M, et al. Nonablative versus reduced-intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: dose is relevant for long-term disease control after allogeneic hematopoietic stem cell transplantation. *Blood* 2004;104(3):865–872. [PubMed: 15090449]
96. Tauro S, Craddock C, Peggs K, et al. Allogeneic stem-cell transplantation using a reduced-intensity conditioning regimen has the capacity to produce durable remissions and long-term disease-free survival in patients with high-risk acute myeloid leukemia and myelodysplasia. *J. Clin. Oncol* 2005;23(36):9387–9393. [PubMed: 16314618]
97. McClune B, Weisdorf DJ, DiPersio JF, et al. Non-myeloablative hematopoietic stem cell transplantation in older patients with AML and MDS: results from the Center for International Blood and Marrow Transplant Research (CIBMTR). *Blood* 2008;112(11):135. Abstract 346.
98. Mohty M, Labopin M, Milpied N-J, et al. Impact of cytogenetics risk on outcome after reduced intensity conditioning (RIC) allogeneic stem cell transplantation (allo-SCT) from an HLA identical sibling for patients with acute myeloid leukemia (AML) in first complete remission (CR1). *Blood* 2008;112(11):134–135. Abstract 345.
99. Pfeifer T, Schleuning M, Eder M, et al. Improved outcome for patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) with poor risk cytogenetics - result from an analysis on 172 patients receiving FLAMSA-RIC conditioning for allogeneic stem cell transplantation (SCT). *Blood* 2008;112(11):688. Abstract 1971.
100. Gyurkocza B, Storb R, Storer BE, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. *J. Clin. Oncol.* 2010 DOI:10.1200/JCO.2009.27.1460. Epub ahead of print.
101. Cutler C, Lee S, Greenberg P, et al. A decision analysis of allogeneic stem cell transplantation for MDS: delayed transplantation for low risk MDS is associated with improved outcome. *Blood* 2002;100(Pt 1):74a. Abstract 270.
102. Deeg HJ, Storer B, Slattery JT, et al. Conditioning with targeted busulfan and cyclophosphamide for hemopoietic stem cell transplantation from related and unrelated donors in patients with myelodysplastic syndrome. *Blood* 2002;100(4):1201–1207. [PubMed: 12149198]
103. Scott BL, Sandmaier BM, Storer B, et al. Myeloablative vs nonmyeloablative allogeneic transplantation for patients with myelodysplastic syndrome or acute myelogenous leukemia with multilineage dysplasia: a retrospective analysis. *Leukemia* 2006;20:128–135. [PubMed: 16270037]
104. Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. *Blood* 2008;112(5):1646–1654. [PubMed: 18502832]
105. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer* 2004;101(12):2788–2801. [PubMed: 15481055]
106. Huguet F, Leguay T, Raffoux E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J. Clin. Oncol* 2009;27(6):911–918. erratum in *J. Clin. Oncol.* 27(15), 2574 (2009). [PubMed: 19124805]
107. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood* 2008;111(4):1827–1833. [PubMed: 18048644]
108. Cornelissen JJ, van der Holt B, Verhoef GE, et al. Myeloablative allogeneic versus autologous stem cell transplantation in adult patients with acute lymphoblastic leukemia in first remission: a prospective sibling donor versus no-donor comparison. *Blood* 2009;113(6):1375–1382. [PubMed: 18988865]

109. Laport GG, Alvarnas JC, Palmer JM, et al. Long-term remission of Philadelphia chromosome-positive acute lymphoblastic leukemia after allogeneic hematopoietic cell transplantation from matched sibling donors: a 20-year experience with the fractionated total body irradiation-etoposide regimen. *Blood* 2008;112(3):903–909. [PubMed: 18519812]
110. Lee S, Kim YJ, Min CK, et al. The effect of first-line imatinib interim therapy on the outcome of allogeneic stem cell transplantation in adults with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 2005;105(9):3449–3457. [PubMed: 15657178]
111. Arnold R, Massenkeil G, Bornhauser M, et al. Nonmyeloablative stem cell transplantation in adults with high-risk ALL may be effective in early but not in advanced disease. *Leukemia* 2002;16(12):2423–2428. [PubMed: 12454748]
112. Gutierrez-Aguirre CH, Gomez-Almaguer D, Cantu-Rodriguez OG, et al. Non-myeloablative stem cell transplantation in patients with relapsed acute lymphoblastic leukemia: results of a multicenter study. *Bone Marrow Transplant* 2007;40(6):535–539. [PubMed: 17618317]
113. Mohty M, Labopin M, Tabrizi R, et al. Reduced intensity conditioning allogeneic stem cell transplantation for adult patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. *Haematologica* 2008;93(2):303–306. [PubMed: 18245655]
114. Sorror ML, Storer BE, Maloney DG, Sandmaier BM, Martin PJ, Storb R. Outcomes after allogeneic hematopoietic cell transplantation with nonmyeloablative or myeloablative regimens for treatment of lymphoma and chronic lymphocytic leukemia. *Blood* 2008;111(1):446–452. [PubMed: 17916744]
115. Kuruvilla J, Pond G, Tsang R, Gupta V, Lipton JH, Messner HA. Favorable overall survival with fully myeloablative allogeneic stem cell transplantation for follicular lymphoma. *Biol. Blood Marrow Transplant* 2008;14(7):775–782. [PubMed: 18541196]
116. Corradini P, Doderio A, Farina L, et al. Allogeneic stem cell transplantation following reduced-intensity conditioning can induce durable clinical and molecular remissions in relapsed lymphomas: pre-transplant disease status and histotype heavily influence outcome. *Leukemia* 2007;21(11):2316–2323. [PubMed: 17597807]
117. Wrench D, Gribben JG. Stem cell transplantation for non-Hodgkin's lymphoma. *Hematol. Oncol. Clin. North Am* 2008;22(5):1051–1079. [PubMed: 18954751]
118. Robinson SP, Goldstone AH, Mackinnon S, et al. Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. *Blood* 2002;100(13):4310–4316. [PubMed: 12393626]
119. Kusumi E, Kami M, Kanda Y, et al. Reduced-intensity hematopoietic stem-cell transplantation for malignant lymphoma: a retrospective survey of 112 adult patients in Japan. *Bone Marrow Transplant* 2005;36(3):205–213. [PubMed: 15937505]
120. Rezvani AR, Storer B, Maris M, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in relapsed, refractory, and transformed indolent non-Hodgkin lymphoma. *J. Clin. Oncol* 2008;28(2):211–217. [PubMed: 18056679]
121. Khouri IF, McLaughlin P, Saliba RM, et al. Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. *Blood* 2008;111(12):5530–5536. [PubMed: 18411419]
122. Rezvani AR, Norasetthada L, Gooley T, et al. Non-myeloablative allogeneic haematopoietic cell transplantation of relapsed diffuse large B-cell lymphoma: a multicentre experience. *Br. J. Haematol* 2008;143:395–403. [PubMed: 18759762]
123. Maris MB, Sandmaier BM, Storer BE, et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. *Blood* 2004;104(12):3535–3542. [PubMed: 15304387]
124. Tam CS, Bassett R, Ledesma C, et al. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. *Blood* 2009;113(18):4144–4152. [PubMed: 19168784]

125. Schetelig J, van Biezen A, Caballero D, et al. Allogeneic hematopoietic cell transplantation for chronic lymphocytic leukemia (CLL) with 17p deletion: a retrospective EBMT analysis. *Blood* 2007;110(11 Pt 1):22a–23a. Abstract 47.
126. Sorror ML, Storer BE, Sandmaier BM, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. *J. Clin. Oncol* 2008;26(30):4912–4920. [PubMed: 18794548]
127. Castagna L, Sarina B, Todisco E, et al. Allogeneic stem cell transplantation compared with chemotherapy for poor-risk Hodgkin lymphoma. *Biol. Blood Marrow Transplant* 2009;15(4):432–438. [PubMed: 19285630]
128. Devetten MP, Hari PN, Carreras J, et al. Unrelated donor reduced-intensity allogeneic hematopoietic stem cell transplantation for relapsed and refractory Hodgkin lymphoma. *Biol. Blood Marrow Transplant* 2009;15(1):109–117. [PubMed: 19135949]
129. Bruno B, Rotta M, Patriarca F, et al. Non-myeloablative allografting for newly diagnosed multiple myeloma: the experience of the Gruppo Italiano Trapianti di Midollo. *Blood* 2009;113(14):3375–3382. [PubMed: 19064724]
130. Storb R, Yu C, Zaucha JM, et al. Stable mixed hematopoietic chimerism in dogs given donor antigen, CTLA4Ig, and 100 cGy total body irradiation before and pharmacologic immunosuppression after marrow transplant. *Blood* 1999;94(7):2523–2529. [PubMed: 10498626]
131. Jochum C, Beste M, Zellmer E, Graves SS, Storb R. CD154 blockade and donor-specific transfusions in DLA-identical marrow transplantation in dogs conditioned with 1-Gy total body irradiation. *Biol. Blood Marrow Transplant* 2007;13:164–171. [PubMed: 17241922]
132. Mielcarek M, Storb R. Graft-versus-host disease after non-myeloablative hematopoietic cell transplantation. *Leuk. Lymphoma* 2005;46(9):1251–1260. [PubMed: 16109601]
201. National Marrow Donor Program. 2009. www.marrow.org/md

Figure 1. Indications for allogeneic hematopoietic cell transplantation in North America 2005
 Data from the Center for International Blood and Marrow Transplant Research (CIBMTR).
 AML: Acute myeloid leukemia; ALL: Acute lymphoblastic leukemia; CML: Chronic myelogenous leukemia; MDS: Myelodysplastic syndrome; MPD: Myeloproliferative disorders; NHL: Non-Hodgkin lymphoma.
 Reprinted with permission from CIBMTR (2009).

Figure 2. Trends in allogeneic transplantation by recipient age (1987–2006)

Data from from the Center for International Blood and Marrow Transplant Research (CIBMTR). Reprinted with permission from CIBMTR (2009).

Figure 3. Data from the US National Marrow Donor Program (NMDP)
Reprinted with permission from [201].

Figure 4. Nonmyeloablative conditioning regimen for hematopoietic cell transplantation developed at Fred Hutchinson Cancer Research Center (WA, USA)

CSP: Cyclosporine; MMF: Mycophenolate mofetil; TBI: Total-body irradiation.

Figure 5. Spectrum of intensity of commonly used conditioning regimens for hematopoietic cell transplantation

ATG: Antithymocyte globulin; BU: Busulfan; CY: Cyclophosphamide; FLU: Fludarabine; MP: Melphalan; TBI: Total-body irradiation; TT: Thiotepa.

Reproduced from [132].