pheresis sessions. In the autologous setting, transplantation of >2.5 × 10^6 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 10–20% of patients who fail to mobilize sufficient CD34+ cells with growth factor alone, the addition of plerixafor, an antagonist of CXCR4, may be useful. Compared to the use of autologous marrow, use of peripheral blood stem cells results in more rapid hematopoietic recovery, with granulocytes recovering to 500/μL by day 12 and platelets recovering to 20,000/μL by day 14. Although this more rapid recovery diminishes the morbidity rate of transplantation, no studies show improved survival.

Hesitation in studying the use of peripheral blood stem cells for allogeneic transplantation occurred because peripheral blood stem cell products contain as much as 1 log more T cells than are contained in the typical marrow harvest; in animal models, the incidence of GVHD is related to the number of T cells transplanted. Nonetheless, clinical trials have shown that the use of growth factor–mobilized peripheral blood stem cells from HLA-matched family members leads to faster engraftment without an increase in acute GVHD. Chronic GVHD may be increased with peripheral blood stem cells, but in trials conducted so far, this has been more than balanced by reductions in relapse rates and nonrelapse mortality rates, with the use of peripheral blood stem cells resulting in improved overall survival. However, in the setting of matched unrelated donor transplantation, use of peripheral blood results in more chronic GVHD without a compensatory survival advantage, favoring the use of bone marrow in this setting.

Umbilical cord blood contains a high concentration of hematopoietic progenitor cells, allowing for its use as a source of stem cells for transplantation. Cord blood transplantation from family members has been explored in the setting where 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 engraftment and 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 more than 500,000 units are cryopreserved 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 transplant-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 the use of double cord transplants diminishes the risk of graft failure and early mortality even though only one of the donors ultimately engrafts. Survival rates are now similar with unrelated donor and cord blood transplantation.

THE TRANSPLANT PREPARATIVE REGIMEN

The treatment regimen administered to patients immediately preceding transplantation is designed to eradicate the patient's underlying disease and, in the setting of allogeneic transplantation, immunosuppress the patient adequately to prevent rejection of the transplanted marrow. The appropriate regimen therefore depends on the disease setting and source of marrow. For example, when transplantation is performed to treat severe combined immunodeficiency and the donor is a histocompatible sibling, no treatment is needed because no host cells require eradication and the patient is already too immunoincompetent to reject the transplanted marrow. For aplastic anemia, there is no large population of cells to eradicate, and high-dose 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 in order to eradicate hyperplastic host hematopoiesis. A variety of different regimens have been developed to treat malignant diseases. Most of these regimens include agents that have high activity against the tumor in question at conventional doses and have myelosuppression as their predominant dose-limiting toxicity. Therefore, these regimens commonly include busulfan, cyclophosphamide, melphalan, thiotepa, carmustine, etoposide, and total-body irradiation in various combinations.

Although high-dose treatment regimens have typically been used in transplantation, the understanding that much of the antitumor effect of transplantation derives from an immunologically mediated GVT response has 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 reduced-intensity regimens have been studied, ranging from the very minimum required to achieve engraftment (e.g., fludarabine plus 200 cGy total-body irradiation) to regimens of more immediate intensity (e.g., fludarabine plus melphalan). Studies to date document that engraftment can be readily achieved with less toxicity than seen with conventional transplantation. Furthermore, the severity of acute GVHD appears to be somewhat decreased. Complete sustained responses have been documented in many patients, particularly those with more indolent hematologic malignancies. In general, relapse rates are higher following reduced-intensity conditioning, but transplant-related mortality is lower, favoring the use of reduced-intensity conditioning in older patients and those with significant comorbidities. High-dose regimens are favored in younger, fitter patients.

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 contaminating tumor cells in autologous transplantation. Marrow donation 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 occasionally patients develop fever, cough, or shortness of breath. These symptoms typically resolve with slowing of the infusion. When the stem cell product has been cryopreserved using dimethyl sulfoxide, patients more often experience short-lived nausea or vomiting due to the odor and taste of the cryoprotectant.

ENGRAFTMENT

Peripheral blood counts usually reach their nadir several days to a week after transplant as a consequence of the preparative regimen; then cells produced by the transplanted stem cells begin to appear in the peripheral blood. The rate of recovery depends on the source of stem cells, the use of posttransplant growth factors, and the form of GVHD prophylaxis used. If marrow is the source of stem cells, 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 speeds the rate of recovery by ~1 week when compared to marrow, whereas engraftment following cord blood transplantation is typically delayed by ~1 week compared to marrow. Use of a myeloid growth factor (G-CSF or GM-CSF) after transplant can accelerate recovery by 3–5 days, whereas use of methotrexate to prevent GVHD delays engraftment by a similar