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River of Life

Grace Marshall's days are measured in homework, gymnastic classes and schoolyard friendships, but the 9-year-old's life is measured by the love of her family and an extraordinary gift from her 12-year-old sister.

Grace's mother can't pinpoint the day that the Marshall family's lives began to unravel, but sometime in 1997 unexplained bruises began to appear on her youngest daughter's body. The once-animated 4-year-old had lost much of her energy, and the Marshalls feared the worst.

The devastating diagnosis that Grace had acute lymphocytic leukemia sent the family careening through a two-and-a-half-year cycle of grave illness and recovery, until they thought the disease had finally been conquered. But after a brief remission, the leukemia returned and specialists at The University of Texas Southwestern Medical Center at Dallas counseled the Marshalls that Grace's best — if not only — chance for long-term survival was a bone marrow transplant.

Once the family decided to go forward with the procedure, Grace's physicians had to find a suitable donor, which, say experts, can be akin to finding a needle in a haystack. For Grace, the process was made simpler by the fact that she had three siblings, one of whom had tissue that carried

the genetic match necessary for a successful bone marrow transplant.

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Bone Marrow Transplants

When the blood is affected by disorders such as Hodgkin disease, leukemia and other blood-borne cancers, bone marrow transplant (also referred to as stem-cell transplant) often is the patient's best treatment option.

"The implication of stem-cell transplant — what we know now and what we will discover in the very near future — is tremendously exciting," said Dr. Robert Collins Jr., director of the UT Southwestern Hematopoietic Cell Transplant Program. "It is immensely gratifying to see how many people's lives have been saved through a procedure that relies so heavily on the generosity of others."



Grace Marshall (front) received a bone marrow transplant from her sister Shelby.

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Bone marrow — the soft, sponge-like material found inside bone — contains immature cells called stem cells. Stem cells are responsible for producing white blood cells (which fight infection), red blood cells (which carry oxygen to and remove carbon dioxide from organs and tissues) and platelets (which enable the blood to clot).

Blood stem cells can be garnered from one of three sources for transplant: marrow, circulating blood and umbilical cord blood. Regardless of their source, they accomplish much the same thing — the ability to help a patient heal himself.

There are three types of blood stem-cell transplants: autologous, which uses the patient's own blood stem cells; allogenic, which requires the blood stem cells of a donor; and the less common, syngeneic, in which patients receive stem cells from their identical twin.

Hunting for a Match

For children and adults with leukemia and blood-related cancers and diseases, healthy stem cells from a donor are needed. For these allogenic transplants, the donor can be either related (usually a sibling, as in Grace Marshall's case) or unrelated to the patient. If no tissue-type match can be found within a

patient's family, UT Southwestern doctors turn to the National Marrow Donor Program's registry of more than 4.5 million potential donors for a match.

To increase the likelihood of successful transplantation and to minimize potential complications, it is crucial that the transplanted marrow match the patient's own marrow as closely as possible.

People are equipped with different sets of proteins, called human leukocyte-associated (HLA) antigens, on the surface of their cells. The success of allogenic transplantation depends largely on how well the HLA antigens of the donor's marrow match those of the recipient's marrow. Close relatives, especially brothers or sisters, are more likely than unrelated people to have HLA-matched bone marrow; however, only 30 percent to 40 percent of patients have an HLA-matched sibling or parent, and the chance of obtaining HLA-matched marrow from an unrelated donor is small.

"The uncertainty of finding a match is one of the most frustrating elements for patients to deal with," said Dr. Preet Chaudhary, associate professor of internal medicine and molecular biology. "Many do, fortunately, but the disappointment of those few who can't is very difficult for everyone. The more educated people become about the importance of donating bone marrow, the greater the number of patients who can beat the odds."

Patients with disorders that have not affected the bone marrow are often "transplanted" with their own stem cells, which are collected from their marrow and frozen. After the patient has received high-dose chemotherapy and/or radiation therapy to kill the affected cells, the stem cells are introduced back into the patient's body to begin their job of repopulating the bone marrow.

Although the science behind the inner life of stem cells is infinitely complex, the transplant itself is a relatively straightforward concept. Much like a heart or lung transplant, the diseased "organ" (in this case, bone marrow) is removed, providing a clean slate on which new stem cells can begin their work. Stem-cell transplants are surprisingly simple procedures.

"The transplant itself is almost anticlimatic, but what the body then is required to do with the new cells is elegant," said Dr. Robert Ilaria Jr., assistant professor of internal medicine and molecular biology.

The Procedure

Much of the process at UT Southwestern takes place in the outpatient clinic at the Harold C. Simmons Comprehensive Cancer Center, where more than 60 stem-cell transplantations are performed each year. Hospitalization in the bone marrow transplant unit at Zale Lipshy University Hospital or Children's

Medical Center of Dallas is often required for the typical six- to eight-week recovery period.

Prior to the transplant, the donor's stem cells are collected either from the bone marrow in a simple surgical procedure requiring anesthesia or from veins in the arm or under the collarbone through a relatively painless procedure called apheresis. Pediatric patients (who require much smaller quantities of stem cells) also can receive transplants from umbilical cord blood. For several days before the transplant, the patient is treated with high doses of chemotherapy, with or without radiation, in order to destroy the "sick" bone marrow cells.

Stem cells then are infused intravenously in a process much like a blood transfusion. Within two to four weeks, the transplanted stem cells begin to engraft, or produce healthy marrow cells (white blood cells, platelets and red blood cells).

Thanks to ongoing research, cancers that were once considered invariably fatal can often be vanquished. Before a new double-transplant technique was developed, cancers such as neuroblastoma — a deadly cancer that affects the nervous system — were considered incurable. Dr. Victor Aquino, assistant professor of pediatrics and the first to conduct a tandem stem-cell transplant for neuroblastoma in North Texas, is conducting a clinical trial of this new treatment, which is repeated in back-to-back treatments.

While this kind of stem-cell transplant and chemotherapy is the only hope for a cure, it's still a risky proposition. Two out of every three neuroblastoma patients ultimately die from a recurrence of the cancer. For those who survive, however, the procedure is a lifeline.

"We treat diseases that for decades have been dismissed as incurable, so I think it's all the more important to stay focused on what we can do now, while looking to the future for even better treatment options," said Aquino, who performs about 20 transplants each year at Children's Medical Center. "Despite the unavoidable risks, transplant is a chance for life when otherwise there would be none."

A Sibling's Gift

Much like Grace Marshall, Dr. Alphonso Jones turned to an older sister after receiving an unsettling diagnosis.

As a Fort Worth family physician, Jones had seen the devastation of serious illness first-hand, but until a leukemia diagnosis last year forced him into a personal battle, his experience with illness had been strictly professional.

When Jones noticed a lump near his collarbone, the 55-year-old's intuition told him there might be something seriously wrong. Once the diagnosis of

acute myelogenous leukemia was confirmed, Jones was referred to specialists at UT Southwestern, who recommended a stem-cell transplant.

"I was told soon after my diagnosis that the curability rate for my leukemia was low without the option of transplant," said Jones. "I tried to stay away from detailed medical literature about my disease — which can often be pessimistic and anxiety-provoking — because it was a frightening thing to know that my life was hinging on one procedure. I also knew that my chances for a successful transplant would depend largely on finding a well-matched donor."

As luck would have it, Jones' 65-year-old sister proved a suitable tissue match.

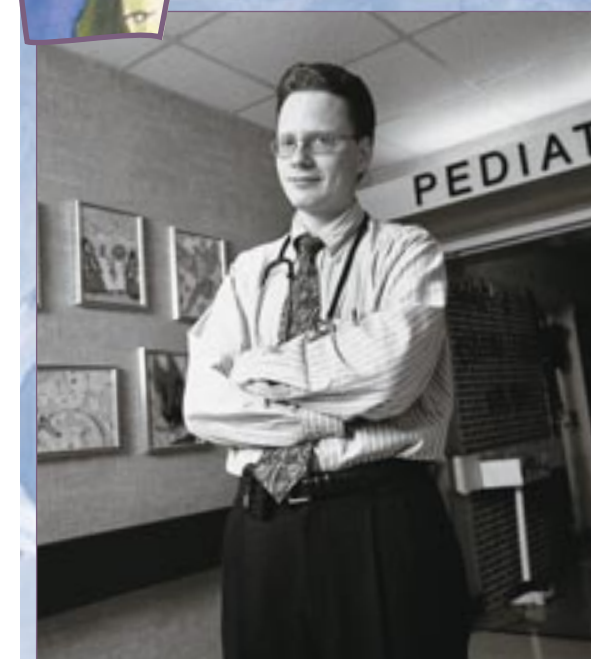
Jones has now been cancer-free for a year. "I really do feel that my sister is a blessing, and I will be eternally grateful for her gift," he said.

Graft-Versus-Host Disease

Despite the success rate of stem-cell transplants, they are not without significant risk. One of the most dangerous complications for allogenic transplant recipients is graft-versus-host disease (GVHD). In this condition the recipient's new immune system — created by the stem cells provided by the donor — attacks the patient's body, treating it as a foreign invader. Symptoms of GVHD, which range from cosmetic (skin rash) to life-threatening (intestinal problems and liver dysfunction), can arise immediately after transplant or develop slowly and linger for months or years.

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Dr. Victor Aquino was the first to conduct a tandem stem-cell transplant for neuroblastoma in North Texas.



Dr. Robert Collins Jr. (left), directs the UT Southwestern Hematopoietic Cell Transplant Program.



Patient Dr. Alphonso Jones received bone marrow from his sister in a transplant performed by Collins.

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—Dr. Robert Collins Jr.

Graft-versus-host disease is one of the chief subjects of transplant research,” said Collins, who holds the Sydney and J.L. Huffines Distinguished Chair in Cancer Research, in Honor of Eugene Frenkel, M.D., and the H. Lloyd and Willye V. Skaggs Professorship in Medical Research. “We still have a lot of work to do, but we are hopeful that current research will help us navigate a better path toward broader applications of stem-cell transplants and more effective ways of turning GVHD around. If we can determine why some patients are more susceptible to the disease, we will be another step forward in making bone marrow transplant an ideal treatment for a multitude of disorders.”

One researcher who is doing just that is Dr. Ellen Vitetta, director of the Cancer Immunobiology Center and holder of the Scheryle Simmons Patigian Distinguished Chair in Cancer Immunobiology.

“Our goal is to find a way to harness the more desirable graft-versus-tumor effect [which occurs when donor cells recognize and attack cancer cells] in the absence of GVHD,” she said. “Through the use of immunotoxins, which kill T-cells that mediate GVHD but spare the T-cells that attack the cancer, we hope to greatly improve the outcome of these transplants. Experiments in the laboratory already have demonstrated that this approach works *ex vivo*. We soon will launch a clinical trial to determine if this works in patients. If it does, it will be a major step forward.”

In the meantime, a new blood transfusion treatment, called photopheresis, is offering hope and new possibilities to patients battling GVHD.

During photopheresis, the patient is connected to a machine that withdraws a quantity of blood in a manner similar to kidney dialysis. The machine separates the blood into red blood cells, white blood cells and plasma. The white blood cells are collected in a bag, and the red cells and plasma are returned to the patient.

“Many of the patients we see have been dealing with GVHD for many years, and their lifestyles have become greatly diminished because of its side effects,” said Dr. Ravindra Sarode, associate professor of pathology and director of the transfusion medicine and coagulation laboratory. “One of modern medicine’s great ironies is that even though something as deadly as leukemia can be defeated through bone marrow transplant, the life-giving cells can turn so violently on their new ‘host.’ Photopheresis can help reverse that effect by giving cells a new way to approach healthy tissue.”

Minitransplants

Led by Collins, researchers at the medical center are evaluating a new “minitransplant” for the treatment of several types of cancer, including leukemia, lymphoma, multiple myeloma, melanoma and kidney cancer.

A minitransplant uses lower, less toxic doses of chemotherapy and/or total body radiation therapy to prepare the patient for an allogenic transplant. This approach eliminates some, but not all, of the patient’s bone marrow (as opposed to traditional chemotherapy and radiation treatments, which destroy it completely). Minitransplants also reduce the number of cancer cells and suppress the patient’s immune system to prevent transplant rejection.

“The idea of a low-toxicity transplant is immensely important on many different fronts,” said Collins. “When bone marrow transplant was developed 35 years ago, there was only one way of doing things. It proved to be salvation for many patients, but the process was, and still is, highly toxic and risky. It’s time to move away from that framework and find a gentler, highly targeted way of performing transplants. We are heading in that direction, but we still have a long, promising way to go.” ❖

For more information on UT Southwestern’s Bone Marrow Transplant Program, please call 214-648-7070 or go to www2.swmed.edu/bmt.

For more information on becoming a donor, contact Carter BloodCare, Dallas: 800-DONATE-4, ext. 8150; www.nmdpdallas.org.

The Future of Bone Marrow Stem-Cell Transplantation

Researchers at UT Southwestern, who have long been committed to finding new ways to combat complications of organ and bone marrow transplantation, continue to uncover the complexities behind the human immune system.

Dr. Michael Bennett, professor of pathology and pediatrics and holder of the A.J. Gill Professorship in Pathology, has spent the past four decades studying natural killer (NK) cells and their behavior in bone marrow transplants.

In healthy people, NK cells target tumor cells and protect the body against a wide variety of infections by targeting “invaders” and delivering a lethal burst of chemicals, killing their targets on contact. Although the NK cell is a biological necessity, its aggressiveness can backfire in transplant patients. Because NK cells recognize donor cells as foreign, they do not hesitate to wage war — often wiping out the trespassers.

T-cells, which are crucial to the body’s immune defense, are responsible for keeping NK cells in check. Functioning in a kind of “yin-yang” partnership, they fight tumors and infection together, explained Bennett. In the absence of T-cells, which are intentionally destroyed before allogenic bone marrow transplants to reduce the risk of graft-versus-host disease (GVHD), the NK cells’ natural instincts take over — leaving the door open for transplant rejection.

“The natural killer cell is a force to be reckoned with,” said Bennett. “It would be impossible for our bodies to fight off infection without it, but its resistance to radiation and other foreign properties poses problems for transplant recipients. I believe, however, these cells can be an extremely powerful tool in achieving the desirable graft-versus-tumor effect, without the threat of GVHD. Once we can learn how to fine-tune the NK cells’ response to foreign cells, we will be well on our way to changing the

outlook and reducing the complications for transplant patients.”

Dr. Robert Ilaria Jr., assistant professor of internal medicine and molecular biology, also has made a career of studying the molecular and cellular culprits in leukemia and solid tumors. His work on the molecular pathophysiology of Bcr/Abl, a protein responsible for a spectrum of leukemic illnesses, has made widely recognized strides in the testing and discovery of antileukemia drugs. Ilaria’s recent research on gleevec, a popular cancer medication, has paved the way for further studies in gleevec-resistant patients with myelogenous leukemia.

“We know that one of the most dangerous causes of relapse in transplant patients is their resistance to drugs that inhibit Bcr/Abl,” said Ilaria. “If we can figure out how and why certain patients randomly mutate the gene, we will take a major step forward in treating patients with diseases like myelogenous leukemia, which is notoriously difficult to control.”

There also is much to suggest that bone marrow stem-cell transplantation may one day reach far beyond the treatment of cancer and blood disorders. Recent published reports on the ability of stem cells to give rise to new human tissue (pluripotency), have brought biomedical research to the edge of a new frontier.

Stem cells have the ability to divide for indefinite periods and “grow” specialized cells, explained Dr. J. Victor Garcia-Martinez, professor of internal medicine and microbiology. For example, blood stem cells can give rise to red blood cells, white blood cells and platelets, and liver stem cells can give rise to the various types of other liver cells.

“What all this means is that there is an amazing amount of untapped potential,” he said. “There is a very real possibility that we one day may find a way to repair organs damaged by disease, such as the heart or liver, by streamlining the stem cell’s unparalleled ability to create.” ❖



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