ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Advances in CML: The Role of Allogeneic Hematopoietic Stem Cell Transplantation

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H&O What is the role of stem cell transplantation in chronic myelogenous leukemia (CML) patients?

BA There have been many developments in the field of blood and marrow stem cell transplantation in the last 5–10 years, including major improvements in safety and the ability to improve nonlethal complications. A stem cell transplant for a patient with leukemia or lymphoma should no longer be considered a last-ditch effort, but it should be an integrated part of an overall program that is aimed at preventing the patient from succumbing to the disease. When stem cell transplantation is used earlier rather than later, it greatly improves the patient's chances of survival. In the case of CML, however, care should be taken to first exclude patients who can have long-term remission of their disease without having to resort to a stem cell transplant.

H&O Which types of CML patients are likely to benefit from allogeneic hematopoietic stem cell transplantation?

BA The treatment approach to CML has changed substantially in the past decade with the introduction of imatinib (Gleevec, Novartis) and subsequent development of even more potent and highly specific tyrosine kinase inhibitors (TKIs). At M.D. Anderson Cancer Center, we reserve allogeneic hematopoietic stem cell transplantation for CML patients who have failed TKI–based therapy. By failing, we mean that the patients progressed after initial response to first-line TKI-based therapy and then did not achieve complete response, or they progressed after initial complete response to second-line TKI-therapy. If patients achieve molecular remission with TKI-based therapy, the remission may be long-term. Over the long-term, this approach may be more expensive, but it is medically less risky and therefore remains our preferred route. There should be a fairly quick response to TKI treatment—first hematologic, then cytogenetic. Ultimately, there will be a molecular disappearance of the disease. CML patients who do not respond to TKI-based therapy can move into an accelerated and subsequently terminal phase of the disease, during which they will die from progressive leukemia.

H&O Could you describe the use of reduced-intensity conditioning regimens?

BA Many programs are investigating reduced-intensity–type regimens, but I am not a strong supporter of this approach for patients with advanced disease. The concept dates back to the 1980s and 1990s, when there was growing frustration with the myeloablative or full-dose regimens that were used. The treatment complications of these regimens were associated with an early mortality rate of between 15% and 35% in the first 100 days after transplant, depending on which program was used. Therefore, reduced-intensity conditioning regimens were

introduced to reduce complications and mortality. The aim of these regimens was not to reduce the leukemia, but to achieve enough immunosuppression to get the graft established. It was hoped that once that was accomplished, a graft-versus-leukemia effect would be exerted by the allogeneic graft, and the rest of the leukemia would disappear. Sometimes that works, but often it does not work very well—you get the graft in, but the leukemia survives, too.

One of the things we learned in the past 10 years is that full-dose conditioning can be safely administered with a new approach, primarily based on intravenous (IV) busulfan (Busulfex, Otsuka America Pharmaceutical) and nucleoside analogs, such as fludarabine or clofarabine (Clolar, Genzyme). We refer to this approach as reduced-toxicity conditioning therapy. It has reduced the 100-day treatment-related mortality to 2–3% from previous rates in excess of 30% and reduced 1-year treatment-related mortality—which in the 1990s was 40–50%—down to 10–15%. Most of the adverse reactions are now immune complications and infections, the same as what is experienced with reduced-intensity conditioning therapy.

A reduced-intensity program may be preferred in specific subgroups of patients, such as older patients (in their late 60s and 70s) and patients who have other comorbid problems, such as long-standing diabetes mellitus and heart failure. These patients might benefit from a reduced-toxicity program in addition to a reduction in dosing. The picture is getting more varied; it is not just "full-dose" versus "half-dose," as was the question in the late 1990s.

H&O What are the survival rates of patients who undergo allogeneic hematopoietic stem cell transplantation?

BA At M.D. Anderson, the reduced-toxicity approach with full-dose conditioning and a well-matched donor has been associated with a disease-free survival rate at 3–5 years of 80–85% in patients with early-stage leukemia. That rate is for young patients, up to age 40. If we include patients up to age 65, that rate is 70–75%. These results are significantly better than what they were 10 years ago.

H&O What are the available conditioning regimens?

BA There have been new developments with the reduced-intensity regimens. Reduced-intensity conditioning therapy may be beneficial in certain subgroups of patients, such as some lymphoma patients with indolent, slowly progressing disease. Reduced-intensity regimens might also be appropriate for patients in whom there is time to build a new immune system that can fight residual disease. In these patients, the immune system has time to start killing off remaining lymphoma cells, even if the majority of these cells were not eradicated with the upfront chemotherapy. This is an area of active investigation. A reduced-intensity approach might also be appropriate for certain patients who do not have malignant disease but have conditions such as aplastic anemia, myelofibrosis, and myeloproliferative diseases that are distantly related to leukemia but not considered malignant per se.

It should be noted that CML patients with previously TKI-unresponsive disease may, after a stem cell transplant, either enter a molecular remission and have no further need for medical intervention for their leukemia, or—if they have molecular evidence of remaining leukemia—they may become sensitive to TKI-based therapy such that a combination of stem cell transplant with post-transplant TKI-maintenance therapy may still accomplish long-term remission and eradicate all clinical signs of leukemia.

With the high-dose programs, there are 3 different types of conditioning. First, there are those based around total body radiation. This approach was started in the 1960s at the Fred Hutchinson Cancer Research Center in Seattle. Today, it is still favored by many groups. Second, there are regimens comprising a double alkylating agent/double DNA damaging agent, exemplified by busulfan with cyclophosphamide. Third, there are newer regimens developed at M.D. Anderson together with a group in Calgary, under Dr. James A. Russell, based on IV busulfan as a DNA-damaging agent combined with one or more nucleoside analogs—that is, IV busulfan with either fludarabine or clofarabine, or a combination of the two. Low-dose antithymocyte-globulin is added to minimize the risk of immune complications in the post-transplant period. With this approach, we have seen dramatically improved safety, as alluded to above, yet without any appreciable loss of the antitumor effect.

H&O What are the implications of CIGNA Health Plan's recent approval of IV busulfan for its formulary?

BA I hope the significance will be that IV busulfan-based pretransplant chemotherapy is recognized more as the basis for standardized pretransplant conditioning therapy. With a series of publications using IV busulfan with fludarabine over the past few years from several different groups, this approach could be recognized as the new standard in stem cell transplantation. It should get even wider acceptance now that a major insurance carrier, like CIGNA has endorsed the use of IV busulfan as a suitable, possibly preferred, backbone for pretransplant conditioning therapy.

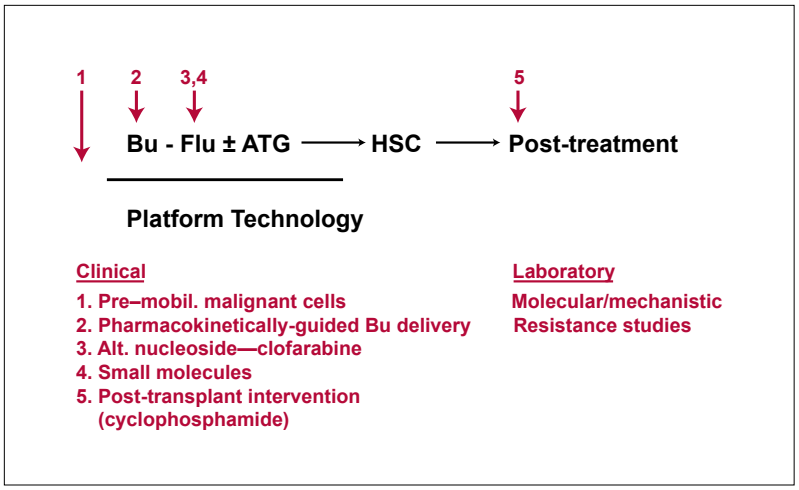

Figure 1. This conditioning platform describes the basic pretransplant chemotherapy regimen. The numbers indicate possible new approaches that can be investigated.

ATG=antithymocyte-globulin; Bu=intravenous busulfan; Flu=fludarabine; HSC=hematopoietic stem cell.

Adapted from *Biology of Blood and Marrow Transplantation,* volume 15, issue 5, Ciurea SO, Andersson BS. Busulfan in hematopoietic stem cell transplantation. Pages 523-536. Copyright 2009, with permission from the American Society for Blood and Marrow Transplantation.

H&O Do you anticipate any advances in the use of allogeneic hematopoietic stem cell transplantation?

BA We anticipate continued rapid advances in several areas. The contribution of the group at M.D. Anderson has been to provide the transplant community with what we refer to as a pretransplant conditioning "platform" (Figure 1). This platform is based on the use of IV busulfan and a nucleoside analog. The prototype nucleoside analog is fludarabine. Depending on the type of donor and how well-matched the donor is, fludarabine is administered with or without the addition of low-dose rabbit-antilymphocyte globulin to decrease the risk for post-transplant immune complications, or graft-versus-host disease.

We consider this approach to be a platform for several reasons. First, as I mentioned, we find it to be very safe, with significant reductions in mortality from treatment-related complications. Another important factor with the busulfan/fludarabine regimen is that all the associated toxic effects have more or less healed after 6 weeks. As soon as the graft is functioning, at 3–4 weeks, other treatments can be added if indicated. A comparison with other regimens, such as radiation-based programs, will show that if additional (chemo-) therapy is needed to treat recurrent leukemia within the next 6 months, the body responds poorly, because of the residual toxicity. This toxicity is not obvious, however, until the patient receives additional chemotherapy.

This benefit is important. At M.D. Anderson, we transplant many patients with active, often chemotherapy-refractory disease. Many groups have elected not to transplant these patients because there is a high risk for both treatment-related complications and an increased risk that the disease will recur fairly quickly after the transplant. With a conditioning program like ours, however, patients can receive maintenance therapy—even chemotherapy—after transplantation to increase the chance of remaining in remission, and this is an area of active investigation at our institution. There are certain new drugs on the market, like azacitidine (Vidaza, Celgene), which could not even be considered for these patients a few years ago. Now we can use them without a significant increase in the risk of added toxicity. There are some early studies suggesting that when we add in treatments such as azacitidine, we prolong remissions, which is the next step in trying to consolidate and solidify the remission, so that the leukemia does not come back.

The busulfan/fludarabine regimen is an example of a new approach, but it is not the end. We invite other investigators to apply the platform as it is or to use it as a starting point for asking questions on how to further improve therapy.

Suggested Readings

Ciurea SO, Andersson BS. Busulfan in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2009;15:523-536.

Valdez BC, Andersson BS. Interstrand crosslink inducing agents in pretransplant conditioning therapy for hematologic malignancies. *Environ Mol Mutagen.* 2010; 51:659-668.

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