Cord blood effective alternative to matched donor stem cells for kids with rare disorder

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Transplants of blood-forming stem cells from umbilical cord blood may be an effective alternative to transplants of matched donor bone marrow stem cells to treat children with a rare, debilitating disease known as Hurler's syndrome (HS), according to results of a study published online today in *Blood*, the Journal of the American Society of Hematology (ASH).

HS is an inherited metabolic disease characterized by the lack of a critical metabolic enzyme (lysosomal α-L-iduronidase) that breaks down long chains of sugar molecules in the body. In the absence of the enzyme, the sugar chains build up in the body and damage vital organs. Children with the disease, who can be diagnosed at birth or as late as age 8, typically have a poor prognosis; serious complications such as deafness, halted growth, joint disease, or heart valve problems can rapidly develop after diagnosis and can lead to death. Recently, hematopoietic cell transplants (HCT) have become a valuable treatment for HS, as transplanted cells can generate new, healthy, enzyme producing blood cells to replace the diseased cells. These donor cells will deliver enzymes to all organs, including the brain, and can prevent disease progression. However, clinicians remain challenged to determine the optimal cell source and appropriate conditioning regimens to prepare patients for transplant that will maximize survival and minimize transplant-related morbidity and mortality.

"Cord blood has been proposed as an alternative stem cell source for children with HS since it has been suggested that cord blood may

increase their levels of lysosomal α-L-iduronidase, which consequently may allow them to live longer with fewer complications," said lead study author Jaap Jan Boelens, MD, PhD, of the University Medical Center Utrecht, in Utrecht, Netherlands. "However, until now, no studies have compared the safety and efficacy of different stem cell and donor sources among a large group of patients to determine which may be the ideal transplant source."

With this aim, Dr. Boelens and a team of investigators conducted a retrospective analysis analyzing outcomes of HS patients treated with HCT in centers affiliated with the European Group for Blood and Marrow Transplantation (EBMT), Eurocord, and the Center for International Blood and Marrow Transplant Research (CIBMTR). A total of 258 infants and children with HS (ranging from 2 months to 18 years, with a median age of 16 months at transplant) who received an HCT between 1995 and 2007 were selected for analysis based upon certain criteria: a confirmed diagnosis of HS; a transplant of cells from a matched sibling donor (MSD), a matched or mismatched unrelated donor (UD), or cells from a single, unrelated cord blood (UCB) unit; and pre-transplant treatment containing a high dose of chemotherapy to help prevent their immune systems from rejecting donated cells.

Nearly half of the children evaluated in the study (45%) had received transplants of unrelated cord blood (81% of which was from mismatched donors) with the others receiving transplants of bone marrow stem cells from unrelated donors or matched sibling donors. All the patients received pre-transplant high-dose chemotherapy, and 19 percent had previously received intravenous enzyme replacement therapy with lysosomal α-L-iduronidase. Taking into consideration stem cell source and pre-transplant conditioning, the team compared the rates of overall survival (OS), event-free survival (EFS), engraftment (the degree to which transplanted donor cells were able to reproduce into new cells) or graft failure, or death.

The team noted encouraging survival rates among the children with HS who had received an HCT, regardless of source, with 5-year estimated OS and EFS at 74 percent and 63 percent, respectively. Importantly, EFS rates were similarly high for children who had received donations of matched sibling cells or fully matched unrelated umbilical cord blood (MSD or UCB, 81%), compared to EFS rates for patients transplanted with cells from matched unrelated donors (66%) or unmatched unrelated cord blood donors (68%). EFS rates were highest among infants who received transplants at age 16 months or younger, indicating the importance of transplantation as early as possible after diagnosis for these children, when treatment may help prevent further disease burden or damage.

Within two months of undergoing transplants, nearly all patients (91%) showed evidence of donor cell recovery (as noted by increasing levels of white blood cells in the blood). Only 12 percent of children experienced secondary graft failure (when the body rejects donor cells).

As is common in patients receiving stem cell transplants, investigators observed reports of graft-versus-host disease (GVHD, which occurs when the donated immune cells attack the patient's cells as foreign tissue) among the patient sample. At 100 days post-transplant, roughly one-fourth of transplant recipients experienced moderate to severe acute GVHD, and only 16 percent experienced chronic GVHD (remaining at five years post-transplant).

After completing their analysis of the children, whose progress had been tracked for approximately five years post transplant, Dr. Boelens' team concluded that the children who received UCB transplants experienced on average a higher rate of donor cell engraftment (complete replacement of the bone marrow by donor cells) and normal enzyme levels than those who had received transplants of matched sibling cells or matched/unmatched unrelated bone marrow stem cells. Nearly all (98%)

of the cord blood recipients whose transplanted cells were successfully engrafted had normal enzyme levels, supporting a link between high levels of lysosomal α-L-iduronidase in cord blood and suggested improvements in long-term outcomes among HS patients who receive UCB transplants.

"These results are important to the transplant community because they provide strong evidence that umbilical cord blood can be a useful and effective source of stem cells for a transplant when a well-matched source of cells is not available," said Dr. Boelens. "Further, our ongoing research, which is currently in the analysis phase, may help refine how we treat young patients with Hurler's syndrome by providing additional evidence on the link between cord blood enzyme levels and long-term outcomes. International networks are of utmost importance to improve the outcomes of treatments in rare diseases like HS."

Provided by American Society of Hematology