Hematopoietic Stem Cell Sources for Transplantation

Historically, stem cell transplantations have employed allogeneic bone marrow stem cells aspirated from the posterior iliac crest of the donor and intravenously infused into the patient after myeloablation and immunosuppressive therapy. The process of engraftment or reconstitution of normal hematopoietic function takes several weeks. Patients often require almost daily platelet and red blood cell transfusions, and they are hospitalized during this period of prolonged neutropenia to minimize life-threatening bacterial, viral, and fungal infections. Other complications include severe mucositis, hemorrhagic cystitis, GVHD, relapsed disease, and graft failure.

The discovery that high-dose G-CSF treatment mobilizes large numbers of CD34+ hematopoietic progenitor and stem cells from bone marrow sites into circulating blood (i.e., 10-fold to 15-fold increase over baseline levels) led to the use of PBSCs collected by apheresis procedures in place of bone marrow stem cells for allogeneic transplantation. Compared with marrow-derived stem cells, PBSCs engraft more rapidly after myeloablation. Patients receiving allogeneic PBSC transplants have decreased neutrophil recovery time, lower transfusion requirements, fewer inpatient hospital days, and similar rates of acute GVHD and long-term survival outcomes as traditional marrow-transplanted patients. Because PBSC collections often contain threefold to fourfold more CD34+ stem cells and 10-fold more lymphoid cells than harvested marrow grafts, higher rates of chronic GVHD may occur.

Umbilical cord blood (UCB) stem cells are a rich source of immature CD34+ HSCs. The less stringent HLA-compatibility requirements for UCB HSC matches prompted increasing use of these transplants as a therapy for patients lacking fully compatible HLA-matched PBSCs or bone marrow donors. Although still considered experimental, some transplantation centers have reported long-term outcomes after UCB HSC transplants similar to those for conventional marrow or peripheral PBSC transplants for primary hematologic diseases. However, the relatively limited numbers of CD34+ stem cells found in harvested UCB units accounts for a much slower hematopoietic recovery after the procedure and a statistically higher risk for nonengraftment compared with other stem cell sources. For this reason, UCB transplantation procedures have been limited to pediatric patients and smaller adults or to adult patients for whom there is more than one HLA-compatible UCB unit.

Aplastic Anemia

Definition and Epidemiology

Aplastic anemia (AA) is a rare disorder characterized by pancytopenia with a markedly hypocellular bone marrow. This disease was first described in 1888 by Paul Ehrlich, who observed that autopsy bone marrow specimens from a young woman who died of severe anemia and neutropenia were extremely hypoplastic. Later studies demonstrated that patients with severe AA possessed only a fraction of normal pluripotent stem cell numbers despite normal functional marrow stromal cells and normal or even elevated levels of stimulatory cytokines.

The incidence of AA ranges from 1 to 5 cases per million people in the general population. It occurs predominantly in young adults (20 to 25 years old) and older adults (60 to 65 years old). The incidence is threefold higher in developing countries (e.g., Thailand and China) compared with industrialized Western nations (e.g., Europe and Israel), a fact that is not explained by differences in drug or radiation exposure. A few AA cases occur in the context of a congenital bone marrow failure disorder, such as Fanconi's anemia, Shwachman-Diamond syndrome, and dyskeratosis congenita. The most common congenital AA, Fanconi's anemia, is an autosomal recessive disorder arising from mutations in genes encoding DNA repair proteins.

Pathology

The known causes of acquired AA are numerous (Table 45-4) and range from myeloablative radiation exposure to common viruses and medications. Prior bone marrow toxicity from drugs, chemicals (e.g., benzene, cyclic hydrocarbons found in petroleum products, rubber glue, insecticides, chemical dyes), or radiation predisposes to AA because these agents directly injure proliferating and differentiating HSCs by inducing DNA damage. In contrast, cytotoxic chemotherapy (especially with alkylating agents) and radiation therapy target all rapidly cycling cells and often induce reversible bone marrow aplasia. Despite the many causes of acquired AA, most cases are idiopathic.

Acquired and congenital AAs appear to be etiologically linked through abnormal telomere maintenance. Telomeres are repeated nucleotide sequences that cap and protect chromosome ends from degradation. Cell division leads to normal telomere erosion; when telomeres reach a critically short length, cells cease to proliferate, senesce, and undergo apoptosis, often with accompanying DNA damage and genomic instability. Telomerase enzyme in normal HSCs preserves long telomeres and promotes quiescence and a prolonged cellular lifespan. Patients with autosomal dominant dyskeratosis congenita have mutations in the genes for telomerase complexes, predisposing to premature aging and enhanced marrow failure in the setting of accelerated telomere shortening. One third of patients with acquired AA also have short telomeres, likely due to a combination of genetic, environmental, and epigenetic factors.

Autoreactive host lymphocytes can destroy normal hematopoiesis in AA. Bone marrow stromal cells and cytokine levels in patients with AA are normal. The fact that AA also occurs in diseases of immune dysregulation and after viral infections

TABLE 45-4 CAUSES OF ACQUIRED APLASTIC ANEMIA

Drugs (dose related): chemotherapeutic agents, antibiotics (chloramphenicol, trimethoprim-sulfamethoxazole)
Idiosyncratic causes (many unproved): chloramphenicol, quinacrine, nonsteroidal anti-inflammatory drugs, anticonvulsants, gold, sulfonamides, cimetidine, penicillamine
Toxins: benzene and other hydrocarbons, insecticides
Viral infection: hepatitis, Epstein-Barr virus, human immunodeficiency virus (HIV)
Immune disease: graft-versus-host disease in immunodeficiency, hypogammaglobulinemia
Paroxysmal nocturnal hemoglobinuria (PNH)
Radiation exposure
Pregnancy