Gene therapy outpaces haplo for SCID-X1

Donald B. Kohn  UNIVERSITY OF CALIFORNIA, LOS ANGELES

In this issue of Blood, Touzot et al1 report that autologous gene therapy/hematopoietic stem cell transplantation (HSCT) for infants with X-linked severe combined immune deficiency (SCID-X1) lacking a matched sibling donor may have better outcomes than haploidentical (haplo) HSCT. Because gene therapy represents an autologous transplant, it obviates immune suppression before and after transplant, eliminates risks of graft versus host disease (GVHD), and, as the authors report, led to faster immunological reconstitution after transplant than did haplo transplant.

These same investigators at Hôpital Necker–Enfants Malades in Paris presented the first evidence that clinical gene therapy could be efficacious when they reported evidence of immune reconstitution in a series of infants with SCID-X1 treated by autologous transplantation of bone marrow CD34+ cells corrected by retroviral vector–mediated introduction of a normal copy of the IL2RG complementary DNA.2 Gene therapy transplants by this group and by investigators following a similar approach at University College London led to immune reconstitution in at least 18 of 20 treated infants.3,4 However, these results were seriously marred by the development of vector-related T lymphoproliferation in 5 of the subjects, resulting in 1 death.5,6 Notably, these investigators, working with other collaborators, retooled the y-retroviral vector to produce a safer self-inactivating (SIN) retroviral vector carrying the IL2RG complementary DNA and recently reported successful immune reconstitution without evidence of clonal expansion (by deep sequencing of vector integrations sites) in the initial period.7

Here, they have compared clinical and immunological outcomes in patients with SCID-X1 transplanted using either haplo (parental), T-cell–depleted (CD34-enriched) HSCT (n = 13), or autologous, y-retroviral vector IL2Rg gene-modified HSCT (n = 14). No cytotoxic chemotherapy was used for any of the subjects, but the recipients of haplo grafts did receive pretransplant rabbit antithymocyte globulin. The type of graft the patients received was basically determined by the time period of their treatment. Enrollment into the first gene therapy trial was exclusively between 1999 and 2002, then into the haplo protocol while the gene therapy trial was on hold between 2003 and 2010, and then into either a second gene therapy trial with the newer SIN vector for patients with active infections or into haplo transplant for those without infection between 2010 and 2012. Both types of transplants use T-cell–deplete grafts, either from the intentional T-cell depletion of the haplo grafts by CD34 selection to minimize GVHD or from the CD34 selection of the autologous bone marrow used to enrich for transduction targets as well as the inherent T-cell deficiency of the SCID-X1 patients.

Because SCID patients may have either preexisting or new infections until their immunity is restored after transplant, a critical issue is which approach better supports rapid and robust immunological reconstitution. In fact, immune reconstitution was significantly better in the gene therapy group assessed by multiple parameters, including T-cell subset counts in the first year, development of naive T lymphocytes (persisting even after 5 years) and regulatory T cells, proliferative responses to phytohemagglutinin, natural killer cell numbers, and immunoglobulin M levels (although these remained subnormal in all). All 10 evaluable haplo recipients continued to require intravenous immunoglobulin replacement, whereas 4 of 7 of the gene therapy recipients in the first trial and 0 of 4 in the second trial were able to discontinue immunoglobulin replacement. Importantly, there were significantly fewer days of rehospitalization for the gene therapy patients and quicker clearance of preexisting infections, which may indicate the tangible clinical benefits of the earlier immune reconstitution that was achieved.

Clinical outcomes were essentially similar between the 2 treatments, with survival and immune reconstitution in most of the SCID-X1 infants. Although the requirement for active infection for inclusion in the second gene therapy trial might be expected to bias toward worse outcomes in that group, survival rates were similar with both graft types (11/13 haplo vs 12/14 gene therapy). But still, there were 2 deaths in each group and severe adverse events in both sets of SCID-X1 patients. Viral infections present at the time of diagnosis or that were acquired early after transplant led to 1 death in each of the 2 groups. There were 3 episodes of graft failure necessitating a second transplant among the haplo transplants and 1 in the gene therapy group. There were immunological complications of acute grade 2 GVHD7 and autoimmune complications2 in haplo recipients, and genotoxicity complications causing T lymphoproliferation in gene therapy patients4 treated with the older vector. These yet imperfect results indicate the ongoing need to improve diagnosis and treatments for SCID patients to provide the best outcomes.

This is a truly unique clinical series, making the first direct comparison between outcomes from haplo HSCT and autologous gene therapy HSCT for SCID-X1. Although it was a retrospective analysis with irregular enrollment for the 2 different treatments over time rather than a contemporaneous randomized trial, it nonetheless represents an informative comparison because all patients were treated and evaluated for clinical and immunological results at a single expert center.

Several possible factors may explain the better immune reconstitution after autologous gene therapy, including the avoidance of the serotherapy that was used for haplo transplants and could impair immune recovery, the lack of GVHD with autologous gene therapy that may impede immune recovery after allogeneic HSCT, and the use of the younger autologous stem cells from the SCID infants that may have better lymphoid potential than those from the adult haploidentical donors.8

Obviously, this is a small single series of subjects; larger studies are needed to form firm conclusions about relative efficacy and safety of these 2 transplant modalities. Several
Clinical trials using SIN retroviral and lentiviral vectors for SCID-X1 are under way that will provide further information on the course and nature of the immune reconstitution from autologous gene therapy to compare with those from haplo-HSCT. SCID continues to set a fast pace for advances in the treatment of inherited blood cell diseases.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

© 2015 by The American Society of Hematology

Lymphoid Neoplasia

Comment on Peterson et al, page 3588

DUB-ling down on B-cell malignancies

Lawrence H. Boise  Emory University

In this issue of Blood, Peterson et al demonstrate that inhibition of both Usp9x and Usp24 results in efficient degradation of Mcl-1, induction of apoptosis, and inhibition of tumor growth in B-cell malignancies.1

Inhibition of apoptosis is required for tumorigenesis and is a potential barrier to therapeutic activity in cancer. Therefore, directly targeting antiprototic proteins is a promising approach for the treatment of B-cell malignancies. Indeed, early reports have suggested preclinical and clinical activity of the Bcl-2/Bcl-xL/Bcl-w inhibitor navitoclax and the Bcl-2–selective inhibitor venetoclax in diseases like B-cell chronic lymphocytic leukemia (B-CLL).2 However, Mcl-1 is not targeted by these agents; therefore, expression of this Bcl-2 family member results in drug resistance. MCL1 is found on a region of chromosome 1 that is amplified in 10% of all cancers, making it likely to be a significant contributor to drug resistance beyond just Bcl-2 inhibitors.3 Additionally, in multiple myeloma, navitoclax and venetoclax are not likely to be effective in most patients, as the survival of most myelomas is primarily dependent on Mcl-1.4 Therefore, strategies to target Mcl-1 could be effective to overcome drug resistance in Bcl-2–dependent diseases like B-CLL and to treat Mcl-1–dependent diseases like myeloma. Currently there are few publications on Mcl-1–selective agents, and thus far they either are early in preclinical studies or have not been particularly potent.5

Although targeting Mcl-1 function holds great promise, targeting its expression could be equally effective and there have been several different approaches tested that are based on the finding that Mcl-1 protein has a short half-life. Inhibition of transcription with CDK9 inhibitors like flavopiridol appears to work in part because Mcl-1 protein is rapidly depleted when transcription is inhibited.6 Filanesib activity has also been attributed to Mcl-1 degradation in cells that are arrested in M-phase.7 However, these approaches are likely to have numerous effects on cells, making it hard to pinpoint the activity to Mcl-1 degradation. The demonstration that the deubiquitinating enzyme (DUB) Usp9x regulates Mcl-1 protein stability opened the possibility for more selective targeting.8

Using the DUB inhibitor WP1130, Peterson et al demonstrate inhibition of Usp9x activity, a decrease in Mcl-1 protein, and cleavage of poly(ADP-ribose) polymerase, indicating induction of apoptosis in myeloma, lymphoma, and B-CLL cell lines and/or patient samples. Importantly, the decrease in Mcl-1 is at least partially reversed by addition of proteasome inhibitors, consistent with degradation of Mcl-1 protein. Because WP1130 is known to inhibit multiple DUBs, the authors attempt to confirm their findings by silencing Usp9x. Surprisingly, they find that although silencing Usp9x can induce cell death, it does not appear to affect Mcl-1 protein levels or DUB activity and is significantly weaker than silencing Mcl-1. Together, these findings suggest that Usp9x may not be the only Mcl-1 DUB that is inhibited by WP1130. Usp24 is a structurally similar DUB that has been shown to have overlapping activities with Usp9x. Interestingly, Peterson et al find that it is upregulated in 2 cell lines when Usp9x is silenced and is expressed in patient samples. Unlike Usp9x, silencing of Usp24 resulted in similar death to Mcl-1 silencing and although a decrease in Mcl-1 was observed it was not as great as that seen following Mcl-1 silencing. Several conclusions can be drawn from these findings. First, Usp24 could be the primary DUB for Mcl-1 in myeloma despite higher Usp9x expression levels. Second, the regulation of these 2 DUBs may be distinct, as silencing of Usp24 does not result in upregulation of Usp9x allowing for loss of Mcl-1. This was the case in 1 cell line, and
Gene therapy outpaces haplo for SCID-X1

Donald B. Kohn