

Cord Blood: Research Progress and Future Promise

By Al Staropoli, AABB Contributing Writer

Sue Fister found out she had leukemia when she was 50 years old. Doctors suggested a bone marrow transplant as a life-saving option but after two failed transplants she was getting ready to give up. “It was heartbreaking when I found out I had lost my second graft,” said Fister. “I thought, ‘This is it.’”

But another relatively new option still remained: an umbilical cord blood transplant. Fister received her third transplant nearly five years ago, and since then she’s been disease-free. “The birth of a child saved my life,” she said. “It was quite a miracle.”

The option of a cord blood transplant, however, was available to her only as a result of a body of research painstakingly accumulated by clinical researchers and scientists over 20 years.

Two Decades of Research Progress

Research sometimes progresses slowly, building from single case studies to multicenter clinical trials. Such is the case with cord blood.

The first successful and widely reported cord blood transplant was conducted in Paris on a 5-year-old American boy. The team included Hal Broxmeyer, PhD, of Indiana University and Eliane Gluckman, MD, of the Hôpital Saint-Louis. The child had a rare disease called Fanconi’s anemia, a condition that leads to bone marrow failure. He was successfully treated with umbilical cord blood obtained from his newborn sibling in 1988 and was later deemed disease-free.

The use of cord blood transplants in the U.S. became increasingly feasible with the opening of the first public cord blood bank. The New York Blood Center formally proposed the concept of a public cord blood bank to the National Institutes of Health in 1989, but its doors opened in 1992.

A few years after the establishment of the first public bank, scientists at Emory University made one of the first unrelated cord blood donor transplants on a 12-year-old boy with sickle cell anemia who had significant pain and was at high risk for stroke. Complications followed the transplantation, but it was eventually deemed successful. Today he is able to produce new blood cells without sickle cell disease and is free of chronic transfusions and pain crises.

In 1996, Jean-Philippe Laporte, MD, PhD, of Hôpital St. Antoine in Paris reported in the *New England Journal of Medicine* the case of a 26-year-old woman with acute myelogenous leukemia who was infused with cord blood. Cord blood transplants still were uncommon in those days, especially in adults. Only about 200 transplants had been performed worldwide at that time. “The patient’s course after transplantation was uncomplicated by infection ...[and] at this writing the patient is well and has returned to work,” he wrote in the article.

The following year, Eurocord — then a group of physicians who began studying and transplanting cord blood — published a comprehensive review of cord blood transplants mostly performed on children between 1988 and 1996. The group, led by Gluckman, reported that 95 of 143 cord blood transplants had been used to treat hematologic cancers such as leukemia. The overall survival rate

at one year post-transplant was 49 percent, and the median time needed to reach an absolute neutrophil count, or ANC, of at least 500 cells per mm³ was 30 days. (ANC is a measure of absolute neutrophil recovery and an assessment of an individual's ability to fight infection).

Successful cord blood transplantation in children rose quickly and by 2002 was seen as a curative option for many cancers and genetic diseases. A study published at the time showed that 36 of 44 children with thalassemia major, generally a lifetime condition, were completely free of disease after a cord blood transplant.

By 2004, substantial reports of adult cord blood transplants began to surface. Eurocord compared outcomes of adults with acute leukemia who were transplanted. Of 682 adults, 98 received cord blood transplants, and 584 received bone marrow from an unrelated donor. Researchers found neutrophil recovery to be significantly delayed when using cord blood compared to bone marrow transplantation.

Scientists correctly hypothesized that a longer time to engraftment was partially due to the difference in volume and certain cells in both products. Typically one quart of bone marrow is transplanted, while a unit of cord blood after processing contains only about 5 percent of that amount.

Researchers had noted that a major limiting factor for cord blood transplants in adults was the small volume used compared to bone marrow. As a result, there are fewer CD34+ cells, which have the capacity to generate multiple hematopoietic lineages, and nucleated cells in the graft.

Other researchers also began to see a correlation between the concentration of hematopoietic progenitors, such as CD34+ cells, and the speed of myeloid engraftment after transplantation.

A strategy to overcome the low cell count in adult cord blood transplants was to use two cord blood units rather than one. A 2004 paper published in the journal *Blood* evaluated the safety of using two partially HLA-matched cord blood units in adults as a strategy to increase cell count. A total of 23 adult patients were transplanted with double cord units between 2000 and 2003. Neutrophil engraftment was seen at a median of 23 days and disease-free survival was 57 percent at one year. Subsequent studies showed a significantly increased survival in double cord adult transplants when compared with single units.

In an effort to increase survival, Karen Ballen, MD, an associate professor at Harvard Medical School, used a reduced-intensity conditioning regimen in adult patients prior to double cord blood transplantation. The results were encouraging. The median time to an absolute neutrophil count was 20 days, and one-year disease-free survival was 67 percent. Ballen also noted that of the two cord blood units transplanted, only one seemed to eventually predominate after the transplant. In her study, the predominant unit was usually the first unit to be infused. Most of the units were infused three-and-a-half to four-and-a-half hours apart. In the article, Ballen suggested that "one possible explanation for this is that there may be limited opportunities to fill the hematopoietic stem cell niche after conditioning and the first umbilical cord blood infused may be more likely to fill this niche."

However, studies presented at the 2008 annual meeting of the American Society of Hematology by Juliet Barker, MBBS, of the Memorial Sloan-Kettering Cancer Center show that graft interaction can be key. Experiments in mice transplanted with human double cord blood units show that the

“winner” is determined by the origin of the CD34- fraction. This supports the idea that absolute unit dominance is linked to graft-versus-graft interaction.

Use of two cord units became a standard procedure for cord blood transplantation in adults, especially in the United States.

Lolie Yu, MD, director of Children’s Hospital of New Orleans’ hematology/oncology department, and colleagues, in collaboration with the biopharmaceutical company Celgene Cellular Therapeutics in New Jersey, are studying the safety of human placenta-derived stem cells, or HPDSCs. The idea is to enrich cord blood transplants with CD34+ cells from the placenta to increase the likelihood of a successful and earlier engraftment, when compared to using cord blood alone.

The team reported preliminary results of a transplant at the February 2009 meeting of the American Society of Blood and Marrow Transplantation. Researchers transplanted a 5-year-old boy suffering from acute lymphoblastic leukemia with HPDSC-enriched cord blood. The patient was discharged by day 15 and complete donor chimerism was seen on day 30. The patient has been disease-free for more than six months. Although further studies are needed, the fact that there were no clinically significant infusion reactions show that the strategy is safe and may have therapeutic benefit.

Researchers also began further exploration into the use of different types of conditioning and their potential impact on engraftment. Favorable results were published in a study that used a nonmyeloablative conditioning regimen — a pre-transplant chemotherapy and/or radiation therapy that does not completely destroy the bone marrow.

A total of 93 out of 110 patients with a median age of 51 years received this type of regimen along with double cord blood units. Results showed a shorter median neutrophil recovery. In the vast majority of patients, recovery averaged only 12 days. The study, published in the June 2007 issue of Blood, had finally established the use of double cord blood transplantation with nonmyeloablative conditioning as a viable treatment option.

Throughout the years, cord blood has grown from an experimental treatment in a child to a proven transplantation option for many children as well as adults.

Research Today

One important area of research today is cell expansion. Researchers are trying to increase the total nucleated cell dose by taking cord blood and “expanding” key cells in the lab before transplantation. Scientists believe that increasing the cell dose could result in a shorter engraftment period, thus making patients less vulnerable to infections and other complications.

Earlier studies by Italian researchers from the University of Torino showed that they could effectively obtain a several-fold expansion of CD34+ cells ex vivo by using hematopoietic growth factors. Elizabeth Shpall, MD, a professor of medicine at the University of Texas MD Anderson Cancer Center, also has been able to achieve this.

“We are improving the strategies for the ex vivo expansion of cord blood,” she said. “We culture the cord [cells] out of the body for 14 days with various growth factors as a means to grow the number of engraftment cells.”

In a 2002 study, Shpall reported a 56-fold increase in total nucleated cells as well as a fourfold increase in CD34+ cells. Other scientists have subsequently developed processes that can yield as much as a 400-fold expansion of total nucleated cells and a 20-fold expansion of CD34+ cells.

Expansion studies are now undergoing clinical trials. Preliminary results from one of these trials were presented by Shpall in 2008. The trial involved 71 patients who were divided into two groups — one group that received two unexpanded cord blood units and another group that received one unexpanded unit plus an expanded unit.

Significant improvements to this procedure have been made recently. Researchers have added marrow stromal cells from donors to the cord blood expansion cultures. In the patients who have received this newer product, ANC recovery appears to be faster than has been observed in previous cord blood trials. These results, however, are preliminary. “It’s very early,” Shpall cautioned. “We can’t say anything definitive yet.”

Shpall also is pursuing other expansion strategies involving cord blood natural killer cells that may help fight the cancer without causing major side effects in the patients. She is collaborating with Catherine Bollard, MD, associate professor at Baylor College of Medicine. Bollard’s laboratory is expanding cord blood T cells, which can help fight infections and prevent cancer recurrence. Clinical efficacy of T-cell expansions have been planned for the future.

“It’s an exciting time to be involved with cord blood transplantation,” Shpall said.

Clinical Applications and Future Promises

Research is taking place at a furious pace to determine potential future clinical applications of cord blood. Thus far, cord blood transplants have helped to treat or cure more than 80 diseases, including various types of leukemia, sickle cell disease, thalassemia major, Hodgkin’s disease and many others.

“We estimate that about 8,000 to 10,000 cord blood transplants have occurred worldwide to date,” Ballen said. “But the number is rising rapidly.”

Admittedly, the majority of the treatments thus far have focused on hematologic diseases. According to the National Cord Blood Program at New York Blood Center, as of 2006 nearly 60 percent of the program’s cord blood units had been transplanted to treat leukemias, myelodysplastic syndrome, lymphomas or multiple myeloma. The next-highest category was bone marrow diseases, at 10 percent.

But cord blood also has been used to treat other types of disease. Metabolic diseases such as Krabbe disease, which breaks down the nerve’s myelin cover, or adrenoleukodystrophy, which can result in progressive damage to the brain, have both been treated with cord blood.

Additional research is now being undertaken to treat more common diseases with cord blood, such as cardiovascular disease, Alzheimer’s and diabetes, but these studies are still unproven.

In 2008, mice with a disease resembling Alzheimer’s were infused with human umbilical cord blood peripherally. Results published in *Stem Cells and Development* showed a decrease in amyloid plaques — a hallmark of the disease — in the brains of mice.

Cord blood also has been used to treat mouse models of amyotrophic lateral sclerosis, more commonly referred to as Lou Gehrig's disease, which causes neurons to degenerate and eventually leads to death. Results showed an increased lifespan and reduction in disease progression in some of the mice that received cord blood.

Two years ago, at the University of Florida Clinical Research Center, pediatric endocrinologist Michael Haller, MD, led a pilot study to determine the effect of using cord blood in patients with type 1 diabetes. In this type of diabetes the immune system attacks specific pancreatic cells. To date, 23 recently diagnosed children ages 2 to 10 were infused with cord blood to determine if it could stop or slow down disease progress. Patients were evaluated on the amount of insulin produced, blood sugar levels and the function of key immune cells.

Preliminary results, presented at the American Diabetes Association's 67th Scientific Sessions in Chicago in mid-2007, showed that transfused patients required significantly less insulin and maintained better sugar levels than other similarly aged children with type 1 diabetes. "More impressive than the insulin requirements or blood sugar control was that we observed a significant increase in peripheral blood regulatory T cells for up to six months after infusion of autologous cord blood," Haller said. "These types of cells are thought to be beneficial in reversing autoimmune disease in general and may be able to help preserve insulin production." Researchers are now recruiting for a second randomized study.

Haller cautions, however, that these results are preliminary, and further studies are needed to fully understand the role of cord blood infusions as a therapy for type 1 diabetes. "The metabolic advantages to date have been relatively small and difficult to confirm, as our initial study did not include a control group," he said.

A Long Way

Cord blood has come a long way in the past 20 years. Two decades of research and clinical experience have led to the discovery that it can cure diseases that were previously thought to be incurable.

As a result, the use of cord blood has been rising steadily. The National Marrow Donor Program reported in 2008 that in the transplants it facilitated, pediatric cord blood transplants had already outnumbered pediatric bone marrow transplants. This increase is partially attributable to the fact that a perfect match is not required for cord blood transplants as it is for bone marrow. This also has allowed children and adults who were previously ineligible for a bone marrow transplant to obtain therapeutic treatment using cord blood.

Additionally, new strategies for cord transplantation developed over the years have helped to increase efficacy and safety, and research in cell expansion could further improve this. The types of conditions treated with cord blood also has expanded, from purely blood-related diseases to other types of applications.

All of this has led to an increase in the collection and storage of cord blood units from a few thousands to millions worldwide. These advances will likely cause cord blood transplantations to continue to both rise and be safer in children as well as adults well into the future.

This article was published in the current issue of [AABB News](#).