For Hematologic Malignancies, Cord Blood Ready for Adult Transplant Prime Time

BY PETER GOODWIN

SAN FRANCISCO—For patients requiring allogeneic transplantation for their hematologic malignancies, umbilical cord blood represents an increasingly viable option as a source of stem cells when compared with unrelated bone marrow or peripheral blood, according to two studies presented here at the ASH Annual Meeting.

In the first, efficacy was compared between transplanting progenitor cells derived from cord blood in some patients and from matched unrelated donor bone marrow or peripheral blood in others. In a cohort of 1,240 adult patients with acute myeloid or acute lymphoblastic leukemia the investigators found that cord blood can be nearly as good as matched unrelated donor transplants and preferable when time is short or among ethnic minorities where the donor pool is small.

And in the second study, ex-vivo stem cell expansion proved capable of providing larger cell doses for transplant from limited cord blood samples, which have engrafted more speedily than conventional cord blood cells, are viable after transplantation into human hosts, and can be durable.

Armand Keating, MD, Professor of Medicine and Director of the Division of Hematology at the University of Toronto and Head of the Cell Therapy Program at Princess Margaret Hospital in Toronto, who moderated a news conference covering these developments, said afterwards: "The message from these studies is that cord blood transplantation should be a serious consideration—particularly for patients who belong to minorities, where standard registries are not as representative."

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Study Details

Mary Eapen, MBBS, MS, Associate Scientific Director of Medical College of Wisconsin, reported the first study of adults over age 16 with acute leukemia who received their allogeneic progenitor

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that the time to a complete cytogenetic response (CCyR) was not a concern and advised clinicians not to switch to a second-generation TKI too quickly.

Patients in the IRIS trial with a late complete cytogenetic response had similar survival times at six months, he noted. "My advice is not to switch too early to a second-generation TKI. A minority of patients, between seven and 10 percent, achieve CCyR after 18 months, which is the current time listed in guidelines. It might be more reasonable to wait until 24 months, since some patients may take longer to achieve CCyR."

> "Imatinib is a good treatment for CML. But we are not happy with what we have. A 70% optimum response is a good outcome, but not good enough."

Italian Study

The third study, conducted by the Gruppo Italiano Malattie Ematologiche dell'Adulto and reported by Gianantonio Rosti, MD, of the Institute of Hematology Seragnoli at the University of Bologna, is an ongoing, open-label, single-stage, multicenter Phase II clinical trial, designed to evaluate the therapeutic efficacy and safety of nilotinib at 800 mg a day as a first-line treatment. The trial has to date enrolled 73 patients with newly diagnosed Ph+ CML in early chronic-phase disease.

Dr. Rosti reported that after six months of treatment, 97% of patients achieved a complete cytogenetic response, and 66% had a major molecular response at six months. The percentage of patients achieving this level of response rapidly increased after one month of treatment. The responses were similar for older and younger patients, showing that older patients can tolerate full doses, he noted.

Adverse reactions were manageable with dose adaptations, he said. Most adverse events were Grade 1. No patient had peripheral edema of more than 4%, and the incidence of any Grade 2 or 3 nonhematologic adverse events decreased considerably between the first to third months and the fourth to sixth months.

"Only 4% of patients had neutropenia and 3% of patients had thrombocytopenia, which is low in respect to other TKIs, particularly imatinib," he said.

The main reason 40% of patients were not able to take the full dose of nilotinib were increases in amylase levels. Seven patients received less than 400 mg daily, but they responded and achieved a complete cytogenetic response; and five of these seven patients had a major molecular response.

Summing Up

Summing up, Dr. Rosti said, "This high-dose intensity treatment led to results that were independent of age. The adverse events recorded so far are mainly of Grade 1 or 2; and the response to nilotinib seems durable. Still, we need longer follow-up to evaluate the effects of these early results on the long-term outcome."

When asked during the question-and-answer session when he would start upfront second-generation TKI therapy for CML patients, Dr. Rosti responded: "From the heart, I would start tomorrow. From the brain, in a couple of years."

When GIANANTONIO ROSTI, MD, was asked when he would start upfront second-generation TKI therapy for CML patients, he responded: "From the heart, I would start tomorrow. From the brain, in a couple of years."

And don't forget allogeneic stem cell transplantation (ASCT) for patients who do not have an excellent early response to imatinib, Dr. Larson said: "ASCT needs to be considered early on if a patient has difficulty with imatinib. If you see evidence of resistance to imatinib and are thinking of a switch to a second-generation TKI, you might consider ASCT.

"The durability of response to second-generation TKIs has not been established yet. Treatment is disease-phase specific—chronic-phase CML patients who switch to a second-generation TKI do better than advanced-phase patients."

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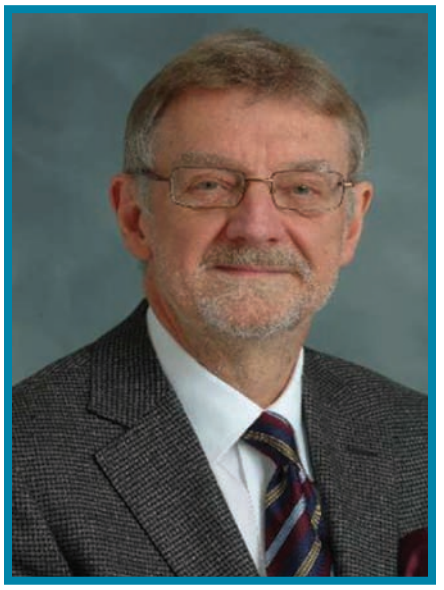
cells from donated umbilical cord blood, comparing their outcomes with those of patients who received transplants from unrelated bone marrow or peripheral blood sources.



ARMAND KEATING, MD: "The message from these studies is that cord blood transplantation should be a serious consideration—particularly for patients who belong to minorities, where standard registries, are not as representative."

"In the past there were concerns about delays in hematologic recovery, and toxicity due to delayed immune recovery. But it is increasingly appearing that the outcomes of mismatched cord blood are similar to those of closely matched unrelated marrow or peripheral blood grafts."

Bone marrow and peripheral blood-derived transplants were matched according to the most recent and stringent "allele level" tissue-typing criteria—requiring matches at eight out of eight alleles for (human leukocyte antigen) HLA-A, -B, -C and -DRB1 loci in order to be classed as fully matching. Grafts were classed as "mismatched" if they had only seven of eight alleles matching.

Most of the cord blood transplant samples were mismatched for two out of six alleles, but such cells are considered to be immunologically immature and therefore more tolerant to mismatching. Each unit contained the standard minimum dose of $2.5x10^7$ nucleated cells per kilo.

Neutrophil recovery, transplant-related mortality, chronic graft-vs-host disease (GVHD), and overall survival were all assessed, and there was only a relatively small spread between outcomes between each of the donor sources. Two-year overall survival with cord blood was—at 35%—(unsurprisingly) lower than with matched bone marrow (48%) or matched peripheral blood (45%)— but almost as good as mismatched bone marrow (38%) and mismatched peripheral blood (36%).

Only 25% of cord blood graft recipients had GVHD, compared with 55% receiving peripheral blood cells. Neutrophil recovery was slower with cord blood (back to 79% at 50 days) compared with matched peripheral blood cell recipients (96% recovery at 50 days).

Transplant-related mortality (at 24 months) was 11% worse with cord blood cells (at 41%) than with cells from the best performing source—i.e., matched bone marrow (26%).

Dr. Eapen noted that matched donors are hard to find and that this can take time, during which a patient may die. The difference in outcome between using cells from cord blood compared with a 1/8 allele mismatched peripheral blood or bone marrow graft is very small and justifies going ahead with cord blood for patients for whom an 8/8 match cannot be found, especially among ethnic minorities for whom the hunt for a matched donor could take too long or may be fruitless, she said.

"Your survival rate was best if you received a matched unrelated donor bone marrow or peripheral blood graft. However, if you look at the probability of finding such a donor: it's about 50% for Caucasians, and very low for African-Americans, at 17%."

But Dr. Eapen acknowledged that cord blood patients "have difficulty getting the graft in"—which explains, she said, why the rates of transplant-related complication and mortality are high. Still, these occur mostly within the first year, beyond which the outlook for cord-blood transplant recipients is good.

When asked for this article what her formula is for deciding how to advise patients about which type of transplant to go for, she said: "If you have an eight-out-of-eight donor, and you have the luxury of waiting two and a half to three months to work that donor out, by all means transplant using marrow or peripheral blood—because you cannot decide who's going to survive the initial period, and who will not. However, if you don't have the luxury of waiting, or you don't have a matched unrelated donor, then go ahead and do a cord blood transplant—don't wait!"

"There has been significant persistence of in-vivo engraftment from our expanded cells, suggesting that we do retain long-term repopulating ability, and in one patient it lasted up to 300 days."

And Dr. Keating's verdict—that there are good reasons for additional impetus for the increased use of cord blood transplantation: "In the past," he said, "there were concerns about delays in hematologic recovery, and toxicity due to delayed immune recovery. But it is increasingly appearing that the outcomes of mismatched cord blood are similar to those of closely matched unrelated marrow or peripheral blood grafts."

Ex-Vivo Stem Cell Expansion Study

The impetus toward using cord blood might grow still further in the not-too-distant future if developments reported with ex-vivo expansion of progenitor cells from cord blood fulfill the promise of an early study reported at the ASH meeting, which was featured in the same news conference.

MARY EAPEN, MBBS, MS: "If you have an eight-out-of-eight donor, and you have the luxury of waiting two and a half to three months to work that donor out, by all means transplant using marrow or peripheral blood—because you cannot decide who's going to survive the initial period, and who will not. However, if you don't have the luxury of waiting, or you don't have a matched unrelated donor, then go ahead and do a cord blood transplant—don't wait!"

Colleen Delaney, MD, MSc, Director of the Cord Blood Transplant Program and Assistant Professor of Pediatrics at the University of Washington, Fred Hutchinson Cancer Research Center, described how her group observed rapid myeloid reconstitution in patients who received CD34 cord blood progenitor cells amplified in numbers by a method known as notch-mediated ex-vivo expansion.

There were no toxicities, and in some cases the cells persisted in vivo, suggesting a long-term repopulating potential.

Six patients each received two separate units of cord blood—one unit was unprocessed (giving all patients "standard therapy"), and the second was expanded and had T-cells removed.

Expansion was viewed as a means of increasing the dose of stem cells from cord blood to provide the quantities needed for transplantation into adults, and reducing the risk of transplant-related mortality by avoiding delays in neutrophil and platelet recovery, Dr. Delaney explained in an interview.

"We were able to show—first in the murine system—that if you manipulated the notch-signaling pathway in primary stem cells, that this resulted in multi-log increases in a stem cell population that translated in vivo in transplants. We wanted to look at whether we could activate endogenous notch signaling—harnessing the cell's own signaling—which would then

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AML: Androgens in Post-Remission Induction Improves Outcome in Elderly Patients

BY ROBERT H. CARLSON

SAN FRANCISCO—Researchers in the multicenter Phase III randomized open-label trial by the French GOELAMS (Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang) group report that adding androgens to post-remission induction therapy is associated with an improved outcome in elderly patients with de novo acute myelogenous leukemia (AML).

The improved outcome seen in the GOELAMS SA-2002 trial occurred especially in patients achieving complete remission or remaining in remission for at least one year, the authors reported, and also was observed in males and in patients with low proliferative disease.

> Norethandrolone was associated with an improved outcome both in terms of survival and relapse incidence, mainly in patients with low-proliferative AMLs.

"Norethandrolone was associated with an improved outcome both in terms of survival and relapse incidence, mainly in patients with low-proliferative AMLs," said principal investigator Arnaud Pigneux, MD, PhD, a hematologist/oncologist at University Hospital Bordeaux. He said the beneficial effects were delayed in time and had an impact on outcomes starting the first year after treatment.

And males might benefit more from this treatment than females, he said.

The 330 patients in the study received the ICL induction protocol (idarubicin at 8 mg/m^2 on Days 1-5, cytarabine at 100 mg/m^2 on Days 1-7, and lomustine at 200 mg/m^2 on Day 1).

Patients in complete or partial remission then received maintenance therapy of six courses of idarubicin at 8 mg/m^2 on Day 1, and cytarabine at 100 mg/m^2 on Days 1-5, once every three months. A continuous regimen of methotrexate and 6-mercaptopurine was given between the re-induction courses.

Patients were randomly assigned at diagnosis to receive norethandrolone at 10 to 20 mg per day, according to body weight, or assigned to the control arm.

Androgen was started after recovery from aplasia, between the 20th and 30th days following induction chemotherapy, and was to be continued during two years of maintenance therapy.

Patients, median age of 70, were treated between June 2002 and January 2005. Patients with acute promyelocytic leukemia or prostate-specific antigen (PSA) levels above 4 ng/mL were not included.

Median follow-up from induction chemotherapy was 1.1 years for the overall group, and 3.6 years for patients alive at last report.

> The beneficial effects were delayed in time and had an impact on outcomes starting the first year after treatment.

Complete remission rates were similar at Day 80: 79% for patients receiving norethandrolone and 83% for controls.

But univariate analysis of the 250 patients who achieved complete or partial remission following ICL induction showed a five-year overall survival rate in favor of norethandrolone: 35% vs 25% for controls.

There was also a similarity in overall survival at five years for patients with white blood counts higher than 4 G/L—approximately 25% for each study arm. But for patients with WBC counts lower than that, the five-year survival rate was 48% for the norethandrolone group vs 23% for controls.

In an analysis of the outcomes by patient age at inclusion, the five-year overall survival rates for patients age 65 or older again were similar for the two groups, at approximately 40%.

But for patients younger than 65, the five-year overall survival rates were 34% for the androgen group vs 16% for controls.

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> "Androgens have previously been demonstrated to be useful in the treatment of aplastic anemia, which led them to be tested with variable success in AML, and more recently, encouraging data obtained in vitro have revived their potential interest as maintenance drugs in conjunction with low dose chemotherapy."

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turn on signaling in the recipient stem cell."

During the 16-day expansion culture period prior to transplantation there was a median 165-fold increase in the number of stem cells (range of 41- to 470-fold). While this was going on, the patients received the ablative preparative regimen; and then on Day 0, they received the unmanipulated transplant with its full complement of T-cells as a normal donor stem cell transplant.

Four hours later patients received their expanded cells, with the primary aim of trying to bridge the period of neutropenia during immune reconstitution—not as a long-term repopulating cell (since they were T-cell depleted). Significantly greater numbers of stem cells were achieved—up to 13 million CD 34 positive stem cells per kilo per patient from a single unit of cord blood, compared with a usual target of only 150,000 per kilo.

"In two patients there has been significant persistence of in-vivo engraftment from our expanded cells, suggesting that we do retain long-term repopulating ability," Dr. Delaney said. "In one patient it lasted up to 300 days. And our current patient—six months post-transplant—is still a complete 50-50 chimera."

Still, she noted, the technique is far from being at a stage where it could become routine.

And Dr. Keating noted that "the dichotomy" that currently exists between public cord blood banks and private ones could be overcome. "I think it may be a while before we can really be definitive about this—but this has been long in coming, and I think this has been an important step," he said.

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Peter Goodwin

COLLEEN DELANEY, MD, MSc: "We wanted to look at whether we could activate endogenous notch signaling—harnessing the cell's own signaling—which would then turn on signaling in the recipient stem cell."