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119 Hematopoietic Cell Transplantation

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Hematopoietic Cell Transplantation Bone marrow transplantation was the original term used to describe the collection and transplantation of hematopoietic stem cells, but with the demonstration that peripheral blood and umbilical cord blood are also useful sources of stem cells, hematopoietic cell transplantation has become the preferred generic term for this process. Hematopoietic cell transplantation is used to treat patients with an abnormal but nonmalignant lymphohematopoietic system by replacing it with one from a normal donor. Hematopoietic cell transplantation is also used to treat malignancy by allowing the administration of higher doses of myelosuppressive therapy than would otherwise be possible and, in the setting of allogeneic hematopoietic cell transplantation, by conferring an immunologic graft-versus-tumor effect. The use of hematopoietic cell transplantation is increasing, as it becomes safer and applicable to more diseases and as donor availability expands. The Worldwide Network for Blood and Marrow Transplantation (http://www.wbmt.org) estimates that worldwide more than 100,000 transplants were performed in 2022. The frequency of transplanta tion varied widely from country to country, with a close association of transplant rates with gross national income (GNI) per capita. However, even among countries with similar GNIs per capita, there are substan tial differences between countries and regions regarding the frequency of transplantation, disease indications, and choice of donor type. PART 4 Oncology and Hematology THE HEMATOPOIETIC STEM CELL Several features of the hematopoietic stem cell (HSC) make trans plantation clinically feasible, including its remarkable regenerative capacity, its ability to home to the marrow space following intravenous injection, and the ability of the stem cell to be cryopreserved (Chap. 101). Transplantation of a single stem cell can replace the entire lympho hematopoietic system of an adult mouse. In humans, transplantation of a small percentage of a donor’s bone marrow volume regularly results in complete and sustained replacement of the recipient’s entire lymphohematopoietic system, including all red cells, granulocytes, B and T lymphocytes, and platelets, as well as cells comprising the fixed macrophage population, including Kupffer cells of the liver, pulmonary alveolar macrophages, osteoclasts, and Langerhans cells of the skin. Homing of HSCs to their marrow niche initially involves interactions between P- and E-selectins on marrow sinusoidal endothelium with integrins including VLA-4 on HSCs. Once tethered to the vascular endothelium, changes in integrin conformation result in tight adhesion following which stem cells migrate through the endothelium and extra cellular matrix eventually reaching the stem cell niche. This last step is facilitated by CXCL12 produced by the niche stroma interacting with the chemokine CXCR4 on HSCs. Human

hematopoietic stem cells can survive freezing and thawing with little, if any, damage, making it pos sible to remove and store a portion of the patient's own bone marrow for later reinfusion following treatment of the patient with high dose myelotoxic therapy. CATEGORIES OF HEMATOPOIETIC CELL TRANSPLANTATION Hematopoietic cell transplantation can be described according to the relationship between the patient and the donor and by the anatomic source of stem cells. In ~1% of cases, patients have identical twins who can serve as donors. With the use of syngeneic donors, there is no risk of graft-versus-host disease (GVHD), and unlike the use of autologous mar row, there is no risk that the stem cells are contaminated with tumor cells. Allogeneic transplantation involves a donor and a recipient who are not genetically identical. Following allogeneic transplantation, immune

cells transplanted with the stem cells or developing from them can react against the patient, causing GVHD. Alternatively, if the immuno suppressive preparative regimen used to treat the patient before trans plant is inadequate, immunocompetent cells of the patient can cause graft rejection. The risks of these complications are influenced by the degree of matching between donor and recipient for human leukocyte antigen (HLA) molecules encoded by genes of the major histocompat ibility complex. HLA molecules are responsible for binding antigenic proteins and presenting them to T cells. The antigens presented by HLA molecules may derive from exogenous sources (e.g., during active infections) or may be endogenous proteins. If individuals are not HLA-matched, T cells from one individual will react strongly to the mismatched HLA, or "major antigens," of the second. Even if the individuals are HLAmatched, the T cells of the donor may react to differing endogenous or "minor antigens" presented by the HLA of the recipient. Reactions to minor antigens tend to be less vigorous. The genes of major relevance to transplantation include HLA-A, -B, -C, and -D; they are closely linked and therefore tend to be inherited as haplotypes, with only rare crossovers between them. Thus, the odds that any one full sibling will match a patient are one in four, and the probability that the patient has an HLA-identical sibling is $1 - (0.75)n$, where n equals the number of siblings. With conventional techniques, the risk of graft rejection is 1–3%, and the risk of severe, life-threatening acute GVHD is ~15% following transplantation between HLA-identical siblings. The incidence of graft rejection and GVHD increases progressively with the use of family member donors mismatched for one, two, or three antigens. Newer approaches to GVHD prophylaxis, including the use of posttransplant high-dose cyclophosphamide, have diminished the impact of HLA mismatching, making transplantation between donor/recipient pairs who share only one HLA haplotype possible. Since the formation of the National Marrow Donor Program and other registries, HLA-matched unrelated donors can be identified for many patients. The genes encoding HLA antigens are highly polymorphic, and thus the odds of any two unrelated individuals being HLA identical are extremely low, somewhat less than 1 in 10,000. However, by recruiting >40 million volunteer donors, HLA-matched donors can be found for ~60% of patients for whom a search is initiated, with higher rates among whites and lower rates among minorities and patients of mixed race. It takes, on average, 3–4 months to complete a search and schedule and initiate an unrelated donor transplant. With improvements in HLA typing and supportive care measures, survival following matched unrelated donor transplantation is essentially the same as that seen with HLA-matched siblings. Allogeneic hematopoietic cell transplantation can be carried out across ABO blood barriers by removing isoagglutinins and/or incom patible red blood cells from the donor graft. However, depending on the direction of the mismatch, hemolysis of donor cells by persistent isoagglutinins in the host, or hemolysis of recipient red cells by isoag glutinins in the graft or developing from it may occur despite appropri ate manipulation of the donor cell product.

Autologous transplantation involves the removal and storage of the patient’s own stem cells with subsequent reinfusion after the patient receives high dose myeloablative therapy. Unlike allogeneic transplan tation, there is no risk of GVHD or graft rejection with autologous transplantation. On the other hand, autologous transplantation lacks a graft-versus-tumor (GVT) effect, and the autologous stem cell product can be contaminated with tumor cells, which could lead to relapse. A variety of techniques have been developed to “purge” autologous prod ucts of tumor cells, but no prospective randomized trials have shown that any approach decreases relapse rates or improves disease-free or overall survival. Bone marrow aspirated from the posterior and anterior iliac crests initially was the source of hematopoietic stem cells for transplantation. Typically, anywhere from 1.5 to 5 × 108 nucleated marrow cells per kilogram are collected for allogeneic transplantation. Several studies have found improved survival following both matched sibling and

unrelated transplantation by transplanting higher numbers of bone marrow cells. Hematopoietic stem cells circulate in the peripheral blood but in very low concentrations. Following the administration of a myeloid growth factor such as granulocyte colony-stimulating factor (G-CSF) and during recovery from intensive chemotherapy, the concentration of hematopoietic progenitor cells in blood, as measured either by colony-forming units or expression of the CD34 antigen, increases markedly. This makes it possible to harvest adequate numbers of stem cells from the peripheral blood for transplantation. Donors are typi cally treated with 4 or 5 days of hematopoietic growth factor, following which stem cells are collected in one or two 4-h pheresis sessions. In the autologous setting, transplantation of >2.5 × 106 CD34 cells per kilogram, a number that can be collected in most circumstances, leads to rapid and sustained engraftment in virtually all cases. In the 5–10% of patients who fail to mobilize enough CD34+ cells with growth fac tor alone, the addition of plerixafor, an antagonist of CXCR4, may be useful. Blocking CXCR4 allows more stem cells to escape the marrow. When compared to the use of autologous marrow, use of periph eral blood stem cells results in more rapid hematopoietic recovery. Although this more rapid recovery diminishes the morbidity rate of transplantation, no studies show improved survival. In the setting of allogeneic transplantation, the use of growth factor– mobilized peripheral blood stem cells also results in faster engraftment than seen with marrow but at the cost of more chronic GVHD because of donor T-cell contamination. With matched sibling donors, the increased chronic GVHD is more than balanced by reductions in rates of relapse and nonrelapse mortality, resulting in improved overall sur vival. However, in the setting of matched unrelated donor transplanta tion, use of peripheral blood results in more chronic GVHD without a compensatory survival advantage. Nonetheless, because of ease of collection, peripheral blood continues to be the more commonly used source of stem cells. Umbilical cord blood contains a high concentration of hematopoietic progenitor cells, allowing for its use as a source of stem cells for trans plantation. Cord blood transplantation from family members has been used when the immediate need for transplantation precludes waiting the 9 or so months generally required for the baby to mature to the point of donating marrow. Use of cord blood results in slower peripheral count recovery than seen with marrow but a lower incidence of GVHD, perhaps reflecting the low number of T cells in cord blood. Multiple cord blood banks have been developed to harvest and store cord blood for possible transplantation to unrelated patients from material that would otherwise be discarded. Currently >800,000 units are cryopre served and available for use. The advantages of unrelated cord blood are rapid availability and decreased immune reactivity allowing for the use of partially matched units, which is of particular importance for those without matched unrelated donors. The risks of graft failure and trans plant-related mortality are related to the dose of cord blood cells per

kilogram, which previously limited the application of single cord blood transplantation to pediatric and smaller adult patients. Subsequent trials have found that for patients without suitable single cord units, the use of double cord transplants diminishes the risk of graft failure and early mortality even though only one of the donors ultimately engrafts. Given the similar survival rates seen with cord blood, matched unrelated, and haploidentical family member donors, a source of allogeneic stem cells can now be found for almost every patient in need (Table 119-1). TABLE 119-1 Probability of Identifying a Donor Based on Stem Cell Source and Patient Ethnicity UNRELATED ADULT % UNRELATED CORD % HAPLOIDENTICAL Ethnicity 8/8a 7/8a ≥4/6b Caucasian

> “ 95

Hispanic

Black

aMatching for HLA-A, -B, -C, and DRB1. bMatching for HLA-A, -B, and DRB1.

THE TRANSPLANT PREPARATIVE REGIMEN The treatment regimen administered to patients immediately preced ing transplantation is designed to eradicate the patient’s underlying disease and, in the setting of allogeneic transplantation, immunosup press the patient adequately to prevent rejection of the transplanted stem cells. The appropriate regimen therefore depends on the dis ease setting and graft source. For example, when transplantation is performed to treat severe combined immunodeficiency and the donor is a histocompatible sibling, no preparative regimen is needed because no host cells require eradication, and the patient is already too immune incompetent to reject the transplanted graft. For aplastic anemia, there is no large population of cells to eradicate, and highdose cyclophosphamide plus antithymocyte globulin are sufficient to immunosuppress the patient adequately to accept the marrow graft. In the setting of thalassemia and sickle cell anemia, high-dose busulfan is frequently added to cyclophosphamide to eradicate hyperplastic host hematopoiesis. A variety of different regimens have been developed to treat malignant diseases. Most regimens include agents with high activity against the tumor in question at conventional doses and with myelosuppression as their predominant dose-limiting toxicity. There fore, these regimens commonly include busulfan, cyclophosphamide, melphalan, thiotepa, carmustine, etoposide, and total-body irradiation in various combinations.

CHAPTER 119 Although high-dose treatment regimens were the initial approach to transplantation for malignancies, the realization that much of the antitumor effect of transplantation derives from an immunologically mediated GVT response led investigators to ask if reduced-intensity conditioning regimens might be effective and more tolerable. Evidence for a GVT effect comes from studies showing that posttransplant relapse rates are lowest in patients who develop acute and chronic GVHD, higher in those without GVHD, and higher still in recipients of T cell–depleted allogeneic or syngeneic marrow. The demonstration that complete remissions can be obtained in many patients who have relapsed after transplant by simply administering viable lymphocytes from the original donor further strengthens the argument for a potent GVT effect. Accordingly, a variety of alternative regimens have been studied, ranging from nonmyeloablative, which are the very

minimum required to achieve engraftment (e.g., fludarabine plus 200 cGy totalbody irradiation) and would cause only transient myelosuppression if no transplant were performed, to so-called reduced-intensity regi mens, which would cause significant but not necessarily fatal myelo suppression in the absence of transplantation (e.g., fludarabine plus melphalan). With the use of nonmyeloablative and reduced-intensity regimens, engraftment is readily achieved with less toxicity than seen with conventional transplantation. In general, relapse rates are higher following reduced-intensity conditioning, but transplant-related mor tality is lower, favoring the use of reduced-intensity conditioning in older patients and those with significant comorbidities. High-dose regimens are favored in those felt able to tolerate the treatment, par ticularly if patients have any evidence of measurable disease at the time of transplantation. Hematopoietic Cell Transplantation ■ ■THE TRANSPLANT PROCEDURE Marrow is usually collected from the donor's posterior and sometimes anterior iliac crests, with the donor under general or spinal anesthesia. Typically, 10–15 mL/kg of marrow is aspirated, placed in heparinized media, and filtered through 0.3- and 0.2-mm screens to remove fat and bony spicules. The collected marrow may undergo further processing depending on the clinical situation, such as the removal of red cells to prevent hemolysis in ABO-incompatible transplants, the removal of donor T cells to prevent GVHD, or attempts to remove possible con taminating tumor cells in autologous transplantation. Marrow dona tion is safe, with only very rare complications reported. Peripheral blood stem cells are collected by leukapheresis after the donor has been treated with hematopoietic growth factors or, in the setting of autologous transplantation, sometimes after treatment with a combination of chemotherapy and growth factors. Stem cells for transplantation are infused through a large-bore central venous

catheter. Such infusions are usually well tolerated, although occasion ally patients develop fever, cough, or shortness of breath. These symp toms typically resolve with slowing of the infusion. When the stem cell product has been cryopreserved using dimethyl sulfoxide, patients sometimes experience short-lived nausea or vomiting due to the taste (and smell) of the cryoprotectant.

■ ■ENGRAFTMENT AND IMMUNE RECONSTITUTION Peripheral blood counts reach their nadir several days to a week after transplant as a consequence of the preparative regimen; then cells pro duced by the transplanted stem cells begin to appear in the peripheral blood. The rate of recovery depends on the source of stem cells and use of posttransplant growth factors. If marrow is the source, recovery to 100 granulocytes/μL occurs on average by day 16 and to 500/μL by day 22. Use of G-CSF–mobilized peripheral blood stem cells speed the rate of recovery by ~1 week compared to marrow, whereas engraftment following cord blood transplantation is typically delayed by ~1 week. Use of a myeloid growth factor after transplant accelerates recovery by 3–5 days. Platelet counts usually recover shortly after granulocytes. While granulocytes and other components of innate immunity recover rapidly after hematopoietic cell transplantation, adaptive immu nity, which consists of cellular (T cell) and humoral (B cell) immunity, may take 1–2 years to fully recover. Survival and peripheral expansion of infused donor T cells is the dominant mechanism for T-cell recovery in the first months after hematopoietic cell transplantation and results in mostly CD8+ T cells with a limited repertoire. After several months, de novo generation of donor-derived CD4+ and CD8+ T cells becomes dominant, providing a more diverse T-cell repertoire. B-cell counts recover by 6 months after autologous hematopoietic cell transplantation and 9 months after allogeneic hematopoietic cell transplantation. In gen eral, immune recovery occurs more rapidly after autologous than alloge neic hematopoietic cell transplantation and after receipt of unmodified grafts compared to the setting of in vivo or ex vivo T-cell depletion. PART 4

Oncology and Hematology Following allogeneic transplantation, engraftment can be docu mented using fluorescence in situ hybridization of sex chromosomes if donor and recipient are sex-mismatched or by analysis of short tandem repeat polymorphisms after DNA amplification. ■ ■COMPLICATIONS FOLLOWING HEMATOPOIETIC CELL TRANSPLANTATION Early Direct Chemoradiotoxicities The transplant preparative regimen may cause a spectrum of acute toxicities that vary according to the intensity of the regimen and the specific agents used but fre quently include nausea, vomiting, and mild skin erythema (Fig. 119-1). Pancytopenia Neutropenia Thrombocytopenia Regimen-related toxicities Mucositis SOS Idiopathic pneumonia Graft-vs-host disease Acute GVHD Chronic GVHD Infections

Bacterial

Fungal

Viral Gram positive Gram negative Encapsulated bacteria Candida Aspergillus HSV CMV and adenovirus VZV Day 0 Day 30 Day 60 Day 90 Day 180 Day 360 FIGURE 119-1 Major syndromes complicating marrow transplantation. CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSV, herpes simplex virus; SOS, sinusoidal obstructive syndrome (formerly venoocclusive disease); VZV, varicellazoster virus. The size of the shaded area roughly reflects the period of risk of the complication.

High-dose cyclophosphamide can result in hemorrhagic cystitis, which can usually be prevented by bladder irrigation or with the sulfhydryl compound mercaptoethanesulfonate (MESNA). Most high-dose pre parative regimens will result in oral mucositis, which typically develops 5–7 days after transplant and often requires narcotic analgesia. Use of a patient-controlled analgesic pump provides the greatest patient satisfac tion and results in a lower cumulative dose of narcotic. Keratinocyte growth factor (palifermin) can shorten the duration of mucositis by several days following autologous transplantation. Patients begin losing their hair 5–6 days after transplant and by 1 week are usually profoundly pancytopenic. Depending on the intensity of the conditioning regimen, 3–10% of patients will develop sinusoidal obstruction syndrome (SOS) of the liver (formerly called venoocclusive disease), a syndrome that results from direct cytotoxic injury to hepatic-venular and sinusoidal endo thelium, with subsequent deposition of fibrin and the development of a local hypercoagulable state. This chain of events leads to the clinical symptoms of tender hepatomegaly, ascites, jaundice, and fluid reten tion. These symptoms can develop any time during the first month after transplant, with the peak incidence at day 16. Predisposing fac tors include prior exposure to intensive chemotherapy, pretransplant hepatitis of any cause, and use of more intense conditioning regimens. The mortality rate of sinusoidal obstruction syndrome is ~30%, with progressive hepatic failure culminating in a terminal hepatorenal syndrome. Treatment of severe SOS with defibrotide, a polydeoxyribo nucleotide, reduces mortality. Although most pneumonias developing early after transplant are caused by infectious agents, in a small percentage of patients, a diffuse interstitial pneumonia will develop that is a result of direct toxicity of high-dose preparative regimens. Bronchoalveolar lavage usually shows alveolar hemorrhage, and biopsies are typically characterized by diffuse alveolar damage, although some cases may have a more clearly inter stitial pattern. High-dose glucocorticoids or anti–tumor necrosis factor therapies are sometimes used as treatment, although randomized trials proving their utility have not been reported. Transplant-associated thrombotic microangiopathy is seen in 5–10% of patients,

appearing on average about 1 month after transplant. The syndrome is characterized by presence of schistocytes on peripheral smear, elevated lactate dehydrogenase, thrombocytopenia, and acute kidney injury and is the result of endothelial injury and complement activation. Since calcineurin and mTOR inhibitors are thought to contribute to the pathogenesis of the syndrome, changing immunosup pressive regimens is sometimes effective. Patients sometimes respond to eculizumab. Late Direct Chemoradiotoxicities Two categories of chronic pulmonary disease occur in patients >3 months after hematopoietic cell transplantation. Cryptogenic organizing pneumonia is a restrictive lung disease characterized by dry cough, shortness of breath, and chest imaging showing a diffuse, fluffy infiltrate. Biopsy shows granula tion tissue within alveolar spaces and small airways and no infectious agents. The disease responds well to corticosteroids and is entirely reversible. Bronchiolitis obliterans is an obstructive disease presenting with cough, progressive dyspnea, and radiologic evidence of air trap ping. Pathology shows collagen and granulation tissue in and around bronchial structures and eventually obliteration of small airways. The disease is usually associated with chronic GVHD, and although it may respond to increasing immunosuppression, complete reversal is uncommon. Other late complications of the preparative regimen include decreased growth velocity in children and delayed development of secondary sex characteristics. These complications can be partly ameliorated with the use of appropriate growth and sex hormone replacement. Most men become azoospermic, and most postpubertal women will develop ovarian failure, which should be treated. However, pregnancy is possible after transplantation, and patients should be counseled accordingly. Thyroid dysfunction, usually well compen sated, is sometimes seen. Cataracts develop in 10–20% of patients and are most common in patients treated with total-body irradiation and

those who receive glucocorticoid therapy after transplant for treat ment of GVHD. Aseptic necrosis of the femoral head is seen in 10% of patients and is particularly frequent following chronic glucocorticoid therapy. Both acute and late chemoradiotoxicities (except those due to glucocorticoids and other agents used to treat GVHD) are less frequent in recipients of reduced-intensity compared to high-dose preparative regimens. Graft Failure Although complete and sustained engraftment is usually seen after transplant, occasionally marrow function either does not return or, after a brief period of engraftment, is lost. Graft failure after autologous transplantation can be the result of inadequate num bers of stem cells being transplanted, damage during ex vivo treatment or storage, or exposure of the patient to myelotoxic agents after trans plant. Infections with cytomegalovirus (CMV) or human herpesvirus type 6 have also been associated with loss of marrow function. Graft failure after allogeneic transplantation can also be due to immunologic rejection of the graft by immunocompetent host cells. Such rejection is generally thought to be mostly T-cell–mediated, but the presence before hematopoietic cell transplantation of donor-specific HLA anti bodies in the patient is associated with poor engraftment, leading to the recommendation for screening for donor-directed anti-HLA anti bodies in recipients prior to transplant. Immunologically based graft rejection is more common following use of less immunosuppressive preparative regimens, in recipients of T-cell–depleted stem cell prod ucts, and in patients receiving grafts from HLA-mismatched donors or cord blood. Treatment of graft failure involves removing all potentially myelo toxic agents from the patient’s regimen and attempting a short trial of a myeloid growth factor. Persistence of lymphocytes of host origin in allogeneic transplant recipients with graft failure indicates immu nologic rejection. Reinfusion of donor stem cells in such patients is usually unsuccessful unless preceded by a second immunosuppressive preparative regimen. Standard high-dose preparative regimens are tolerated

poorly if administered within 100 days of a first transplant because of cumulative toxicities. However, reduced-intensity condi tioning regimens have been effective in some cases. Graft-Versus-Host Disease Acute GVHD occurs within the first 3 months after allogeneic transplant with a peak onset around

4 weeks and is characterized by an erythematous maculopapular rash; by persistent anorexia or diarrhea, or both; and by liver disease with increased serum levels of bilirubin, alanine and aspartate aminotrans ferase, and alkaline phosphatase. Because many conditions can mimic acute GVHD, the diagnosis usually requires skin, liver, or endoscopic biopsy for confirmation. In all these organs, endothelial damage and lymphocytic infiltrates are seen. In skin, the epidermis and hair follicles are damaged; in liver, the small bile ducts show segmental disruption; and in intestines, destruction of the crypts and mucosal ulceration may be noted. A commonly used rating system for acute GVHD is shown in Table 119-2. Grade I acute GVHD is of little clinical significance, does not affect the likelihood of survival, and does not require treat ment. In contrast, grades II to IV GVHD are associated with significant symptoms and a poorer probability of survival and require aggressive TABLE 119-2 Clinical Staging and Grading of Acute Graft-Versus-Host Disease CLINICAL STAGE SKIN LIVER—BILIRUBIN, kmol/L (mg/dL) GUT

Rash <25% body surface 34–51 (2–3) Diarrhea 500–1000 mL/d

Rash 25–50% body surface 51–103 (3–6) Diarrhea 1000–1500 mL/d

Generalized erythroderma 103–257 (6–15) Diarrhea >1500 mL/d

Desquamation and bullae

> 257 (>15) Ileus OVERALL CLINICAL GRADE SKIN STAGE LIVER STAGE GUT STAGE I 1–2

II 1–3

III 1–3 2–3 2–3 IV 2–4 2–4 2–4

therapy. The incidence of acute GVHD is higher in recipients of stem cells from mismatched or unrelated donors, in older patients, and in patients unable to receive full doses of drugs used to prevent the disease.

Historically, the standard approach to GVHD prevention was the administration of a calcineurin inhibitor (cyclosporine or tacrolimus) paired with an antimetabolite (most commonly methotrexate) follow ing transplantation. Prospective randomized trials have demonstrated the benefit of adding a third drug, either mycophenolate mofetil, abata cept, or posttransplant cyclophosphamide, to the two-drug regimen. Other approaches include the addition of anti–T-cell immune globulin (ATG) to the GVHD prophylactic regimen or the removal of subsets or all T cells from the stem cell inoculum. Despite prophylaxis, significant acute GVHD will develop in ~30% of recipients of stem cells from matched siblings. Factors associated with a greater risk of acute GVHD include HLA-mismatching

between recipient and donor, patient and donor age, use of more intense pre parative regimens, and use of multiparous women as donors. Presum ably, multiparous women have more alloreactivity based on carriage of genetically disparate fetuses. Disruption of the intestinal microbiota leading to loss of diversity and overgrowth by a single taxon is associ ated with a higher risk of GVHD and transplant-associated mortality. Biomarkers, including ST2, REG32, and TNF R1, have been identified that predict the severity of acute GVHD. The disease is usually treated with prednisone at a daily dose of 1–2 mg/kg. Patients in whom the acute GVHD fails to respond to prednisone sometimes respond to the oral JAK2 inhibitor ruxolitinib. CHAPTER 119 Chronic GVHD occurs most commonly between 3 months and 2 years after allogeneic transplant, developing in 20–50% of recipients. The disease is more common in older patients, with the use of periph eral blood rather than marrow as the stem cell source, in recipients of mismatched or unrelated stem cells, and in those with a preceding epi sode of acute GVHD. The disease resembles an autoimmune disorder with malar rash, sicca syndrome, arthritis, obliterative bronchiolitis, and bile duct degeneration with cholestasis. Mild chronic GVHD can sometimes be managed using local therapies (topical glucocorticoids to skin and cyclosporine eye drops). More severe disease requires systemic therapy usually with prednisone, which leads to responses in 40–60% of patients. Three drugs have received U.S. Food and Drug Administration approval for the treatment of steroid-resistant chronic GVHD: ibrutinib, ruxolitinib, and belumosudil. All three are kinase inhibitors, a class of compounds that reduces growth signals and activation of key cellular proteins involved with cell activation, migra tion, and proliferation. Mortality rates from chronic GVHD average around 15% but range from 5 to 50% depending on severity. In most patients, chronic GVHD resolves, but it may require 1–3 years of immunosuppressive treatment before these agents can be withdrawn without the disease recurring. Because patients with chronic GVHD are susceptible to significant infection, they should receive prophylactic trimethoprim-sulfamethoxazole, and all suspected infections should be investigated and treated aggressively. Hematopoietic Cell Transplantation Although onset before or after 3 months after transplant is often used to discriminate between acute and chronic GVHD, occasional

patients will develop signs and symptoms of acute GVHD after 3 months (late-onset acute GVHD), whereas others will exhibit signs and symp toms of both acute and chronic GVHD (overlap syndrome). No data suggest that these patients should be treated differently than those with classic acute or chronic GVHD.

From 3 to 5% of patients will develop an autoimmune disorder following allogeneic hematopoietic cell transplantation, most com monly autoimmune hemolytic anemia or idiopathic thrombocyto penic purpura. Unrelated donor source and chronic GVHD are risk factors, but autoimmune disorders have been reported in patients with no obvious GVHD. Treatment is with prednisone, cyclosporine, or rituximab. Infection Posttransplant patients, particularly recipients of allo geneic transplantation, require unique approaches to the problem of infection. Early after transplantation, patients are profoundly neutro penic, and because the risk of bacterial infection is so great, most cen ters place patients on broad-spectrum antibiotics once the granulocyte count falls to <500/μL. Prophylaxis against fungal infections reduces rates of infection and improves overall survival. Fluconazole is often used for patients with standard risk, while prophylaxis with mold active agents (voriconazole, posaconazole, or isavuconazonium) should be considered for patients at higher risk, such as those with a prior fun gal infection. Patients seropositive for herpes simplex should receive acyclovir or valacyclovir prophylaxis. One approach to infection pro phylaxis is shown in Table 119-

3. Despite these prophylactic measures, most patients will develop fever and signs of infection after transplant. The management of patients who become febrile despite bacterial and fungal prophylaxis is a difficult challenge and is guided by individual aspects of the patient and by the institution’s experience. PART 4 Oncology and Hematology The general problem of infection in the immunocompromised host is discussed in Chap. 148. Once patients engraft, the incidence of bacterial infection dimin ishes; however, patients, particularly allogeneic transplant recipients, remain at significant risk of infection. During the period from engraft ment until about 3 months after transplant, the most common causes of infection are gram-positive bacteria, fungi (particularly Aspergillus), and viruses including CMV. CMV disease, which in the past was fre quently seen and often fatal, can be prevented in seronegative patients transplanted from seronegative donors using either seronegative blood products or products from which the white blood cells have been removed. In seropositive patients or patients transplanted from seropositive donors, either prophylaxis or preemptive therapy is used. Letermovir administered over the first 3 months after transplant is effective as prophylaxis. An alternative approach is to monitor blood of patients after transplant using polymerase chain reaction assays for viral DNA and to treat reactivation preemptively with ganciclovir before clinical disease develops. Foscarnet is effective for some patients who develop CMV antigenemia or infection despite the use of ganci clovir or who cannot tolerate the drug, but it can be associated with severe electrolyte wasting. TABLE 119-3 Approach to Infection Prophylaxis in Allogeneic Transplant Recipients ORGANISM AGENT APPROACH Bacterial Levofloxacin 750 mg PO or IV daily Fungal Fluconazole 400 mg PO qd to day 75 posttransplant Pneumocystis jirovecii Trimethoprimsulfamethoxazole 1 double-strength tablet PO bid 2 days/week until day 180 or off immunosuppression Viral Herpes simplex Acyclovir 800 mg PO bid to day 30 Varicella-zoster Acyclovir 800 mg PO bid to day 365 Cytomegalovirus Ganciclovir 5 mg/kg IV bid for 7 days, then 5 (mg/kg)/d 5 days/week to day 100

Pneumocystis jirovecii pneumonia, once seen in 5–10% of patients, can be prevented by treating patients with oral trimethoprim-sulfa methoxazole for 1 week before transplant and resuming the treatment once patients engraft. Respiratory viruses that cause community-acquired infections, including respiratory syncytial virus (RSV), parainfluenza virus, influ enza virus, and metapneumovirus, can be life threatening or fatal in the posttransplant patient. Protection of patients from infected visitors and staff by avoiding such contacts is critical. Neuraminidase inhibi tors are effective for influenza infections. Oral or inhaled ribavirin is sometimes used for RSV. The risk of infection diminishes considerably beyond 3 months after transplant unless chronic GVHD requiring continuous immu nosuppression develops. Most transplant centers recommend continu ing trimethoprim-sulfamethoxazole prophylaxis while patients are receiving any immunosuppressive drugs and also recommend careful monitoring for late CMV reactivation. In addition, many centers rec ommend prophylaxis against varicella-zoster, using acyclovir for 1 year after transplant. Antibody titers to vaccine-preventable diseases (e.g., tetanus, polio, mumps, rubella, and encapsulated organisms) decline after allogeneic or autologous transplantation if the recipient is not revaccinated. Vaccination begins at 3 months after transplantation for SAR-CoV-2 and 6 months for influenza (or 3–4 months when seasonal prevalence is high). Other nonlive routine childhood vaccinations should be repeated, usually starting at 12 months after transplantation. Live vaccines (measles, mumps, and rubella [MMR] or MMR plus varicella [MMR-V]) are generally not administered before 2 years after hematopoietic cell transplantation. TREATMENT Nonmalignant Diseases Evidence-based indications for hematopoietic cell transplantation have been published by several organizations and are guided not only by disease-related factors but

also by patient comorbidities, socioeconomic issues, caregiver and donor availability, and patient preference. IMMUNODEFICIENCY DISORDERS By replacing abnormal stem cells with cells from a normal donor, hematopoietic cell transplantation can cure patients of a variety of immunodeficiency disorders including severe combined immu nodeficiency, Wiskott-Aldrich syndrome, and Chédiak-Higashi syndrome. The widest experience is with severe combined immu nodeficiency disease, where cure rates of >90% can be expected with allogeneic transplantation from a suitable related or unrelated donor when carried out shortly after birth (Table 119-4). Treatment of severe refractory autoimmune diseases with hematopoietic stem cell transplantation is also beginning to be explored (see below). APLASTIC ANEMIA Transplantation from matched siblings after a preparative regimen of high-dose cyclophosphamide and antithymocyte globulin cures

> 95% of patients age <40 years with severe aplastic anemia. Histori cally, results in older patients and in recipients of mismatched fam ily member or unrelated marrow were less favorable, and therefore, a trial of immunosuppressive therapy was recommended for such patients before considering transplantation. However, results with transplantation have improved leading many to recommend trans plantation as initial therapy. Transplantation is effective in all forms of aplastic anemia including, for example, the syndromes associated with paroxysmal nocturnal hemoglobinuria and Fanconi’s anemia. Patients with Fanconi’s anemia are abnormally sensitive to the toxic effects of alkylating agents, and so less intensive preparative regi mens are used in their treatment (Chap. 107). HEMOGLOBINOPATHIES Marrow transplantation from an HLA-identical sibling following a preparative regimen of busulfan and cyclophosphamide can cure

TABLE 119-4 Estimated 3-Year Survival Rates Following Transplantationa DISEASE ALLOGENEIC, % AUTOLOGOUS, % Severe combined immunodeficiency

NA Aplastic anemia

NA Thalassemia

NA Acute myeloid leukemia First remission

ID Second remission

ID Acute lymphocytic leukemia First remission

ID Second remission

ID Chronic myeloid leukemia Chronic phase

NA Accelerated phase

NA Blast crisis

NA Chronic lymphocytic leukemia

NA Myelodysplasia

NA Multiple myeloma—initial therapy NA

Non-Hodgkin’s lymphoma First relapse/second remission

Hodgkin’s disease First relapse/second remission

aThese estimates are mostly based on results of transplants performed between 2010 and 2020 reported by the Center for International Blood and Marrow Transplant Research (CIBMTR). The analysis has not been reviewed by their Advisory Committee. Abbreviations: ID, insufficient data; NA, not applicable. 80–90% of patients with thalassemia major. The best outcomes can be expected if patients are transplanted before they develop hepa tomegaly or portal fibrosis and if they have been given adequate iron chelation therapy. Among such patients, the probabilities of 5-year survival and disease-free survival are 95 and 90%, respec tively. Although prolonged survival can be achieved with aggressive chelation therapy, transplantation is the only curative treatment for thalassemia. Transplantation is potentially curative for patients with sickle cell anemia. Two-year survival and disease-free survival rates of 95 and 85%, respectively, have been reported following matched sibling or cord blood transplantation. Decisions about patient selec tion and the timing of transplantation remain difficult, but trans plantation is a reasonable option for children and young adults who have suffered complications of sickle cell anemia including stroke, recurrent vasoocclusive pain, sickle cell lung disease, or sickle nephropathy (Chap. 103). As new gene therapies become available, the indications for allogeneic hematopoietic cell transplantation for thalassemia and sickle cell disease may change. OTHER NONMALIGNANT DISEASES Theoretically, hematopoietic cell transplantation should be able to cure any disease that results from an inborn error of the lymphohe matopoietic system. Transplantation has been used successfully to treat congenital disorders of white blood cells such as Kostmann’s syndrome, chronic granulomatous disease, and leukocyte adhesion deficiency. Congenital anemias such as Blackfan-Diamond anemia can also be cured with transplantation. Since the penetrance of some congenital marrow failure states is variable, potential family member donors should be carefully screened before use to assure they are not affected. Infantile malignant osteopetrosis is due to an inability of the osteoclast to resorb bone, and because osteoclasts derive from the marrow, transplantation can cure this rare inherited disorder. Hematopoietic cell transplantation has been used as treatment for several storage diseases caused by enzymatic deficiencies, such as Gaucher’s disease, Hurler’s syndrome, Hunter’s syndrome, and

infantile metachromatic leukodystrophy. Transplantation for these diseases has not been uniformly successful, but treatment early in the course of these diseases, before irreversible damage to extra medullary organs has occurred, increases the chance for success.

Transplantation is being applied as a treatment for severe acquired autoimmune disorders. These approaches are based on studies demonstrating that transplantation can reverse autoimmune disorders in animal models and on the observation that occasional patients with coexisting

autoimmune disorders and hematologic malignancies have been cured of both with transplantation. A prospective randomized trial found that patients with severe sclero derma have improved event-free and overall survival if treated with hematopoietic cell transplantation. Randomized studies are explor ing a similar approach for patients with multiple sclerosis. ACUTE LEUKEMIA Allogeneic hematopoietic cell transplantation cures ~30% of patients who do not achieve a complete response after induction chemotherapy for acute myeloid leukemia (AML) and is the only form of therapy that can cure such patients. Thus, all patients with AML who are possible transplant candidates should have their HLA type determined soon after diagnosis to enable hematopoietic cell transplantation for those who fail to enter remission. Cure rates of 45–50% are seen when patients are transplanted in sec ond remission or in first relapse. The best results with allogeneic transplantation are achieved when applied during first remission, with long-term disease-free survival rates averaging 55–60%. Metaanalyses of studies comparing matched related donor transplanta tion to chemotherapy for adult AML patients age <60 years show a survival advantage with transplantation. This advantage is greatest for those with adverse and intermediate-risk disease but is not seen in patients with favorable-risk AML. Some centers rely on measure ments of minimal residual disease (MRD) as determined by either multidimensional flow cytometry or molecular methods to further define transplant candidacy, proceeding with transplantation in otherwise favorable risk patients if MRD positive and withholding transplantation in MRD-negative intermediate-risk patients. While hematopoietic cell transplantation can be performed in patients up to age 80, prospective trials comparing hematopoietic cell trans plantation with chemotherapy are lacking for older patients. Autol ogous transplantation has no defined role in the treatment of AML. CHAPTER 119 Hematopoietic Cell Transplantation Similar to patients with AML, adults with acute lymphocytic leukemia who do not achieve a complete response to induction chemotherapy can be cured in ~30% of cases with immediate transplantation. Cure rates improve to 40–50% in second remis sion, and therefore, transplantation can be recommended for adults who have persistent disease after induction chemotherapy or who subsequently relapse. Transplant outcomes in second remission are improved if carried out when MRD assessments are negative, and so use of agents such as blinatumomab to achieve an MRD-negative state before transplantation is recommended. Transplantation in first remission results in cure rates of about 65%. Transplanta tion appears to offer a survival advantage over chemotherapy for patients with high-risk disease as defined by molecular profiling. Debate continues about whether adults with standard-risk disease should be transplanted in first remission or whether transplanta tion should be reserved until relapse. Autologous transplantation is associated with a higher relapse rate but a somewhat lower risk of nonrelapse mortality when compared to allogeneic transplanta tion. Autologous transplantation has no obvious role in treatment for acute lymphocytic leukemia in first remission, and for secondremission patients, most experts recommend use of allogeneic stem cells if an appropriate donor is available. CHRONIC LEUKEMIA Allogeneic hematopoietic cell transplantation is indicated for patients with chronic myeloid leukemia (CML) who are in chronic phase but have failed therapy with two or more tyrosine kinase inhibitors. In such patients, cure rates of 70% can be expected.

Hematopoietic cell transplantation is also recommended for patients with CML who present or progress to accelerated phase or blast crisis, although lower cure rates are seen in such patients (Chap. 110).

Although allogeneic transplantation can cure patients with chronic lymphocytic leukemia (CLL), it has not been extensively studied because of the chronic nature of the disease, the age profile of patients, and more recently, the availability of multiple effective therapies. In those cases where it was studied, complete remissions were achieved in the majority of patients, with disease-free survival rates of ~65% at 3 years, despite the advanced stage of the disease at the time of transplant. MYELODYSPLASIA AND MYELOPROLIFERATIVE DISORDERS Between 40 and 65% of patients with myelodysplasia can be cured with allogeneic transplantation. Results are better among younger patients and those with less advanced disease. However, patients with early-stage myelodysplasia can live for extended periods with out intervention, and so transplantation is generally reserved for patients with an International Prognostic Scoring System (IPSS) score of Int-2 or higher, or for selected patients with an IPSS score of Int-1 who have other poor prognostic features (Chap. 107). Allo geneic hematopoietic cell transplantation can cure patients with primary myelofibrosis or myelofibrosis secondary to polycythemia vera or essential thrombocythemia, with 5-year progression-free survival rates in excess of 65% being reported. It may require many months for the fibrosis to resolve. LYMPHOMA Patients with disseminated intermediate- or high-grade non-Hodgkin’s lymphoma who have not been cured by first-line chemotherapy and are transplanted in first relapse or second remission can still be cured in 50–60% of cases. This represents a clear advantage over results obtained with conventional-dose salvage chemotherapy. It is unsettled whether patients with high-risk disease benefit from transplantation in first remission. Most experts favor the use of autologous rather than allogeneic transplantation for patients with intermediate- or high-grade non-Hodgkin’s lymphoma, because fewer complications occur with this approach and survival appears equivalent. The use of chimeric antigen receptor T cells targeting CD19 has been reported to yield results similar to those achieved with autologous stem cell transplantation. As yet, no consensus has been reached about how to sequence these two therapies. Although autologous transplantation results in high response rates in patients with recurrent disseminated indolent non-Hodgkin’s lymphoma, the availability of newer agents for this category of patient leaves the role of transplantation unsettled. Reduced-intensity condition ing regimens followed by allogeneic transplantation result in high rates of complete and enduring complete responses in patients with recurrent indolent lymphomas. PART 4 Oncology and Hematology The role of transplantation in Hodgkin’s lymphoma is similar to that in intermediate- and high-grade non-Hodgkin’s lymphoma. With transplantation, 3-year disease-free survival is 40–50% in patients who never achieved a first remission with standard chemo therapy and up to 80% for those transplanted in second remission. Transplantation has no defined role in first remission in Hodgkin’s lymphoma. MYELOMA Patients with myeloma whose disease progresses after first-line therapy can sometimes benefit from allogeneic or autologous trans plantation. Prospective randomized studies demonstrate that the inclusion of autologous transplantation as part of initial ther apy results in improved disease-free survival and overall survival. Further benefit is seen with the use of lenalidomide mainte nance therapy following transplantation. The use of autologous

transplantation followed by nonmyeloablative allogeneic transplan tation has yielded mixed results. SOLID TUMORS Patients with testicular cancer in whom first-line platinum-containing chemotherapy has failed can still be cured in ~50% of cases if treated with high-dose chemotherapy with autologous stem cell support, an outcome better than that seen with low-dose salvage chemotherapy. The use of high-dose chemotherapy with autologous stem cell support is being studied for several other solid tumors, including neuroblastoma and pediatric sarcomas. As in most other settings, the best results were obtained in patients with limited amounts of disease and in

whom the remaining tumor remains sen sitive to conventional-dose chemotherapy. Few randomized trials of transplantation in these diseases have been completed. POSTTRANSPLANT RELAPSE Patients who relapse following autologous transplantation some times respond to further chemotherapy and may be candidates for possible allogeneic transplantation, particularly if the remis sion following the initial autologous transplant was long. Several options are available for patients who relapse following allogeneic transplantation. Treatment with infusions of unirradiated donor lymphocytes results in complete responses in as many as 75% of patients with chronic myeloid leukemia, 40% with myelodysplasia, 25% with AML, and 15% with myeloma. Major complications of donor lymphocyte infusions include transient myelosuppression and the development of GVHD. These complications depend on the number of donor lymphocytes given and the schedule of infusions, with less GVHD seen with lower dose, fractionated schedules. ■ ■FURTHER READING Dadwal SS et al: How I prevent viral reactivation in high-risk patients. Blood 141:2062, 2023. DeFilipp Z et al: Hematopoietic cell transplantation in the treatment of adult acute lymphoblastic leukemia: Updated 2019 evidence-based review from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant 25:2113, 2019. Duarte RF et al: Indications for haematopoietic stem cell transplanta tion for haematological diseases, solid tumours and immune disor ders: current practice in Europe, 2019. Bone Marrow Transplantation 54:1525, 2019. Jamy O et al: Novel developments in the prophylaxis and treatment of acute GVHD. Blood 142:1037, 2023. McDonald GB et al: Survival, nonrelapse mortality, and relapserelated mortality after allogeneic hematopoietic cell transplantation: Comparing 2003-2007 versus 2013-2017 cohorts. Ann Intern Med 172:229, 2020. Miller PDE et al: Joint consensus statement on the vaccination of adult and paediatric haematopoietic stem cell transplant recipients: Prepared on behalf of the British Society of Blood and Marrow Trans plantation and Cellular Therapy (BSBMTCT), the Children’s Cancer and Leukaemia Group (CCLG), and British Infection Association (BIA). J Infect 86:1, 2023. Niederwieser D et al: One and a half million hematopoietc stem cell transplants: Continuous and differential improvement in worldwide access with the use of non-identical family donors. Haematologica 107:1045, 2022. Scott BL et al: Myeloablative versus reduced-intensity conditioning for hematopoietic cell transplantation in acute myelogenous leuke mia and myelodysplastic syndromes: Long-term follow-up of the BMT CTN 0901 clinical trial. Transplant Cell Ther 27:483, 2021. Westin J, Sehn LH: CAR T cells as a second-line therapy for large B-cell lymphoma: A paradigm shift? Blood 139:2737, 2022. Zeiser R, Lee SJ: Three Food and Drug Administration-approved therapies for chronic GVHD. Blood 139:1642, 2022.

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