ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Umbilical Cord Blood Transplantation in Cancer Therapy

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H&O How is umbilical cord blood used in cancer therapy?

EH Umbilical cord blood—the blood collected from the umbilical cord after the birth of a baby—is used as a source of stem cells in transplantation for hematologic malignancies in adults and children. It is also used to treat inborn errors of metabolism and other nonmalignant conditions, particularly in children.

H&O How does umbilical cord blood compare to blood or marrow from living donors?

EH Umbilical cord blood is a very rich source of hematopoietic stem cells. In fact, on a per volume level, it is richer than any other stem cell source used, including mobilized peripheral blood cells and bone marrow. That said, the total volume of umbilical cord blood units is much smaller than that of other sources of stem cells typically used, and therefore recipients of umbilical cord blood transplants receive fewer cells. This probably explains, at least in part, the 2 biggest issues associated with cord blood transplants: delayed hematopoietic recovery or even frank graft failure and increased likelihood of infections. The typical practice when someone with leukemia or lymphoma needs a transplant is to first determine whether they have a suitable sibling match, then look for an unrelated donor, and, finally, if the search appears to be difficult and/or no suitable fully matched donor is identified, to look in the umbilical cord blood registry (or to consider haplotransplantation).

H&O Are there advantages to using umbilical cord blood in cancer patients?

EH Yes—many. First, it expands the donor pool. It is life-saving for transplant patients who have no readily available donors. This advantage is particularly important for people of non-European ancestry, who are less likely to find a match in an unrelated donor registry. There is also a big inventory of "shelf-ready" grafts with umbilical cord blood, so we can move very efficiently to transplantation when using it. For these reasons, any preliminary unrelated donor search that appears to be difficult should prompt a simultaneous search of the cord blood registries, rather than a prolonged and often unsuccessful unrelated donor search. In addition, there are unexpected immunologic properties of umbilical cord blood: a much greater degree of mismatching can be tolerated in umbilical cord blood transplantation, and still the likelihood that acute graft-versus-host disease will develop is actually less in umbilical cord blood transplant than in other types of allogeneic transplantation.

H&O What prompted your recent phase I study on umbilical cord blood transplantation in patients with advanced hematologic malignancies?

EH We are trying to address the issue of delayed recovery of blood counts. It has long been known that T cells are important in promoting engraftment of stem

cells, and we wondered whether umbilical cord blood T cells—all naïve, baby cells—might be better able to promote hematopoietic recovery if they were activated using technology pioneered by Carl June, MD, and Bruce Levine, PhD, whereby cells are incubated with beads conjugated to antibodies directed against CD3 and CD28, leading to a polyclonal expansion and activation of T cells. This method of activation/expansion is also a potential way of storing activated T cells to use later as immunotherapy, if disease returns after transplantation.

H&O What was the study design, and what did it show?

EH It was a phase I safety study that used a single umbilical cord blood graft in a myeloablative setting together with activated T cells for adults without a matched related or unrelated donor. We were encouraged by the very early engraftment we observed, even at very low cell dose levels (as early as 12 days). We were humbled, however, by some of the toxicity, which included graft-versus-host disease. The study suggested real biologic activity, but additional studies and safety data are needed to draw major conclusions.

H&O What is next in the field of umbilical cord blood transplantation?

EH Umbilical cord blood transplantation is a major frontier, and could serve as a platform for all kinds of immunologic and stem cell graft engineering opportunities. Those are the cutting edge aspects of this type of treatment. That said, probably the most important message is that expanding the donor pool is an absolute critical priority. I am convinced that there is a huge pool of pregnant women out there who are very willing to donate umbilical cord blood to public banks. Greater access to cord blood donation (through public banks) would go a long way toward the goal of having outstanding graft options for everyone who needs a transplant.

Suggested Readings

Hexner E, Luger SM, Mangan JK, et al. A phase 1 dose escalation study of infusion of ex vivo CD3/CD28 costimulated umbilical cord blood-derived T cells in adults undergoing transplantation for advanced hematologic malignancies. *Blood* (ASH Annual Meeting Abstracts). 2011;118: Abstract 3032.

Thomas AK, Maus MV, Shalaby WS, June CH, Riley J. A cell-based artificial antigen-presenting cell coated with anti-CD3 and CD28 antibodies enables rapid expansion and long-term growth of CD4 T lymphocytes. *Clin Immunol*. 2002;105:259-272.

Levine BL, Bernstein WB, Aronson NE, et al. Adoptive transfer of costimulated CD4+ T cells induces expansion of peripheral T cells and decreased CCR5 expression in HIV infection. *Nat Med*. 2002;8:47-53.