Half-Match Bone Marrow Transplants May Raise Odds for More Recipients

By Karyn Hede

The advent of bone marrow transplantation (BMT) as a potentially curative treatment for cancers of the blood-forming system has transformed treatment for patients with relatives whose human leukocyte antigen (HLA) types are identical or who can find unrelated donors with matched HLA. But the odds of locating a perfect-match donor, estimated to be better than 50% for whites, drops to less than 10% for ethnic minorities, whose HLA types are much more diverse and who are less likely to participate in donor registries.

But now an innovative approach to BMT that uses half-matched donors has raised the odds for many ethnic minorities and older patients who previously could not find a
suitable donor. Genetic inheritance dictates that a parent or child must be at least a half-match, whereas the chance of a full match for any sibling donor is only 25%. Results from several institutions suggest that outcomes with a half-match are comparable to those of fully matched unrelated donors. The key to the new approach is the use of agents that selectively deplete the activated T-cells that cause graft-versus-host disease and, in the worst cases, graft rejection.

Physicians at Johns Hopkins University developed a new protocol involving a chemotherapeutic regimen, followed by an infusion of donor bone marrow, and finally a regimen of cyclophosphamide, which is thought to kill activated T-cells, sparing quiescent T-cells and immune system-reconstituting stem cells.

“This trick, where you give the cells first, and then you give the cyclophosphamide, is a way of selectively killing the cells that cause graft-versus-host disease and graft rejection to make [the transplant] more like the graft is coming from a good [fully] matched sibling,” said Ephraim Fuchs, M.D., an oncologist and half-match transplant pioneer at Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University in Baltimore.

Physicians there have now performed more than 200 half-match or haploidentical bone marrow transplants on patients with hematological cancers, as well as non-cancerous conditions such as sickle-cell anemia and immunodeficiency syndromes. Fuchs points to a case in which a patient who was infected with HIV and had leukemia received a transplant in Germany and was essentially cured of his HIV infection. The case study, reported in the March 10, 2011 issue of the journal Blood, received international attention and is an example of the outer reaches of the potential for this type of therapy, said Fuchs.

“The more people see this and become believers, then the more they will be willing to apply it earlier, not just for the last-resort type of case but as a curative therapy earlier on in a patient’s disease course,” said Fuchs.

Two-Step, Half-Match

One such early adopter, the Kimmel Cancer Center at Thomas Jefferson University in Philadelphia, has taken the half-match procedure one step further. Neal Flomenberg, M.D., chair of medical oncology at Jefferson, and nurse practitioner Dolores Grosso devised a two-step, half-match procedure that begins with separating the T-cell component of the graft from the stem cell component by using a cell sorter.

Nine to 11 days before the transplant, they give a lower dose of chemotherapy for 3 days (fludarabine, 30 mg/m² of body surface area/day, and cycarabine, 2 g/m²/day) and then give the T-cell portion of the transplant. The patients then receive cyclophosphamide for 2 days to induce T-cell tolerance, followed by a second infusion consisting of CD34⁺ stem cells.

The researchers recently completed a clinical trial testing this regimen on 34 patients. In December 2010 they reported at the American Society of Hematology annual meeting results from a subset of 17 patients older than 66 years, all but two of whom had relapsed disease. Seven patients were alive and disease free up to 30 months later, including both patients who were disease free at transplant.

“People going into half-match [transplant] with active disease have a high frequency of relapsing, so it’s not a magic bullet,” said Grosso.

Furthermore, about 60% of all patients treated with half-matched donors at Jefferson have some degree of graft-versus-host disease, but those symptoms—mostly rash and diarrhea—have been manageable, Flomenberg said. “We saw that our rate of transplant complications was fairly modest and that we did very, very well in patients who came to transplant in remission,” he said.

The two-step transplant results have been so good that Jefferson is offering patients entry into four open clinical trials that test various combinations of drug therapy in addition to the transplant. Flomenberg said the results so far justify recommending that patients at high risk for relapse consider having a half-match transplant early in their disease.

“By waiting until the disease is advanced, you really put yourself behind the eight ball,” he said.

Other Half-Match Approaches

Some investigators who have experience with half-match transplants advise a more conservative approach. Nelson Chao, M.D., division chief of cellular therapy and bone marrow transplantation at Duke University Comprehensive Cancer Center in Durham, N.C., said that although the data from Jefferson are interesting, it is still too early to endorse their half-match transplant technique. Many practitioners remain wary of the procedure, he said.

“I think that a lot of centers haven’t really pushed on [half-match transplants] because of different research agendas, but partly because of the history of bad outcomes,” said Chao. Early attempts at haploidentical transplants conducted in the 1980s and early 1990s focused on depleting donor and recipient T-cell populations with radiation before transplant, but patients who received these transplants had a high rate of infection and graft rejection.

Chao and his colleagues at Duke have developed their own procedure for haploidentical transplants. They use alemtuzumab, a monoclonal antibody–based drug that targets CD52, a cell surface antigen on T-cells but not on stem cell precursors. The procedure is designed to deplete T-cells, much the same as cyclophosphamide.

In a recent Duke study presented at the December 2010 American Society of Hematology meeting, a comparison of
matched-related (29 patients), matched-unrelated (40 patients), and haploididentical (29 patients) transplant recipients yielded 1-year overall survival rates of 66% (95% confidence interval [CI], 43%–82%), 39% (95% CI, 21%–55%), and 34% (95% CI, 16%–53%) respectively. About half the patients had lymphoid cancers, whereas the rest had myeloproliferative disease or acute myeloid leukemia. The study team monitored patients for a median of 15 months. Chao said that the results are encouraging enough to warrant a prospective randomized study of half-match transplants versus other transplant options, such as umbilical cord blood transplant.

The Johns Hopkins group is planning just such a trial, through the Blood and Marrow Transplant Clinical Trials Network, a National Institutes of Health–funded cooperative of 16 transplant centers. Fuchs said they are developing a randomized multicenter prospective trial comparing nonmyeloablative conditioning and transplantation of double-unrelated umbilical cord blood versus HLA-haploididentical related donor bone marrow for leukemia and lymphoma patients at risk of relapse. The trial, to be called BMT CTN 1101, is expected to get under way within the year.

“What we’ve seen is that when other places try what we’ve done, they absolutely love it,” Fuchs said.