blood. For example, exogenous EPO has become a mainstay in the management of anemia caused by renal failure, chemotherapy, and marrow failure syndromes. The use of G-CSF or GM-CSF in patients with febrile neutropenia and documented infection or sepsis after chemotherapy or radiation therapy has reduced hospital stays and shortened the period of high infection risk. Administration of GM-CSF is thought to improve host immune responses to fungal infections. High-dose G-CSF also is routinely used to mobilize CD34+ marrow stem cells into the peripheral blood for collection before and after stem cell transplantation in patients with delayed stem cell engraftment (discussed later).

Early trials of TPO growth factors to stimulate platelet production were halted because of development of antihuman TPO antibodies in some patients, leading to severe thrombocytopenia. Second-generation thrombopoietic agents bearing no structural resemblance to TPO but designed to bind and activate the TPO receptor are in clinical use. Romiplostim, a recombinant Fc-peptide fusion protein (i.e., peptibody) given as a weekly subcutaneous injection, can increase platelet counts, decrease platelet transfusion requirements, and improve quality of life for patients with refractory chronic immune-mediated thrombocytopenia. Eltrombopag is an orally available, small, organic TPO agonist that increases platelet counts and decreases bleeding in similar patients. The application of TPO agonists for management of thrombocytopenia in other marrow failure syndromes is being investigated.

Hematopoietic Stem Cell Transplantation

Types of Transplantations

Improved understanding of HSC biology has fostered the development of techniques to manipulate these cells for therapeutic purposes. The antitumor effects of most chemotherapeutic drugs and radiation therapy are dose dependent, and both cause the major dose-limiting toxicity of myelosuppression.

Before HSC transplantation, intense myeloablative doses of chemotherapy and total body irradiation are administered to eradicate malignant cells. Stem cells from a donor or the same patient are then infused to replete the ablated marrow. Although historically used in the treatment of primary stem cell disorders such as leukemia, the therapeutic potential of transplantation is also employed for patients with nonmalignant hematologic malignancies (e.g., aplastic anemia, sickle cell anemia, congenital immunodeficiencies), solid tumors (e.g., renal cell carcinoma, melanoma), and nonmalignant autoimmune diseases (e.g., amyloidosis, systemic lupus). Younger patients (<50 years) are considered the best candidates for this intensive therapy, although this is changing in the setting of newer supportive modalities.

Several modes of stem cell transplantation have been developed. In *autologous transplantation*, the patient's bone marrow or peripheral blood stem cells (PBSCs) are collected during remission after high-dose chemotherapy or G-CSF administration. These cells are cryopreserved, thawed, and reinfused. This approach incurs a higher risk of relapse as a result of reinfusion of a stem cell product that may remain contaminated with tumor cells.

In *allogeneic stem cell transplantation,* abnormally functioning hematopoietic bone marrow is eradicated and is replaced with normal bone marrow or stem cells from a compatible source (i.e., related or unrelated donor). High-dose chemotherapy with or without total body irradiation is used to destroy the patient's bone marrow, followed by infusion of new stem cells that engraft and restore normal hematopoiesis. Treatment-related morbidity is significant, and the procedure has a mortality rate of 10% to 30%. However, improvements in supportive care and immunomodulatory therapy designed to suppress graft-versus-host disease (GVHD), an autoimmune phenomenon in which intact lymphocytes in the transplanted marrow attack the host tissues, are continuing to improve outcome.

Donor and patient are tested for compatibility of human leukocyte antigen (HLA) and major histocompatibility complex (MHC) proteins expressed on all cells. Three major HLA class I antigens (i.e., A, B, and C) and three MHC class II antigens (i.e., DP, DQ, and DR) have been developed. The six HLA gene loci are tightly linked on chromosome 6 and are almost always inherited on a single cluster of genes, or *haplotype.* All children are a half-match (i.e., haploidentical) to each of their parents, and full siblings have a 25% probability of being HLA identical to one another. HLA-matched, nonrelated transplants have higher rates of GVHD than transplants from HLA-matched, related donors as a result of other minor HLA incompatibilities. Patients who receive an HLA-mismatched stem cell transplantation risk acute GVHD, marrow rejection, and fatal marrow aplasia. Morbidity and mortality rates associated with non–HLA-compatible transplants can be prohibitive.

Evidence indicates that the excellent response of some patients to HSC transplantation is partly related to the active suppression of the patient's original (residual) or relapsing disease by cells from the newly transplanted donor graft, referred to as the *graft-versus-leukemia effect.* Studies have documented that infusion of donor lymphocytes can restore remission in patients with evidence of relapse after allogeneic transplantation for chronic myelogenous leukemia. Conversely, procedures that minimize the reactivity between donor and host increase disease relapse. For example, there is an increased rate of relapse among patients who undergo syngeneic (identical twin) stem cell transplantation and patients who receive T-cell–depleted marrow in an attempt to reduce GVHD.

The observed effectiveness of donor lymphocyte infusions in controlling chronic myelogenous leukemia led to the conclusion that the immunologic effects of transplanted allogeneic cells might be as important as or more important than cytoreduction for the cure of some hematologic malignancies. To exploit these effects, nonmyeloablative stem cell transplantations are performed. Patients receive conditioning and immunosuppressive regimens in doses sufficient to permit donor stem cell engraftment without aggressive cytoreduction. These mini-transplantations result in chimeric marrows (i.e., part patient and part donor) without significant periods of cytopenias or hematopoietic compromise, although most responding patients convert to a fully donor-derived marrow over time. Although still experimental, these procedures are increasingly being used in patients who are otherwise ineligible for traditional myeloablative transplantation regimens (i.e., age greater than 50 to 55 years, other comorbidities) or in individuals with nonmalignant autoimmune or congenital disorders.