Allogeneic HSCT

Allogeneic HSCT is for curative intent: The engraftment of donor HPCs is necessary to correct a marrow-disease process or congenital disorder. It is most commonly employed to treat patients with refractory leukemia; aplastic anemia and other marrow failure syndromes; and primary immunodeficiencies, congenital hemolytic disorders, and some inborn errors of metabolism.[2,25] Allogeneic HSCT requires donors who are HLA matched to the patient at both Class I (A, B) and Class II loci (DR) to ensure engraftment and minimize the risk for graft-vs-host disease (GVHD)—a significant complication of allogeneic HSCT.[32-34]

Allogeneic HSCT is intended to cure marrow disease or correct a congenital disorder.

The recommended CD34+ cell dose for HSCT with matched, related donors is at least 5 million CD34+ cells per kg recipient weight, which is considerably higher than that for autologous HSCT.[35] Higher CD34 transplant doses are associated with faster engraftment and improved overall survival, but it is tempered by higher rates of acute and chronic GVHD.[36,37]

Marrow, peripheral blood, and cord stem cells can all serve as the HPC source for patients undergoing allogeneic HSCT. Historically, stem cells for allogeneic HSCT were usually not cryopreserved. In general, marrow and peripheral blood stem cells were scheduled and collected "just in time" for transplantation and infused as soon as available. By necessity during the recent COVID pandemic, there was a change toward cryopreserved allogeneic HPCs due to uncertainties surrounding the virus, donor availability, and patient readiness for HSCT.[38] Umbilical cord stem cells, on the other hand, are always cryopreserved.

Matched Related Donors

In allogeneic HSCT, the most desired donor is a relative, or matched, related donor (MRD).[32-34] Among MRDs, the most desired MRD is a sibling who is HLA matched and is more likely to match at other minor

antigens that can affect engraftment. In fact, one of the first successful allogeneic transplantations was performed between identical twins.[2]

MRDs tend to be older, with medical conditions that can affect donor safety.

Given the age of most patients and their siblings, MRDs tend to be older with more underlying medical issues that can pose issues for stem cell collection.[39,40] In addition, older donors have lower CD34 mobilization due, in part, to a loss of marrow cellularity with aging.[19,20,39]

Matched Unrelated Donors

If a related donor is not available, transplantation centers will search international marrow or cord cell registries for potential HLA-matched, unrelated donors (MUDs). The National Marrow Donor Program (NMDP, "Be the Match") is the oldest registry and remains the primary source for MUDs in the United States.[2] NMDP also coordinates with international registries to locate the best matched donors for a recipient. Because of stricter age and donor requirements, MUDs skew significantly younger than sibling MRDs.[39,41] Moreover, younger donors are associated with better transplant outcomes.[42,43] Organizations overseeing MUD donations also have stricter collection requirements. For example, NMDP limits the total volume of donor blood to be processed to 24 L total, preferably in a single apheresis collection.[41]

Haploidentical Donors

Haploidentical allogeneic HSCTs are performed when an HLA-matched donor cannot be located. Haploidentical donors are used with increasing frequency for HSCT in sickle cell disease and other hemoglobinopathies.[44] The most common haploidentical HSCTs are between first-degree relatives, such as a parent donating for a child.[44] To avoid fatal GVHD, patients receive cyclophosphamide (CTX) after transplantation (day +3, +4) to kill donor lymphocytes.[44,45] Alternatively, the HPC product can undergo CD34 selection to remove most donor lympho-

cytes before infusion. HLA-alloimmunized patients are at risk for graft rejection.[45]

Haploidentical HSCT is used for refractory leukemia and patients with no HLA-matched donor. Cyclophosphamide is given 48 hours after transplantation to kill donor lymphocytes that could cause GVHD.

Increasingly, haploidentical donors are deliberately used for patients with leukemia as well as some solid-tumor patients.[46,47] The premise is that a graft-vs-tumor response can be elicited by donor-derived T cells that will eradicate residual tumor missed by chemotherapy and radiation. As above, patients are treated with posttransplantation CTX to eliminate alloreactive donor T cells.[48] To maximize graft-vs-tumor effect, some protocols dictate a two-stage HSCT, in which the patient receives a donor lymphocyte infusion (DLI) during pretransplantation conditioning, followed by CTX and CD34-selected HPC(A) from the same donor several days later.[49] Haploidentical HSCT are associated with higher nonrelapse mortality and lower overall survival when compared to MRD donor HSCT.[50]

Donor Evaluation

Donor Suitability

Donor suitability is donor safety—is donation safe for the donor? The assessment of donor suitability is more extensive than that performed for volunteer blood donors.[51] Donor evaluation includes a fairly comprehensive health history including medications and allergies; a full physical exam; as well as basic laboratory studies [electrolytes, urinalysis, liver panel, complete blood count (CBC), WBC differential].[33,34,41,51] (See Table 2.) Donors may require an electrocardiogram (EKG) and chest x-ray based on age and health history.