

139e Hematopoietic Cell Transplantation

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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. The procedure is usually carried out for one of two purposes: (1) to replace an abnormal but nonmalignant lymphohematopoietic system with one from a normal donor or (2) to treat malignancy by allowing the administration of higher doses of myelosuppressive therapy than would otherwise be possible. The use of hematopoietic cell transplantation has been increasing, both because of its efficacy in selected diseases and because of increasing availability of donors. The Center for International Blood and Marrow Transplant Research (<http://www.cibmtr.org>) estimates that about 65,000 transplants are performed each year.

THE HEMATOPOIETIC STEM CELL

Several features of the hematopoietic stem cell make transplantation 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. 89e**). Transplantation of a single stem cell can replace the entire lymphohematopoietic 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, Langerhans cells of the skin, and brain microglial cells. The ability of the hematopoietic stem cell to home to the marrow following intravenous injection is mediated, in part, by an interaction between CXCL12, also known as stromal cell-derived factor 1, produced by marrow stromal cells and the alpha-chemokine receptor CXCR4 found on stem cells. Homing is also influenced by the interaction of cell-surface molecules, termed *selectins*, including E- and L-selectin, on bone marrow endothelial cells with ligands, termed *integrins*, such as VLA-4, on early hematopoietic cells. Human hematopoietic stem cells can survive freezing and thawing with little, if any, damage, making it possible 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), which often complicates allogeneic transplantation, and unlike the use of autologous marrow, 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 immunosuppressive preparative regimen used to treat the patient before transplant is inadequate, immunocompetent cells of the patient can cause graft rejection. The risks of these complications are greatly influenced by the degree of matching between donor and recipient for antigens encoded by genes of the major histocompatibility complex.

The human leukocyte antigen (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 HLA-matched, 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 current 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. Although survival following a one-antigen mismatched transplant is not markedly altered, survival following two- or three-antigen mismatched transplants is significantly reduced. Since the formation of the National Marrow Donor Program and other registries, it has become possible to identify HLA-matched unrelated donors 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 identifying and typing >20 million volunteer donors, HLA-matched donors can now 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.

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 transplantation, 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 products of tumor cells. Some use antibodies directed at tumor-associated antigens plus complement, antibodies linked to toxins, or antibodies conjugated to immunomagnetic beads. Another technique is positive selection of stem cells using antibodies to CD34, with subsequent column adherence or flow techniques to select normal stem cells while leaving tumor cells behind. All of these approaches can reduce the number of tumor cells from 1000- to 10,000-fold and are clinically feasible; however, no prospective randomized trials have yet shown that any of these approaches results in a decrease in relapse rates or improvements in 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 5×10^8 nucleated marrow cells per kilogram are collected for allogeneic transplantation. Several studies have found improved survival in the settings of 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 certain hematopoietic growth factors, including granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-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 has made it possible to harvest adequate numbers of stem cells from the peripheral blood for transplantation. Donors are typically treated with 4 or 5 days of hematopoietic growth factor, following which stem cells are collected in one or two 4-h