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Principles and Overview of Allogeneic Hematopoietic Stem Cell Transplantation

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1.1 Introduction and Historical Perspectives

Hematopoietic stem cell transplantation (HSCT) is the process and intravenous infusion of hematopoietic stem and progenitor cells to restore normal hematopoiesis and/or treat malignancy [1, 2]. The term “hematopoietic stem cell transplantation” has replaced the term “bone marrow transplantation” (BMT) because hematopoietic stem cells can be derived from a variety of sources other than the bone marrow, including the peripheral blood and umbilical cord blood [2, 3]. Stem cells used for HSCT are distinguished as being of hematopoietic origin, as there is growing interest in using more primitive stem cells for regenerative therapy due to their plasticity and unique biologic characteristics [4]. Hematopoietic stem cells are further characterized according to their source, that is, from whom they are obtained. Hematopoietic stem cells obtained from the patient him- or herself are referred to as autologous [1, 3]. Hematopoietic stem cells obtained from an identical twin are referred to as syngeneic obtained, and hematopoietic stem cells from someone other than the patient or an identical twin are referred to as allogeneic, which is the focus of this chapter.

The clinical application of HSCT originated in the clinical observations of the severe myelosuppressive effects of radiation among nuclear bomb survivors at Hiroshima and Nagasaki [5]. Intensive research efforts were made in the 1950s and early 1960s to develop methods to reverse the myelosuppressive effects of radiation, including the infusion of bone marrow [6–11]. The subsequent determination and understanding of the major histocompatibility complex (MHC) and human leukocyte antigens (HLA) as the major determinants of graft rejection significantly advanced laboratory studies and clinical application of allogeneic HSCT [12–14]. The first successful reports of clinical bone marrow transplantation, utilized for patients with severe combined immunodeficiency disorders, severe aplastic anemia, and advanced acute leukemias, occurred in the late 1960s and early 1970s [15–20]. Allogeneic HSCT has become a standard treatment option for a variety of hematologic malignancies (Table 1.1) [21]. In addition, allogeneic HSCT is a standard treatment for many immunodeficiency states, metabolic disorders (e.g., Hurler’s syndrome), and defective hematopoietic states (e.g., severe aplastic anemia, thalassemia). This chapter focuses primarily on the rationale for the application of allogeneic HSCT in the treatment of malignancy.

The distinctive characteristics of allogeneic HSCT are that the stem cell graft is free of contamination by malignant cells and contains immunologically competent lymphocytes that are capable of mediating a reaction against foreign antigens. This latter characteristic can be

a major advantage if the immunologic response is directed against malignant cells, referred to as the graft-versus-leukemia or graft-versus-tumor (GvT) effect, thus potentially eradicating disease and reducing the chance of disease relapse [22–24]. However, if the immunologic response is directed against antigens present on normal tissues, it can lead to the destruction of normal organs, described clinically as graft-versus-host disease (GvHD). The risk of both graft rejection (host-versus-graft reaction) and GvHD rises with HLA disparity.

The GvT effect was first recognized in animal models and subsequently was noted among patients undergoing allogeneic HSCT for acute and chronic leukemias [22–25]. The clinical importance of the interactions between immunocompetent donor T cells and tumor cells in mediating a GvT effect is supported by an increased rate of relapse in allogeneic stem cell grafts from which T cells have been removed (T-cell depletion), an inverse correlation between relapse and severity of GvHD, and a comparatively increased rate of relapse after syngeneic or autologous HSCT using the same myeloablative conditioning regimen [25]. Finally, the most compelling evidence for a T cell-mediated GvT effect originates from the observation that infusion of allogeneic lymphocytes, a donor lymphocyte infusion (DLI), at a time remote from the transplant conditioning regimen, can treat leukemia relapse successfully after allogeneic HSCT [26–29]. The DLI, without any additional cytotoxic therapy, resulted in sustained cytogenetic and molecular remissions. Over time it became increasingly apparent that a significant part of the curative potential of allogeneic HSCT could be directly attributed to the GvT effect.

1.2 Technical Aspects of Allogeneic Hematopoietic Stem Cell Transplantation

1.2.1 Donor Selection

In allogeneic HSCT, stem cells are obtained from a donor other than the recipient. Donor and recipient usually are identical or “matched” for HLA, which is derived from the MHC located on chromosome 6 [30]. A single set of MHC alleles, described as a haplotype, is inherited from each parent, resulting in HLA pairs. The most important HLAs include HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ loci. Among siblings, the genes which encode for HLA-B and HLA-C are located so close to each other in the MHC that one is rarely inherited without the other. As a result, an HLA match among siblings is referred to a “6 of 6,” as they are matched for HLA-A, -B, and -DR; however, in actuality they are matched for all of the HLA antigens [3]. The other antigens, such as HLA-C, become more important in alternative sources of hematopoietic stem cells, such as unrelated donors and cord blood, which are described in more detail later in this chapter [31, 32].

The choice of donor for an allogeneic HSCT takes into account several factors, including the patient’s disease, disease state, and urgency in obtaining a donor. When allogeneic HSCT is being considered for a patient, a fully HLA-matched sibling is the preferred donor source, because the risk of graft rejection and GvHD is lowest with this source of allogeneic stem cells. As described earlier, a haplotype is inherited from each parent, and by simple Mendelian genetics it would be expected that the probability that two siblings would share

the same haplotypes would be 1:4. The probability of having an HLA-matched sibling increases with the number of siblings within a specific family. The probability can be estimated using the following formula: The chance of having an HLA-matched sibling = $1-(0.75)^n$, where n is the number of potential sibling donors [3]. There is an approximately 1% chance of crossing over (i.e., genetic material switched between chromosomes during meiosis), primarily between the HLA-A and the HLA-B loci. The clinical outcomes for allogeneic HSCT using a sibling with a single HLA mismatch are similar to those with a fully HLA-matched sibling [33].

For patients who lack a fully HLA-matched sibling donor, the preferred alternative sources for allogeneic stem cells include an unrelated fully HLA-matched donor, a partially HLA-matched cord blood unit, or a partially HLA-matched family member [34–36]. A closely HLA-matched volunteer hematopoietic stem cell donor may be identified through a bone marrow donor registry, such as the National Marrow Donor Program (NMDP) in the United States, which includes about six million potential donors. Many HLA phenotypes are possible, which sometimes makes the identification of a matched unrelated donor difficult and time consuming. Depending on the ethnic descent of both patient and donor, the probability of identifying an HLA-matched unrelated donor is between 50% and 80%. Due to advances in HLA-typing (reviewed in Chap. 4 by Baxter-Lowe and Hurley) through the use of molecular typing techniques and improved supportive care over the last decade, current results of matched unrelated donor transplants for malignancy are not significantly different when compared to HSCT from matched sibling donor transplant [32, 37].

One major disadvantage of using an unrelated donor is that the average time required to identify and procure an HLA-matched unrelated donor is approximately 2–3 months, which may be too long for patients with rapidly progressive malignancies [38]. The alternative stem cell source to an unrelated bone marrow donor for allogeneic HSCT is umbilical cord blood [35–39]. The major advantages of umbilical cord stem cells (reviewed in Chap. 10 by Wagner, Brunstein, Tse, and Laughlin) is that they can be obtained in less than 4 weeks and that even cord blood units mismatched in up to 2 of 6 HLA may be used for allogeneic HSCT. This degree of HLA mismatching is acceptable because the overwhelming percentage of T cells within the cord blood unit are naïve, and the incidence of acute GvHD is comparable to or less than that associated with an HLA-matched unrelated bone marrow donor. The major disadvantage of umbilical cord blood units is they are associated with a relatively high degree of graft rejection, especially in adults [35, 39]. Engraftment and treatment-related mortality appear to be directly related to umbilical cord cell dose; the small volume usually available (50–150 mL) of cord blood results in low stem cell doses in adult patients. It may be that the limitation of cell dose can be overcome by the use of more than one cord blood unit or the transient support from $CD34^+$ cells from haploidentical family members [40, 41]. The other significant disadvantage is that once the cord blood unit is used, there is no way to go back and get additional cells for a donor lymphocyte infusion or in the event of graft failure.

The other alternative source of allogeneic hematopoietic stem cells is to identify partially HLA-matched family among the patient’s first-degree relatives who share at least one haplotype (haploidentical) with the potential recipient [36, 42]. The major advantage with

the use of a haploidentical family member is that the donor is readily available for almost all patients. The major disadvantages are an increased risk of graft rejection, GvHD, and severe immune dysregulation, which rises with higher degrees of HLA-mismatching. Haplo-identical allogeneic HSCT has been limited primarily to use in children, although the use of less intense conditioning regimens (discussed below) has increased its applicability in adults [36, 43].

1.2.2 Stem Cell Acquisition

Hematopoietic stem cells for allogeneic HSCT may be obtained from the bone marrow, the peripheral blood, and umbilical cord blood. Bone marrow hematopoietic stem cells usually are harvested by repeated aspirations from the posterior iliac crest until an adequate number of cells have been removed [44]. If sufficient cells cannot be obtained from the posterior iliac crest, marrow also can be harvested from the anterior iliac crest and sternum. The minimal number of nucleated marrow cells required for long-term repopulation in humans is not precisely known. In practice, the number of nucleated marrow cells harvested is usually $1-3\times10^8$/kg of recipient weight, depending on the diagnosis (i.e., higher for aplastic anemia), the type and intensity of pre-transplant conditioning, and whether the marrow graft will be modified in vitro. Marrow sometimes is treated in vitro to remove unwanted cells before it is returned to the patient. In allogeneic HSCT with major ABO incompatibility between donor and recipient, it is necessary to remove the mature erythrocytes from the graft to avoid a hemolytic transfusion reaction [45]. Peripheral blood hematopoietic stem cells are used in approximately 60–70% of allogeneic HSCT [46]. In steady-state, the concentration of hematopoietic stem cells and myeloid progenitor cells is quite low, and prior to collection of peripheral blood hematopoietic stem cells by apheresis, attempts are made to increase or “mobilize” the number of circulating hematopoietic stem cells by administering hematopoietic growth factors, primarily granulocyte colony-stimulating factor (G-CSF; filgrastim) to the donor. The procedure is associated with a very low incidence of complications and can generally be done as an outpatient. In both the autologous and the allogeneic settings, the use of peripheral blood stem cells has been associated with accelerated recovery of hematopoiesis when compared to traditional BMT. In the allogeneic setting, the presence of higher numbers of T cells in the peripheral blood stem cell graft initially raised the concern for greater frequency and severity of GvHD. Several large studies have now demonstrated that the use of peripheral blood in the allogeneic HSCT setting is associated with a decreased relapse rate in hematologic malignancies and improvement in overall and disease-free survival in patients with late-stage disease [47]. However, the use of peripheral blood has been associated with a significant risk of extensive chronic GvHD. After collection and processing, hematopoietic stem cells from bone marrow, peripheral blood, or cord blood may be directly infused or they may be processed with dimethylsulfoxide (DMSO) with or without hydroxyethylstarch and then stored in liquid nitrogen until needed for transplantation [48].

1.2.3 Conditioning

Once an allogeneic stem cell source has been identified, patients are put on regimens with the intent of ”conditioning” or “preparing” them for the infusion of hematopoietic stem cells. Most conditioning or preparative regimens use a combination of radiation and

chemotherapy [1, 3]. They also may contain radio-immunoconjugates and/or monoclonal antibodies that target T cells (e.g., alemtuzumab) [49]. The choice of a specific conditioning regimen depends on the disease that is being treated. The earliest conditioning regimens were designed to permit the administration of maximum doses of chemotherapy and/or radiation (i.e., “high-dose” regimens) for the eradication of disease and to be adequately immunosuppressive to prevent graft rejection. The most commonly used chemotherapy agents in these regimens are alkylating agents (e.g., cyclophosphamide and/or etoposide) with or without total lymphoid or total body irradiation (TBI) at doses varying between 800 and 1440 cGy. The doses of chemotherapy and radiation used in these regimens are referred to as “myeloablative” because they result in a degree of myelosuppression and immunosuppression that is nearly universally fatal without the infusion of hematopoietic stem cells as a rescue product [50].

Though efficacious, TBI is associated with a number of short and long-term complications including secondary malignancies, cataracts, and endocrine dysfunction. More recently a low-dose non-fractionated mode of administration of TBI with 200 cGy has been incorporated in the setting of nonmyeloablative transplants [51]. The toxicities of TBI-containing conditioning regimens led to the development of radiation-free regimens. Of these, the most commonly used chemotherapy is the combination of busulfan and cyclophosphamide, developed initially by Santos and coworkers and subsequently modified by Tutschka et al. [52, 53]. Busulfan is traditionally administered orally as 4mg/kg divided into four daily doses and given on each of four successive days (total dose = 16 × mg/kg) but this oral administration is limited by the erratic absorption of the drug. High plasma levels are associated with increased incidence of hepatic veno-occlusive disease (VOD) and other toxicities [53]. More recently, an intravenous formulation of busulfan has become available which allows more predictable drug delivery [54].

Allogeneic HSCT with myeloablative conditioning regimens has been performed successfully in patients older than 60 years of age; however, survival after these transplants declines with increasing age, limiting the application of allogeneic transplantation to a minority of patients who potentially could benefit from this procedure. The substantial toxicities associated with traditional, myeloablative conditioning regimens have limited the application of allogeneic transplantation to relatively young patients with good performance status. However, the demonstration that an immune-mediated GvT effect plays a central role in the therapeutic efficacy of allogeneic HSCT led to the hypothesis that myeloablative conditioning regimens were not essential for tumor eradication. This idea subsequently led investigators to develop less intense, “nonmyeloablative” conditioning regimens, which were adequately immunosuppressive to permit the engraftment of donor hematopoietic stem cells, while sparing the patient many of the toxicities related to traditional high-dose therapy. A variety of nonmyeloablative and “reduced-intensity” conditioning regimens have been reported [51, 55, 56]. These regimens have been associated with decreased early post-transplant morbidity and mortality and have permitted allografting in older and medically debilitated patients. However, the important clinical question is whether this reduction in toxicity comes at the cost of a loss of anti-tumor activity within the conditioning regimen.

1.2.4 Treatment-Related Toxicities

There are a variety of acute and late toxicities, which can result in significant morbidity and mortality, that are associated with and specific to allogeneic transplantation [57]. The basic principle underlying the supportive care of the transplanted patient is prevention. Most transplant complications have a temporal relation to the conditioning regimen and the transplant. A simple index, based on pre-transplant comorbidities, has been developed that reliably predicts non-relapse mortality and survival [58]. This comorbidity index is useful for patient counseling prior to allogeneic HSCT.

1.2.4.1 Rejection and Graft Failure—The failure to recover hematologic function or the loss of marrow function after initial reconstitution constitutes graft failure. Graft rejection occurs when immunologically competent cells of host origin destroy the transplanted cells of donor origin [59]. Graft failure can occur in 5–11% of HLA-identical recipients and may be mediated by immunologic graft rejection by the host immune system, infections, drugs, or an inadequate stem cell dose. Graft failure generally takes place within 60 days of transplantation, though late graft failure has been known to occur. A number of factors are known to increase the graft failure rate after allografting, among them, low nucleated cell count infused, T-cell depletion, HLA mismatching, and the use of nonmyeloablative conditioning. This complication occurs more commonly in patients who receive transplants from alternative or HLA-mismatched donors, in T-cell-depleted transplants, and in patients with aplastic anemia who receive a non-TBI-containing regimen. Graft rejection is less likely to occur in non-transfused patients with aplastic anemia.

1.2.4.2 Infections—Due to the utilization of post-transplantation immunosuppressive agents, patients undergoing allogeneic HSCT are at increased risk, particularly to fungal and viral infections, as compared to patients undergoing autologous stem cell transplantation (reviewed in Chap. 21 by Wade and Gea-Banacloche). Infection prophylaxis is routinely employed to guard against bacterial, fungal, and viral pathogens. Fluconazole has been shown to reduce the incidence of systemic and superficial fungal infections, but does not affect the incidence of resistant Candida species; intraconazole has been demonstrated to decrease mold infections [60, 61]. Aspergillosis is the most common cause of death due to infection after allogeneic HSCT, and the risk of invasive fungal infections is increased in patients receiving prolonged, systemic corticosteroid for the treatment of GvHD. However, newer anti-fungal agents (e.g., voriconazole, caspofungin) have been demonstrated to successfully treat invasive aspergillosis in the transplant setting. Clinical infections with cytomegalovirus (CMV) have been significantly reduced utilizing a strategy of monitoring for CMV reactivation by detection of CMV DNA in leukocytes, plasma, or serum and upon detection, the pre-emptive administration of ganciclovir before overt CMV disease [62].

1.2.4.3 Genito-Urinary Toxicities—The development of hemorrhagic cystitis is associated with high-dose cyclophosphamide within the conditioning regimen. This complication has been largely abrogated by the use of mesna (sodium 2-sulfanylethanesulfonate) and aggressive hydration. Acute renal failure requiring dialysis during the transplant occurs infrequently [63]. Thrombotic microangiopathy, either idiopathic or associated with the administration of calcineurin-inhibitors (e.g., cyclosporine)

can be a serious complication after allogeneic HSCT, posing a high mortality risk or resulting in end-stage renal disease [64]. Nephrotic syndrome and membranous nephropathy have been described in long-term survivors; these complications seem to be associated more commonly with chronic GvHD and nonmyeloablative conditioning [65].

1.2.4.4 Hepatic Toxicities—The most common liver complication associated with transplantation is veno-occlusive disease (VOD)/sinusoidal obstruction syndrome of the liver [66, 67]. VOD is caused by endothelial damage in the hepatic sinusoids, and is characterized any unexplained weight gain, painful hepatomegaly, and ascites; severe VOD is associated with a high mortality rate. Beneficial treatments for VOD are relatively limited; however, there have been encouraging reports on the treatment of VOD with defibrotide [68]. The prophylactic use of ursodiol has decreased hepatic complications following allogeneic HSCT, especially among patients receiving conditioning regimen containing busulfan [69].

1.2.4.5 Acute Graft-Versus-Host Disease—Graft-versus-host disease represents the most important barrier to allogeneic HSCT. Graft-versus-host disease is described as either acute, generally presenting within the first 100 days post-transplant (reviewed in Chap. 11 by Antin and Korngold), or chronic, generally presenting after the first 100 days post-transplant (reviewed in Chap. 12 by Martin and Pavletic). Risk factors for the development of acute GvHD include a female donor (particularly a multiparous donor), more advanced age in the patient and the donor, and cytomegalovirus sero-positivity of the donor or patient and use of an unrelated donor. Acute GvHD is manifested by symptoms in several organ systems, including the skin, gastrointestinal tract, and liver (Table 1.2) [70]. The skin manifestations range from a maculopapular rash up to generalized erythroderma or desquamation. The severity of liver GvHD is scored on the basis of the bilirubin and the gastrointestinal severity on the quantity of diarrhea per day. Organs may be involved in isolation or simultaneously. However, delayed de novo presentations of acute GvHD are reported. A clinical grading system (Table 1.2) correlates with clinical outcome. Severity is described as Grade I (mild) to Grade IV (severe). The incidence of clinically significant GvHD (Grades II–IV) in recipients of HLA-genotypically identical grafts (T cell replete) and using cyclosporine and methotrexate for GvHD prophylaxis is approximately 40%. Increasing HLA disparity increases both the incidence and severity of resultant GvHD, with recipients of phenotypically matched unrelated donor grafts experiencing a 50–80% incidence of grade II–IV GvHD. Other risk factors for acute GvHD include older age, a parous or alloimmunized donor, less intense immunosuppression, or the use of a T cell replete versus T cell depleted graft.

Acute GvHD can often be diagnosed on the basis of clinical findings. Histologic confirmation can be valuable in excluding other possibilities such as infection. Mild GvHD of the skin may demonstrate vacuolar degeneration and infiltration of the basal layer by lymphocytes. With more advanced disease, histologic findings of necrotic dyskeratotic cells with acantholysis may progress to frank epidermolysis. In the liver, early GvHD may be difficult to distinguish from hepatitis of other causes.

The best therapy for GvHD is prophylaxis. The prophylactic use of cyclosporine and methotrexate are effective in reducing the incidence of acute GvHD as well as the survival of

transplant patients and is the most commonly used form of GvHD prophylaxis. Cyclosporine is a cyclic polypeptide that prevents T cell activation by inhibiting interleukin-2 (IL-2) production and IL-2 receptor expression. While effective as GvHD prophylaxis, cyclosporine imparts significant toxicities including hypertension, nephrotoxicity, hypomagnesemia, a risk for seizures, hypertrichosis, gingival hyperplasia, tremors, and anorexia. Tacrolimus is a macolide lactone which closely resembles cyclosporine in mechanism of action, spectrum of toxicities, and pharmacologic interactions. The combination of tacrolimus and methotrexate was demonstrated to be superior to cyclosporine and methotrexate in reducing Grade II–IV acute GvHD when used as prophylaxis.

Moderate to severe GvHD (Grades II–IV) requires appropriate treatment. The mainstay of therapy has long been corticosteroid therapy. Treatment for acute GvHD includes high-dose corticosteroids, anti-thymocyte globulin (ATG), or various monoclonal antibodies [71–73]. Methylprednisolone, at a dose of 2 mg/kg/d, can be expected to achieve responses in 40–60% of patients. Higher doses of steroids have not been shown to be of greater benefit. Steroid refractory GvHD responds poorly to second line therapies and is associated with increased mortality. ATG is commonly used as a second line treatment with limited success. Novel treatments showing efficacy in preliminary studies include extracorporeal phototherapy and the combination of mycophenolate mofetil and tacrolimus. In general, acute GvHD of the skin is most responsive to treatment while GvHD of the liver is least responsive. The fatality rate for acute GvHD may be as high as 50%.

1.2.4.6 Chronic Graft-Versus-Host Disease—Chronic GvHD occurs in 20–50% of long term survivors. Chronic GvHD occurs most commonly between 100 days and 2 years from the transplant and has polymorphic features similar to a number of autoimmune diseases [74]. It is most likely to develop in older patients who also had acute GvHD or received peripheral blood rather than bone marrow grafts; in 20% of cases there is no history of prior acute GvHD [75]. Adverse prognostic factors include thrombocytopenia, a progressive clinical presentation, extensive skin involvement, and an elevated bilirubin [76]. Common manifestations include the sicca syndrome, lichen planus-like skin rash, scleroderma-like skin changes, esophageal and intestinal fibrosis, obstructive lung disease with or without pneumonitis, and elevated alkaline phosphatase with or without hyperbilirubinemia. Underlying immunologic deficiencies including hypogammaglobulinemia are common, placing patients at increased risk for infectious events.

Chronic GvHD may be limited or extensive [76]. Limited disease implies localized skin involvement with minimal or no liver involvement while extensive disease suggests generalized skin involvement with or without other organ involvement. Patients with limited disease have a good prognosis with 60–70% long-term survival while those with extensive disease experience 20–30% long-term survival. Treatment for chronic GvHD is guided by the extent of disease. Initiation of therapy prior to functional impairment is of critical importance. Treatments for chronic GvHD include corticosteroids, cyclosporine, thalidomide, ultraviolet light treatments, or other immunosuppressive agents [77, 78]. Alternatives include azathioprine, UV light, psoralen-UV-A, extracorporeal photopheresis,

and thalidomide. The most common cause of death in patients with chronic GvHD remains infection so all should receive prophylactic antibiotics with or without intravenous immunoglobulin [78].

1.2.4.7 Late Complications—These include endocrine toxicities such as hypothyroidism, hypogonadism, or growth hormone deficiency in younger patients; pulmonary effects may include obstructive lung disease or pulmonary fibrosis; and other late effects including cataracts and leukoencephalopathy [57].

1.3 Current Indications for Allogeneic Hematopoietic Stem Cell Transplantation for Patients with Malignancy

There is clinical evidence that allogeneic HSCT can provide benefit, defined as freedom of progression or overall survival, for most hematologic malignancies. However, the beneficial effects of allogeneic HSCT vary greatly with each type of malignancy. Data indicate that due to their relative responsiveness to cytotoxic therapy, myeloablative conditioning regimens with allogeneic HSCT result in higher response rates than cytotoxic or conventional agents for almost all hematologic malignancies. However, the durability of these responses and their effect on survival varies from disease to disease. Similarly, there is evidence of a clinical GvT effect in almost every hematologic disease; however, its potency and clinical relevance are highly variable. Interpretation of the results of trials of HSCT always is complicated by issues of patient selection. This can lead to either underestimating the efficacy of allogeneic HSCT if it is used after exhausting all other available therapies or overestimating its efficacy if only the patients with favorable prognostic characteristics are selected. The specific indications for allogeneic HSCT are covered in the chapters for each respective disease. This section briefly addresses the outcomes for malignancies with allogeneic HSCT.

1.3.1 Acute Myeloid Leukemia

With the exception of acute promyelocytic leukemia there is no doubt that allogeneic HSCT offers the highest anti-leukemic activity after a conventional induction and intensification therapy for acute myeloid leukemia (AML; a.k.a. acute myelogenous leukemia) patients in first remission. Randomized controlled trials comparing autologous and allogeneic HSCT to conventional chemotherapy in patients with AML in first complete remission have demonstrated improved leukemia-free survival with both forms of HSCT; however, there has been no significant improvement in overall survival due to increased treatment related mortality with allogeneic HSCT [79, 80]. The one exception has been in pediatric AML, where allogeneic HSCT has been demonstrated to improve both leukemia-free and overall survival for patients transplanted in first complete remission [81]. For AML patients with poor prognostic features (adverse cytogenetics, secondary leukemias, presence of minimal residual disease) there are strong indications for allogeneic HSCT in first complete remission (CR1) [82]. The outcome of HSCT for patients beyond CR1 is worse when compared to the use of transplant while in CR1, but for these patients allografting still remains the most effective strategy to obtain long-term disease control. Reduced-intensity

and nonmyeloablative conditioning regimens may increase the applicability of allogeneic HSCT for older AML patients [83].

1.3.2 Acute Lymphoblastic Leukemia

For adult patients with poor-risk acute lymphoblastic leukemia (ALL), most investigators recommend an allogeneic transplant [84–86]. The results for patients in later remissions, early relapse, or primary refractory disease are clearly inferior to those of patients in CR1, but in nearly all of these circumstances if an HLA donor is available, an allogeneic HSCT is associated with improved outcomes when compared to prior therapy [87].

1.3.3 Chronic Myeloid Leukemia

Before the development of imatinib mesytale chronic myeloid leukemia (CML; a.k.a. chronic myelogenous leukemia) was one of the major indications for allogeneic HSCT, and a well established curative strategy for CML with 5-year disease-free survival rates of 85% [88]. After the advent of imatinib and the new tyrosine kinase inhibitors (TKI), allogeneic transplantation is no longer the first option for CML patients [89]. Use of allogeneic HSCT is limited to those patients in chronic phase who failed one, or in some instances, two lines of TKI [90]. The GvT effect is critical in the potential cure of CML with allogeneic transplantation, thus nonmyeloablative and reduced-intensity conditioning regimens in this group of patients would seem an attractive strategy. However it is not yet possible to conclude that for younger patients, those younger than 40–50 years, either nonmyeloablative or reduced-intensity allogeneic HSCT offers a major advantage to patients who would otherwise be candidates for an allografting with conventional, myeloablative conditioning [90]. Patients with accelerated, blastic or second chronic phase CML can not be cured with imatinib or the new TKI dasatinib, and responses are usually of short duration. Although clinical results of allogeneic HSCT are poor for these advanced phases of CML, it continues to be the only potential curative approach [91].

1.3.4 Myelodysplastic Syndromes

Allogeneic HSCT is the only curative treatment for myelodysplastic syndromes (MDS). Because of the older age of patients with MDS, transplantation has generally been reserved for patients with higher risk MDS or MDS transforming to AML. The best results have been obtained in relatively younger patients, who are earlier in their disease course and have not received any prior therapy. To identify factors influencing transplantation outcome for MDS, the International Bone Marrow Transplantation Registry (IBMTR) studied 452 recipients of HLA-identical sibling transplants for MDS [92]. Three-year transplantation-related mortality, relapse, disease-free survival, and overall survival rates were 37%, 23%, 40%, and 42%, respectively. Multivariate analyses showed that young age and platelet counts higher than 100,000 at transplantation were associated with lower transplant-related mortality and higher disease-free and overall survival rates. Because the optimal timing for transplantation for MDS is unknown, the IBMTR constructed a Markov model to examine three transplantation strategies for newly diagnosed MDS: transplantation at diagnosis, transplantation at leukemic progression, and transplantation at an interval from diagnosis but prior to leukemic progression [93]. Analyses using individual patient risk-assessment data from transplantation and non-transplantation registries were performed using the

International Prognostic Scoring System (IPSS) for MDS with adjustments for quality of life. For low and intermediate-1 IPSS groups, delayed transplantation maximized overall survival. Transplantation prior to leukemic transformation was associated with a greater number of life years than transplantation at the time of leukemic progression. In a cohort of patients under the age of 40 years, an even more marked survival advantage for delayed transplantation was noted. For intermediate-2 and high IPSS groups, transplantation at diagnosis maximized overall survival. There is evidence that reduced-intensity allogeneic HSCT may benefit older patients with MDS [94, 95].

1.3.5 Non-Hodgkin Lymphoma and Hodgkin Lymphoma

Although allogeneic HSCT has been reported to yield long-term disease-free survival for patients with intermediate and high-grade non-Hodgkin's lymphomas (NHL), the demonstration of a potent GvT effect against NHL is less clear, and the efficacy of donor lymphocyte infusion in lymphoma is anecdotal at best [96–99]. Consequently, the specific role of allogeneic HSCT has not been defined. There are data that nonmyeloablative and reduced-intensity allogeneic HSCT may provide benefits for patients with recurrent follicular NHL; however, the data indicate that this approach requires that the disease remains chemotherapy-sensitive [98].

Allogeneic HSCT has had a limited role in the treatment of Hodgkin lymphoma (HL; a.k.a. Hodgkin's disease) due to the efficacy of autologous HSCT, the treatment-related toxicities associated with myeloablative allogeneic HSCT, and a relative lack of evidence of a GvT effect against HL. However, recent data indicate that reduced-intensity allogeneic HSCT may benefit patients with recurrent HL, and a GvT effect against HD may exist [100].

1.3.6 Multiple Myeloma

A graft-versus-myeloma effect has been demonstrated, but the use of allogeneic HSCT for multiple myeloma had been limited since transplant-related mortality in this group of patients with conventional myeloablative regimens was very high, 30–50% [101]. Data with nonmyeloablative regimens are encouraging, and based on the high transplant-related mortality, multiple myeloma was a good model for investigating the feasibility of nonmyeloablative transplants in this type of patients. Although several studies have demonstrated that transplant-related mortality was decreased with nonmyeloablative conditioning regimens, the relapse rate is greater when compared to standard allografting [90]. Results of a prospective biologically assigned study suggest, however, that the use of nonmyeloablative allogeneic HSCT may be superior to autologous HSCT in newly diagnosed myeloma patients [102].

1.3.7 Solid Tumors

There has been considerable interest in investigating the presence of a GvT effect in a variety of solid tumors, including renal cell carcinoma and breast cancer [103–105]. Childs and colleagues reported on a series of 19 patients with metastatic renal cell carcinoma who underwent nonmyeloablative allogeneic stem cell transplantation [103]. Nine patients had responsive disease (47%), of which three were complete responses.

1.4 Conclusion

There has been tremendous success since the 1980s in the increased safety of allogeneic HSCT and in the expanding application of this treatment to more patient populations. Areas currently under development that may further improve the use and efficacy of transplantation include continuous improvements in supportive care for transplant patients, broadened use of alternative donors, more refined graft manipulations, and further improvements in the nonmyeloablative transplantation techniques and GvHD prevention. Future progress depends on our ability to identify safer and better-targeted anti-tumor therapies that can be incorporated in the transplantation regimens without attenuating the GvT responses. This remains a challenge for future clinical research.

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Table 1.1

Clinical indications for allogeneic hematopoietic stem cell transplantation

Malignant disorders
Acute myeloid leukemia
Acute lymphoblastic leukemia
Chronic myeloid leukemia
Myelodysplastic syndromes
Myeloproliferative disorders
Non-Hodgkin’s lymphoma
Hodgkin’s disease
Chronic lymphocytic leukemia
Multiple myeloma
Juvenile chronic myeloid leukemia
Non-malignant disorders
Aplastic anemia
Paroxysmal nocturnal hemoglobinuria
Fanconi’s anemia
Blackfan-Diamond anemia
Thalassemia major
Sickle cell anemia
Severe combined immunodeficiency
Wiskott-Aldrich syndrome
Inborn errors of metabolism

Modified from Copelan EA. N Engl J Med. 2006;354:1813–26

Table 1.2

Classification of patients with acute graft-versus-host disease

Clinical staging				
Stage	**Skin**	**Liver**	**Gut**	
+	Rash < 25%	BSA Total bilirubin 2–3 mg/dL	Diarrhea 500–1000 mL/day	
+ +	Rash 25–50% BSA	Total bilirubin 3–6 mg/dL	Diarrhea 1000–1500 mL/day	
+ + +	Generalized erythroderma	Total bilirubin 6–15 mg/dL	Diarrhea > 1500 mL/day	
+ + + +	Desquamation and bullae	Total bilirubin > 15 mg/dL	Pain, with or without ileus	
Clinical grading				
		Stage		
Grade	**Skin**	**Liver**	**Gut**	**PS**
0 (none)	0	0	0	0
I	+ to + +	0	0	0
II	+ to + + +	+	+	+
III	+ + to + + +	+ + to + + +	+ + to + + +	+ +
IV	+ + to + + + +	+ + to + + + +	+ + to + + + +	+ + +

BSA = body surface area, PS = performance status