

Pediatric ALL: Novel Haplo-Identical HSCT Method Leads to Rapid Engraftment, Low Transplant-Related Mortality

BY MARK FUERST

NEW ORLEANS—A novel strategy to choose an alternative source of stem cells for hematopoietic stem cell transplantation (SCT) for children with acute leukemia speeds the process of finding a matching donor, reduces the risk of serious infections after transplant, and also extends survival. The results were reported here at the American Society of Hematology Annual Meeting (*Abstract 157*).

The new approach uses genetic modifications of haplo-identical (i.e., half-matched) stem cells prior to transplant. Transplants of haplo-identical blood-forming stem cells from a child's mother or father may be an effective option for patients in need of a transplant without a fully matched donor, said the study's lead author, Alice Bertaina, MD, of the Department of Pediatric Hematology/Oncology and Transfusion Medicine at Bambino Gesù Children's Hospital in Rome.

"We now have developed a strategy to permit all acute leukemia patients to have a prompt donor. Normally, patients have to wait for months for a match. Now we can find a donor in two weeks. In the past, less than 60 percent of patients survived with a fully matched donor. Now, in a high-risk population, we found three-quarters of patients have a leukemia-free survival with stem cells from only one relative."

Treatment for children with acute leukemia has traditionally relied on hematopoietic stem cells that are matched for most parts of the human leukocyte antigen (HLA) complex. Half of the genes involved in the HLA complex are inherited from each parent, but only about 25 percent of patients have a sibling with the same pattern. The search for a fully matched, unrelated donor is often difficult and lengthy.

"T-cell depleted HLA-haploidentical hematopoietic stem cell transplantation is a suitable option for patients in need of an allograft who lack a HLA-matched donor. Although it offers the advantage of being immediately applicable to virtually all patients, so far, graft manipulation with removal of all T lymphocyte subsets and of natural killer cells has been associated with an increased risk of life-threatening infections, as well as, in some studies, of leukemia recurrence," Bertaina said.

The team tested the effectiveness of manipulating half-matched donor stem cells in the laboratory before transplantation. Magnetic beads were used to

selectively remove the alpha/beta-positive T cells and CD19-positive B cells from the donor graft, since those are more likely to trigger donor cells to attack recipient cells, resulting in graft-versus-host disease (GVHD). At the same time, the process preserved the healthy, mature, immune-active cells—natural killer cells and gamma/delta-positive T cells—that help prevent disease relapse and protect against infection.

Myeloablative Regimen

A myeloablative regimen, containing total body irradiation in about two-thirds of cases, was given to all children, who also received anti-thymocyte globulin at 12 mg/kg over three days. Rituximab at 200 mg/m² was administered the day before the procedure to further prevent lymphoproliferative disorders. No pharmacological GVHD prophylaxis was employed after transplantation.

A total of 50 patients with acute leukemia were treated with genetically engineered stem cells from one of their parents. All children were transplanted in morphological complete remission (CR)—about one-third in first CR, more than half in second CR, and the rest in more advanced CR.

All patients transplanted in first CR had either poor cytogenetic/molecular characteristics or high levels of minimal residual disease at the end of induction therapy.

After nearly three years of follow-up, transplants engrafted in 41 of the 50 patients, for a cumulative relapse rate of 19 percent. Two patients died—meaning that the rate of transplant-related mortality was four percent.

The estimated leukemia-free survival rate was 77 percent for all patients. Among acute lymphoblastic leukemia patients, the leukemia-free survival was about 80 percent, she said.

The cumulative incidence of GVHD was 26 percent, with no severe GVHD. None of the patients developed gut or liver acute GVHD, although 13 had skin-only GVHD of grades I and II. Only two patients developed skin-limited chronic GVHD, she noted.

One month after transplant, follow-up analyses showed that transplanted cells had persisted in the patients and demonstrated potential anti-leukemic activity, which continued to increase over time.

At a news conference at the meeting that highlighted "precision-



ALICE BERTAINA, MD: "This strategy makes it possible for all acute leukemia patients to have a prompt donor. Normally, patients have to wait for months for a match, but now we can find a donor in two weeks."

medicine approaches for hard-to-treat blood disorders," Bertaina said that the results—"which demonstrate that transplantation of selectively modified, half-matched donor stem cells has success rates equivalent to those of a fully matched transplant, preventing GVHD and reducing transplant-related death—help continue to establish the approach as a viable option for patients without a matched donor.

"This has the potential to make this lifesaving treatment more accessible to a much larger population of patients who may not have a perfect donor match," she said.

At her presentation, she explained that a selective graft manipulation results in effective prevention of both acute and chronic GVHD, rapid recovery of neutrophil and platelet counts, and low treatment-related mortality.

"Although the median observation time is still limited, the lack of disease recurrence is encouraging."

Optimize Recovery of Stem Cell Subsets

She added that the strategy could optimize the recovery of stem cell subsets in the early weeks after hematopoietic transplant and maximize immune-mediated viral and leukemia control with an acceptable risk of GVHD.

At a news conference, she noted that it made no difference whether a mother or father was the stem cell donor, although in the past, clinicians had observed an advantage using the mother's cells.

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Livestrong Foundation Launches Competition to Fund Innovative Ventures Geared Toward Improving Survivorship

BY ERIC T. ROSENTHAL

It may sound like a Showtime program or a throwback to a former era's euphemistic name for what had then been a much-stigmatized disease, but the Livestrong Foundation's next big thing—"The Big C Competition"—is something more closely resembling ABC's "Shark Tank."

Livestrong terms the venture, launched on World Cancer Day, a "global social innovation competition designed to improve the lives of people affected by cancer."

What that translates to is a contest open to individuals or teams with ideas they'd like to carry to fruition that would improve the quality of life of cancer patients, survivors, and everyone one else touched by cancer, and benefit from seed funding and mentoring.

Livestrong President and CEO Doug Ulman wasn't available for an interview since he was on a fundraising expedition climbing Mr. Kilimanjaro at the time, so spokesperson Rae Bazzarre explained that the name for the competition was chosen during staff brainstorming sessions that sought to capture people's attention through a term that had been used when talking about a taboo.

"We wanted to say we are talking about cancer—socially, publicly, and in a big bold way," she said, noting that the initiative was new for Livestrong but in line with what the organization considers a history of taking nontraditional approaches to fighting cancer.

Similar types of challenges have been held recently by the Office of the National Coordinator for Health IT ("Crowds Care for Cancer Challenge: Supporting Survivors"); the Knight Foundation (Knight News Challenge); the New York City Economic Development Corporation and New York City Department of Information Technology & Telecommunications (NYC BigApps Competition); and Dell and the University of Texas at Austin (Dell Social Innovation Challenge).



Livestrong's competition is produced in partnership with Verb Inc., a new company specifically focused on such social entrepreneurship competitions. Verb had formerly been an incubator entity that worked exclusively with the University

of Texas and Dell, and this is its first outside project.

Entries will be accepted through May 15, with 20 of the top 150 applicants moving on to a "venture accelerator phase" from July 14 through September 15 where they will team up with cancer survivors and business mentors to help implement the ideas. The plan is to announce the five finalists on September 29, who will then travel to Austin in mid-October during the "Team Livestrong Challenge Austin" to make their presentations.

The grand prize winner will receive \$25,000, and an additional \$115,000 will be disbursed in varying amounts to another 59 ventures.

The overall competition will include approximately 400 judges representing the social innovation industry; entrepreneurs; venture capitalists who could be potential investors; and the cancer community including cancer survivors.

There are five category tracks:

- Rebuilding Financial Health—A Cancer Diagnosis Shouldn't Equal Financial Catastrophe;
- Regaining Emotional Well-Being—Finding a Sense of Security After Cancer;
- Caring for Caregivers—Families, Friends, and Caregivers Are Fighting Cancer Too;
- Improving Access to Quality Care—Helping Cancer Patients Get the Care They Need; and
- Filling the Knowledge Gap—Empowering Patients' Informed Decisions Through Education.

Further information is available at bigc.livestrong.org, and submitted applications can be viewed as they are posted. ☐

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LAURENCE COOPER, MD, noted that in the past, patients often died during the time it took to search for a donor. "We no longer have to search through a massive registry to locate a donor. Often, we can find a donor in the same room as the patient."

"What this does is widen the field of patients who can be transplanted. Presently, we can choose a donor

from one of the parents. We have the advantage of choosing a haplo-identical relative," Bertaina said.

In an interview, the moderator of the news conference, Laurence Cooper, MD, Professor of Pediatrics at the University of Texas MD Anderson Cancer Center, called the approach an example of the "modern age of HLA typing."

"Previously, we used only HLA genetic differences in antigens to choose donors. Now we recognize through this type of work that we can use immune reconstitution of natural killer cells and T cells, and figure out which preferred donor has the ability to stimulate engraftment in the immune system."

Cooper added that the strategy has two advantages: (1) it pushes technology forward in terms of efficacy by pulling out just the stem cells needed; and (2) it speeds finding an appropriate donor. He noted that patients often died during the time it took to search for a donor. "We no longer have to search through a massive registry to locate a donor," he said. "Often, we can find a donor in the same room as the patient." ☐

iPad Extra!

In a video interview on the iPad edition of this issue with OT reporter Dan Keller conducted at the ASH meeting, OT Editorial Board member **Michael Caligiuri, MD**, Director of Ohio



State University Comprehensive Cancer Center and CEO of the James Cancer Hospital and Solove Research Institute, describes the new James Cancer Hospital and discusses some of the innovations in the design and function—for example, including laboratories right on the patient floors. He also talks about the recently approved drug ibrutinib, which was developed in large part at OSU.



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