Stem Cell Transplantation: Current Research Directions in Leukemia

Steven Devine, MD
Associate Professor of Medicine
Director, Blood and Marrow Transplant Program
Ohio State University School of Medicine
Columbus, Ohio

H&O Could you discuss the interest in using prognostic categories to define candidacy for stem cell transplantation?

SD In acute myeloid leukemia (AML), the current focus is on trying to better define the types of patients who are most appropriate for transplantation in first remission through the use of prognostic categories such as cytogenetics and even molecular genetics. Researchers hope to use cytogenetic categories to define risk of relapse, which are classically broken down into good-, intermediate-, and poor-risk. Many transplant centers are now choosing to transplant patients in first remission based on whether they have an intermediate- or poor-risk, and not transplanting those in the good-risk category. Controversy exists regarding the intermediate-risk category, because there remains a significant risk of treatment-related mortality for patients in first remission. If clinicians could better understand who is at highest risk of relapse, they would have a better ability to judge whether the risk of treatment-related mortality is acceptable. Current research is focusing on trying to better define the patient's risk of relapse at the time of transplant. See Table 1 for a list of selected phase II and III trials in the setting of stem cell transplantation.

H&O What methods are being researched to reduce treatment-related mortality?

SD One of the main complications of transplantation, which has been present for the last 30 years, is graft-versus-host disease (GVHD). GVHD still is the major cause of death, other than relapse, in patients being transplanted. In patients who are under the age of 60, there have been two main approaches to preventing GVHD. The first is to use so-called pharmacologic prophylaxis against GVHD. There are currently studies looking at newer agents to try to prevent GVHD; one these agents is rapamycin, which is currently in randomized trials in comparison to conventional agents based on encouraging data from Dana-Farber Cancer Center. Another approach, which is completely different from pharmacologic prophylaxis, is to remove the T cells from the graft, known as T-cell depletion. There is currently a National Institutes of Health–sponsored national multicenter phase II trial assessing a method of T-cell depletion called positive selection, whereby if the T cells are removed, the patients do not require pharmacologic intervention to prevent GVHD. The current trial uses a magnetic bead method for selecting out the stem cells only, forming a purified graft. If the patient receives a more purified graft, he or she does not receive nearly as many T cells and as a result does not require pharmacologic therapy because the risk of GVHD is greatly diminished. There is some concern, though, that because the patient is not receiving T cells, susceptibility to infection or relapse may increase. The ongoing national trial in patients in first remission will hint whether T-cell depletion may improve overall outcomes.

H&O Do molecular markers exist to predict a risk of GVHD?

SD Not currently. The likelihood of GVHD can be predicted based the degree of match and recipient age, but there are no molecular markers that indicate early in the transplant course whether GVHD will occur. There are some research groups that have tried to use various proteomic techniques involving either the serum or the urine to develop a proteomic signature that might then predict whether GVHD will occur a week or two after the initiation of the transplant course. This method is still very investigational. There are not any reliable markers in the blood or other tissues to predict GHVD, and is an area that researchers are still pursuing.

H&O What other research is currently ongoing in the setting of stem cell transplantation for AML patients?

SD AML is a disease of older patients, with a median age at diagnosis of 68 years, yet traditionally, the average

Table 1. Selected Phase II and III Trials of Stem Cell Transplantation

Trial Identifier	Title
Bone and Marrow Transplant Clinical Trials Network	
Protocol 0201	A Phase III Randomized Multicenter Trial Comparing G-CSF Mobilized Peripheral Blood Stem Cell with Marrow Transplantation from HLA Compatible Unrelated Donors
Protocol 0303	A Single Arm, Multicenter Phase II Trial of Transplants of HLA Matched, CD34+ Enriched, T cell Depleted Peripheral Blood Stem Cells Isolated by the CliniMACS System in the Treatment of Patients with AML in First or Second Morphologic Complete Remission
Protocol 0401	Phase III Rituxan/BEAM vs. Bexxar/BEAM with Autologous Hematopoietic Stem Cell Transplantation (ASCT) for Persistent or Relapsed Chemotherapy Sensitive Diffuse Large B-Cell Non Hodgkin's Lymphoma
Protocol 0402	A Phase III Randomized, Multicenter Trial Comparing Sirolimus/Tacrolimus with Tacrolimus/Methotrexate as GVHD Prophylaxis After HLA Matched, Related Peripheral Blood Stem Cell Transplantation
Protocol 0403	A Phase III, Randomized Double Blind, Placebo Controlled Trial of Soluble Tumor Necrosis Factor Receptor: Enbrel (Etanercept) for the Treatment of Acute Non Infectious Pulmonary Dysfunction (Idiopathic Pneumonia Syndrome) Following Allogeneic Stem Cell Transplantation
Protocol 0501	Multicenter, Open Label, Randomized Trial Comparing Single Versus Double Umbilical Cord Blood (UCB) Transplantation in Pediatric Patients with Leukemia and Myelodysplasia
Protocol 0502	A Phase II Study of Allogeneic Transplant for Older Patients with AML in First Morphologic Complete Remission using a Non myeloblative Preparative Regimen
National Cancer Institute in Collaboration With Other Groups	
CALGB-C10001	Phase II Study of Sequential Chemotherapy, Imatinib Mesylate, and Peripheral Blood Stem Cell Transplantation in Patients With Newly Diagnosed Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia
COG-ASCT0431	Phase III Randomized Study of Graft-Versus-Host Disease Prophylaxis Comprising Tacrolimus and Methotrexate With or Without Sirolimus in Pediatric Patients With Intermediate-Risk or High-Risk Acute Lymphoblastic Leukemia in Second Complete Remission Undergoing Allogeneic Hematopoietic Stem Cell Transplantation
CALGB-100103	Phase II Study of a Nonmyeloablative Preparative Regimen Comprising Fludarabine and Busulfan Followed By Allogeneic Stem Cell Transplantation in Older Patients With Acute Myeloid Leukemia in First Morphologic Complete Remission
ECOG-1900	Phase III Randomized Study of Daunorubicin and Cytarabine With or Without Gemtuzumab Ozogamicin Followed By Autologous Hematopoietic Stem Cell Transplantation in Patients With Acute Myeloid Leukemia
FHCRC-1581.00	Phase II Study of a Non-Myeloablative Conditioning Regimen Comprising Fludarabine and Total Body Irradiation Followed By Allogeneic Peripheral Blood Stem Cell Transplantation in Patients With Imatinib Mesylate-Responsive Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia or Chronic Myelogenous Leukemia in Blast Crisis

age of transplant recipients is the fourth or fifth decade of life. As such, we have been transplanting a skewed population of patients rather than those who actually are most likely to have the disease. As a result, another area of deep interest has been to define new methods permitting transplantation in older patients. The problem in the past has been that the conditioning regimens used to treat the patients have been too stringent, resulting in toxicities far too great for older patients, who might have other comorbidities, such as diabetes or heart disease. Furthermore, as the recipients are older, the risk for GVHD increases somewhat. A major area of research has been to define the role of so-called reduced-intensity conditioning (RIC) or nonmyeloablative stem cell transplantation. RIC regimens are able to suppress the recipient's immune system, so he or she can accept the graft, but if these regimens are much less intensive and do not cause as much damage to the patient's normal tissue as conventional regimens. RIC relies more heavily on the donor graft to exert a graft-versus-leukemia effect than myeloablative conditioning. The concern with RIC is that there might be a higher risk of relapse because the patient is not receiving strong chemotherapy to eradicate any residual leukemia. There is currently a high-priority national multicenter trial examining the role of RIC in patients 60–74 years of age who have AML in first remission.

Furthermore, groups are attempting to stimulate immunity against leukemias based on the expression of

certain tumor antigens on leukemia cells which may serve as targets. In this research, T cells are cultivated from the donor, which might be specific to certain tumor-associated proteins that are not expressed on normal cells. This approach is investigational and is limited to single centers with experience in this difficult method. This approach may become more popular, but it is unlikely that targeting just one specific protein is going to be enough to cure the most patients with AML.

Another approach under investigation is attempts to stimulate natural killer cells. Our group at Ohio State University School of Medicine and others are very interested in this approach. Patients who do not have well-matched donors, either sibling or well-matched unrelated donors, are instead grafted using mismatched relatives, because interestingly enough, those mismatched donors may have natural killer cells, which are part of the donor's immune system, that are more reactive against the patient's leukemia. This approach might be a way of reducing the risk of relapse, especially in patients without a well-matched sibling or unrelated donor. These mismatched related transplants are called haploidentical transplants. The problem with haploidentical transplants is that they tend to be associated with more complications and a higher risk of GVHD, graft rejection, and infection. There are various ongoing trials designed to make haploidentical trials more feasible and safer.

H&O What is the status of research with stem cell transplantation in children?

SD In children, a major area of research has been to define the role of umbilical cord-blood grafts in transplantation. The majority of children do not have a matched sibling donor, and the choice is to use an volunteer unrelated donor or an unrelated cord-blood graft that has been previously banked. Recent data have shown that these cord-blood grafts are just as effective and safe as using volunteer donors' marrow or peripheral blood. Cord-blood banks can be searched to find a compatible graft, and cord blood seems to be associated with less GVHD than volunteer marrow or blood. It is possible to match less well with a graft from cord blood versus a living donor. The cord-blood grafts can effectively produce hematopoietic cells and promote long-term patient survival. It is not completely known why mismatched cord blood grafts are effective, but it is thought that the immune system of the cord blood is less mature and so less aggressive against the recipient. The other advantage of cord blood is that because it is already banked, so it is available quickly, typically within 1–2 weeks. Patients requiring transplantation quickly may benefit more from a cord-blood graft, as there are greater logistical hurdles to identifying and procuring cells from a living volunteer donor. These searches can often take months. Thus, attempts to refine cord-blood transplantation has become an intense area of clinical research in children. One reason cord-blood grafts have been studied more in children has to do with the fact that they contain fewer total stem cells compared to marrow or mobilized blood, and so they have been more effective in physically smaller, hence younger, recipients. In adults, researchers have been looking at trying to increase the stem cell dose by giving two rather than just one cord-blood graft, so-called tandem cord-blood transplants.

H&O What research is ongoing regarding the donor side of stem cell transplantation?

SD An important question has been asked, and answered, regarding whether bone marrow or mobilized blood is the better source of stem cells. If a patient has a sibling, the outcomes seem to be slightly more optimal overall if mobilized blood is used. Virtually all centers are using mobilized peripheral blood if a related donor is available. If a related donor is not available but instead an unrelated donor must be used, there is currently an NIH sponsored national randomized clinical trial comparing bone marrow from a volunteer to mobilized blood from a volunteer. Both the patient and the donor must agree to be randomized. The trial attempts to determine whether mobilized peripheral blood is superior to bone marrow in the setting of an unrelated donor transplant. The problem with mobilized peripheral blood is that it requires administering to the donor injections of a drug for 5 days before collection of the stem cells. Sometimes collection takes place over 2 days. Our group was involved in research with a novel drug called AMD3100 that mobilizes stem cells just 4 hours after being injected. Standard methods use cytokines, which are hormones that stimulate the blood cell to go into cycle, whereas AMD3100 is a chemokine antagonist. This agent antagonizes a key molecule called CXCR4, which tethers the stem cells to the bone marrow microenvironment, and thus causes the stem cells to migrate from the bone marrow into the bloodstream. AMD3100 is very interesting because the donors receive an injection at 8:00am and stem cells are collected at noon the same day. There are few, if any, side effects associated with this agent. We treated 25 donors with this drug and transplanted 20 patients with the stem cells, which engrafted at a rate of 100%. If we could optimize that procedure, AMD3100 may allow for collection of stem cells from donors in 1 or 2 days rather than 5 days.

H&O Could you discuss research into stem cell transplantation in chronic leukemia settings?

SD In chronic lymphocytic leukemia (CLL), many patients do not require treatment or the can be treated successfully with conventional therapies. However, there is a subset of patients who have a much higher risk of relapsing once they need treatment, defined by cyto-

genetic abnormalities—patients with 17p deletions and chromosome 11q abnormalities. There is now interest in performing RIC stem cell transplantation in these patients in first remission to try to reduce the risk of relapse. The other group of CLL patients considered candidates for transplantation are those who have been treated with a fludarabine-based regimens but subsequently relapsed. There have been a number of groups that have reported encouraging results in CLL with the use of RIC allogeneic stem cell transplantation. The disease is never felt to be curable, but there is some interest in whether these transplants will lead to very prolonged remissions in these patients.

Finally, the disease that used to be the most common indication for transplantation, chronic myelogenous leukemia (CML), is now treated successfully with imatinib (Gleevec, Novartis) in most patients. However, patients who develop resistance to imatinib are often treated with a so-called second-generation tyrosine kinase inhibitor such as dasatinib (Sprycel, Bristol-Myers Squibb) or nilotinib (Novartis). If these patients have a response, they are considered for transplantation, provided a donor can be found.

Suggested Readings

Brown JR, Kim HT, Li S, et al. Predictors of improved progression-free survival after nonmyeloablative allogeneic stem cell transplantation for advanced chronic lymphocytic leukemia. *Biol Blood Marrow Transplant*. 2006;12:1056-1064.

Cashen AF, Lazarus HM, Devine SM. Mobilizing stem cells from normal donors: is it possible to improve upon G-CSF? *Bone Marrow Transplant*. 2007;39:577-588.

Cornelissen JJ, van Putten WLJ, Verdonck LF, et al. Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? *Blood*. 2007;109:3658-3666.

Eapen M, Rubinstein P, Zhang M-J, et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. *Lancet.* 2007;369:1947-1954.

Grever MR, Lucas DM, Dewald GW, et al. Comprehensive assessment of genetic and molecular features predicting outcome in patients with chronic lymphocytic leukemia: results from the US intergroup phase III trial E2997. *J Clin Oncol.* 2007;25:799-804.

Hegenbart U, Niederwieser D, Sandmaier BM, et al. Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. *J Clin Oncol.* 2006;24:444-453.

Niederwieser D, Gentilini C, Hegenbart U, et al. Allogeneic hematopoietic cell transplantation (HCT) following reduced-intensity conditioning in patients with acute leukemias. *Crit Rev Oncol Hematol*. 2005;56:275-281.

Rocha V, Gluckman E. Outcomes of transplantation in children with acute leukaemia. *Lancet.* 2007;369:1906-1908.

Rocha V, Labopin M, Sanz G, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N Engl J Med.* 2004;351:2276-2285.

Stem Cell Trialists' Collaborative Group. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. *J Clin Oncol*. 2005;23:5074-5087.