Chronic myelogenous leukemia: The news you have and haven't heard

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■ **ABSTRACT**

Chronic myelogenous leukemia (CML) can usually be cured by bone marrow transplantation from matched donors. Donor T-cell activity from the graft is critical to maintaining remission. Myeloablation may not be necessary for cure. Non-myeloablative but immunosuppressive preparative regimens allow donor engraftment with less toxicity. Early combination therapy with interferon-alfa and cytarabine was the preferred option for patients who could not undergo bone marrow transplantation. Now, the advent of imatinib mesylate, a specific inhibitor of BCR/ABL tyrosine kinase, promises to change existing treatment paradigms

R ECENT YEARS saw two major advances in the treatment of chronic myelogenous leukemia (CML), one of which was widely publicized. The other, although equally important, was not.

The first advance, the approval of imatinib mesylate (Gleevec), received extensive attention in the popular media as heralding a new era in chemotherapy, this drug being the first agent designed specifically to inhibit a cancer-promoting enzyme.

The other advance, less widely known, was the surprising and serendipitous finding that recipients of bone marrow transplants may actually benefit from chronic graft-versus-host disease, and that the cure of CML in transplant recipients may not be due to the myelosuppression per se but to the activity of donor T cells. This finding may translate into less toxic and more effective protocols for bone marrow transplantation, not only in CML but in other types of leukemia as well.

■ **PATHOPHYSIOLOGY AND NATURAL HISTORY OF CML**

CML, a rare disorder of the hematopoietic system, causes abnormal elevations in myeloid cells, erythroid cells, and platelets. The median age of onset is between 40 and 60 years, but the disease may affect patients of any age.

CML begins with a relatively benign chronic phase characterized by neutrophilic leukocytosis, often with splenomegaly, but it then enters an accelerated phase during which it progresses to blast crisis and a rapidly fatal acute leukemia. Patients in blast crisis have an estimated survival measured in months.

CML is caused by a reciprocal translocation of chromosomes 9 and 22 in the hematopoietic stem cells, producing the abnormally short Philadelphia chromosome. The chromosome carries a chimeric gene called *BCR/ABL*. The normal ABL protein is a tyrosine kinase that is very tightly regulated and rarely activated. In contrast, the mutated BCR/ABL tyrosine kinase is constitutively activated (that is, it is always turned on), and it stimulates several intracellular pathways that produce uncontrolled hema-

Chronic graft-versus-host disease actually improves cure rates

topoietic proliferation. Proof that this protein is leukemogenic comes from experiments showing that mice transfected with the abnormal *BCR/ABL* gene develop all the characteristics of CML and progress to acute fatal leukemia.[1]

PRESENTING SIGNS OF CML

The most common presentation of CML is asymptomatic, neutrophilic leukocytosis. Morphologic analysis of peripheral blood shows the entire spectrum of myeloid blood cells, similar to what is seen in bone marrow: neutrophils, bands, metamyelocytes, myelocytes, promyelocytes, and basophils. Basophilia, although not pathognomonic, is highly suggestive of CML in the right clinical setting.

Results of the physical examination are often normal. The most common physical sign is splenomegaly; the spleen can range from barely palpable to filling the entire abdominal cavity. Occasionally, there is lymphadenopathy from extramedullary hematopoiesis, which signifies more advanced disease.

Symptoms, which are present in nearly half of patients, can include fever, sweats, weight loss, and bone pain from the active bone marrow.

DIAGNOSING CML

CML is diagnosed by the presence of the Philadelphia chromosome. Karyotyping can detect the Philadelphia chromosome in 80% of patients with CML; more sensitive techniques such as polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH) are necessary to detect the abnormality in the remaining patients.

In a very few patients with apparent CML, the translocation cannot be detected by any means. These patients have a worse prognosis than those with standard CML, and I think it will be shown someday that they do not have CML.

The only other disease characterized by the Philadelphia chromosome is acute lymphoblastic leukemia. On karyotypic analysis, the abnormal chromosome looks the same in both diseases, but it has a different transcrip-

tion product in acute lymphoblastic leukemia and can be differentiated by PCR.

Differential diagnoses

The most common cause of leukocytosis, especially in an acute care setting, is the leukemoid reaction to acute inflammation or infection. The inflammatory leukemoid reaction is not accompanied by splenomegaly or basophilia, and patients have a relatively high leukocyte alkaline phosphatase level. In contrast, CML is characterized by splenomegaly, basophilia in the peripheral blood smear, and a low leukocyte alkaline phosphatase level. In the intensive care unit, white blood cell counts in the range of 30 to 40×10^9/L generally indicate leukemoid reactions, but CML should still be considered.

Other diseases that must be ruled out are the other myeloproliferative disorders: polycythemia rubra vera, essential thrombocytosis, and myelofibrosis with agnogenic myeloid metaplasia. In addition, chronic myelomonocytic leukemia has many of the features of CML, but it is characterized by high peripheral monocytosis with some myelodysplastic features, which simply means abnormal-looking white cells.

PALLIATIVE MEDICAL THERAPIES

Medical therapies have been used for more than a century to lower the white blood cell count and improve symptoms, but they do not prolong life or halt the progression to acute leukemia. Nonetheless, they still have several uses as palliatives, as part of the preparatory regimen for bone marrow transplantation, and as part of combination therapy for patients who cannot undergo bone marrow transplantation.

Busulfan, which became available in the 1950s, improves symptoms and produces relatively long-lasting hematologic remissions. As a single alkylating agent, it is much easier to give and cheaper than radiotherapy, the previous standard treatment. Unfortunately, the disease recurs as soon as busulfan is discontinued, and the therapy does not appear to affect survival. In addition, it causes serious side effects including interstitial fibrosis and Addison disease.

CML is diagnosed by the Philadelphia chromosome

Hydroxyurea has largely supplanted busulfan. Like busulfan, hydroxyurea improves symptoms and induces lasting hematologic remission, but it has fewer side effects and is very easy to titrate. Hydroxyurea may prolong survival, but it does not alter the natural history of the disease, which still universally progresses to acute leukemia and death.

Cytarabine (also called cytosine-arabinoside or ara-C) alone or in combination with other agents can also temporarily improve symptoms. Cytarabine, however, is a parenteral drug, making it more difficult to administer.

■ BONE MARROW TRANSPLANTATION AS A CURE

In the 1970s, it became clear that allogeneic bone marrow transplantation could actually cure CML in some cases. The earliest experiences were with HLA-matched sibling donors, and cure rates with this donor group are now as high as 70%. Today donations can be made by mismatched family members or unrelated donors from the National Marrow Donor Program, with cure rates of 40% and rising.[2] Stem cell donations from umbilical cord blood have been investigated, as has autologous transplantation with marrow purged of Philadelphia-chromosome clones, with only modest results.

Myeloablation-associated toxicity

The standard transplantation procedure required patients to undergo myeloablation to kill the hematopoietic cells, including the leukemic clone. Until very recently, the myeloablation was thought to be the mechanism by which the leukemia was cured. It required supralethal doses of chemotherapy (busulfan and cyclophosphamide) or chemotherapy plus fractionated total-body irradiation.

Unfortunately, the harsh myeloablation regimen is also highly toxic, and mortality within 100 days after the procedure is 20% to 30%. Leading causes of these early deaths include chemotherapy-induced organ damage and infection from immune dysregulation. Nearly one third of these early deaths are caused by acute graft-versus-host disease, in which donor T cells from the graft recognize minor HLA determinants in the host as foreign and try to reject them.

Unexpected benefits of graft-versus-host disease

In contrast to acute graft-versus-host disease, the less severe chronic form of graft-versus-host disease has unexpectedly been shown to be beneficial.

Patients with chronic graft-versus-host disease have much higher cure rates than patients who experience no graft-versus-host disease at all. In addition, patients who receive T cell-depleted transplants experience less graft-versus-host disease but have extremely high relapse rates.[3]

These were early clues to indicate that donor T-cell activity is critical to curing CML, a phenomenon now called the graft-versus-leukemia effect. In fact, it is now thought that the leukemic cells are eliminated by these allogeneic T cells, not by the myeloablation.

For the best results, the T cells must be allogeneic. In a series of 34 chronic-phase CML patients who received grafts from identical twins, the relapse rate at 4 years was 60%—three times *higher* than the rate for patients who received grafts from HLA-matched sibling donors.[4]

The true proof of the graft-versus-leukemia effect came with the advent of donor lymphocyte infusions. When patients who relapse after an allogeneic transplant are given infusions of lymphocytes from the same donor, the rate of complete remission rises to approximately 70%.[5]

I believe we have established that it is the immunologic reaction of donor against host, not the chemotherapy, that actually cures CML. One theory is that the donor T cells target the digested BCR/ABL proteins that appear on the surface of antigen-presenting cells.

■ MINIMIZING THE TOXICITY OF BONE MARROW TRANSPLANTATION

The graft-versus-leukemia phenomenon also suggests that myeloablation can be replaced with a less toxic preparative regimen. Newer "mini-transplant" procedures under develop-

Toxicity and mortality are much lower with new transplant approaches

ment use a preparative regimen that is just immunosuppressive enough to allow engraftment. Shortly after the transplantation, patients display mixed chimerism in the blood, indicating that the stem cells have engrafted. Ultimately, with or without subsequent donor lymphocyte infusions, hematopoiesis becomes completely donor. The patient's blood type changes, and circulating blood cells originate from the donor cells.

Toxicity and mortality are much lower than with the myeloablative approaches.[6] Patients do not develop the month-long neutropenia typically associated with bone marrow transplant procedures. There are very few late side effects because the radiation dose is much lower.

NEW PROCEDURE IS AVAILABLE TO MORE PATIENTS

The lowered toxicity means that mini-bone marrow transplants could be made available to patients who cannot undergo myeloablation, such as elderly patients and those with comorbidities. The procedure can even be performed in the outpatient setting.

In the procedure used at The Cleveland Clinic, we induce moderate immunosuppression with 3 days of fludarabine followed by a very low dose (200 centigray) of total lymphoid irradiation. We give the patient HLA-matched donor stem cells mobilized by granulocyte colony-stimulating factor. The recipient undergoes immunosuppression with cyclosporine and mycophenolate for the next 56 days to prevent graft rejection and graft-versus-host disease. If graft-versus-host disease develops, treatment is started with prednisone, and the immunosuppression is continued until the graft-versus-host disease resolves. Graft-versus-host disease is the major cause of morbidity and mortality following mini-bone marrow transplantation.

In our first series of 20 patients, early mortality was only 10%, compared with the 20% to 30% associated with myeloablative transplants. Long-term results are still unknown, but at least four patients have had complete remissions. Similar procedures have been tested in chronic granulomatous disease and renal cell carcinoma.

INTERFERON-ALFA FOR NONTRANSPLANT PATIENTS

Unfortunately, bone marrow transplantation is still not available for all patients. Many patients, especially those from minority ethnic groups that are underrepresented in the national registries, cannot find a histocompatible donor. Also, bone marrow transplantation may be contraindicated in very elderly patients and those with serious comorbidities. In addition, many patients and their doctors are afraid to choose bone marrow transplantation because of the still-substantial early mortality rate.

For chronic-phase CML patients who cannot undergo bone marrow transplantation or choose not to, the treatment of choice has traditionally been combination therapy with interferon-alfa and cytarabine. Interferon-alfa alone induces a hematologic response rate of 80%, and sometimes also a long-lasting cytogenetic remission—ie, a period in which the Philadelphia chromosome is no longer detectable. With interferon therapy, the 5-year survival rate is 40%, which is slightly but statistically significantly better than with hydroxyurea. In the patients who show cytogenetic remission, 5-year survival is much higher, about 80%. Nevertheless, interferon does not cure the disease, even in these patients. Three randomized trials confirm that adding cytarabine to interferon improves survival, hematologic response rate, and cytogenetic response rate.[7]

Side effects of interferon. Interferon has extremely serious side effects, especially at the high doses necessary to achieve a cytogenetic remission. These include fatigue, depression, neuropathies, psychiatric problems, and autoimmune problems. In addition, interferon must be continued throughout the patient's life, because mortality increases when it is discontinued. This means a lifetime of daily injections of a drug that makes people sick. Up to 25% of patients simply cannot tolerate the side effects.

The role of interferon in the management of CML is changing with the availability of a new agent, imatinib mesylate, approved in May 2001 after very promising results in preclinical and early clinical trials.

Interferon does not cure CML but it produces lasting remission

■ GLEEVEC CHANGES EVERYTHING

Until May 2001, the decision algorithms for newly diagnosed patients with CML hinged largely on whether patients should accept the risk of bone marrow transplant in an attempt to achieve cure or should embark on therapy with interferon, which offered the opportunity for prolonged survival if not cure. Usually, the decision was made for the patient when he or she could not tolerate interferon or failed to achieve remission while taking it. With the approval of imatinib mesylate as a treatment for CML by the US Food and Drug Administrate (FDA) in May 2001, the old decision tree has been discarded and the new one has yet to be formulated.

Imatinib mesylate (Gleevec) is a synthetic compound designed to inhibit tyrosine kinase. It shows a high degree of specificity for the BCR/ABL tyrosine kinase that characterizes CML. Imatinib mesylate clearly inhibited BCR/ABL-positive leukemic cell lines in culture with no effect on negative cells.

Clinical trials of imatinib
Imatinib was tested in a dose escalation study by Brian Druker and colleagues at the Oregon Health Sciences University.[8] Eighty-three patients with CML were treated at several dose levels of imatinib mesylate over an approximately 2-year period. The maximally tolerated dose was not reached, but every patient who received more than 300 mg by mouth per day achieved a hematologic remission. No patient had to interrupt therapy because of adverse events. Importantly, approximately half the patients treated with at least 300 mg of imatinib mesylate suppressed their Philadelphia chromosome enough to have a cytogenetic remission.

These intriguing responses were confirmed in the larger expanded-access clinical trials in patients who had failed or were intolerant to interferon therapy. The results are so striking that the FDA granted approval for imatinib mesylate within 3 years of the drug's introduction into human clinical trials.

Further work has confirmed imatinib mesylate's activity in more advanced CML. In the population of patients with CML in its accelerated and blast phases, imatinib mesylate results in more adverse effects such as pancytopenia, and the rate of complete hematologic remission is lower.[9] Furthermore, the responses that are achieved are relatively brief. However, the fact that an oral therapy is capable of inducing remissions in what are largely chemotherapy-resistant leukemias places imatinib mesylate as an appropriate first-line therapy in patients with advanced CML.

Role of imatinib
The excitement about imatinib mesylate in the treatment of CML is tempered somewhat by the lack of long-term follow-up. In addition, its role for newly diagnosed patients is uncertain and is currently the focus of a large multinational, prospective, randomized trial comparing imatinib mesylate with interferon-alfa-based initial therapy. The confusion is further heightened by the knowledge that bone marrow transplants have demonstrated curative potential but imatinib mesylate has not. Therefore, both patient and doctor are faced with a difficult decision between a dangerous but potentially curative therapy and a safe but relatively untested alternative therapy. As approved by the FDA, imatinib has three indications:
- CML myeloid blast crisis
- CML accelerated phase
- CML in its chronic phase after failure of interferon treatment.

■ WEIGHING THE ALTERNATIVES

Many factors should be weighed when deciding on a course of action for newly diagnosed patients, especially for patients for whom transplantation is possible but risky and for patients who are reluctant to choose bone marrow transplantation.

Age
The patient's age may play a role in the decision. Interferon therapy may be a poor choice for a 21-year-old because it will not cure the disease, but it may prolong life and reduce symptoms, so it might be appropriate for a 70-year-old.

With imatinib, the old decision tree has been discarded

Timing

The time since diagnosis is also a consideration. Bone marrow transplantation works best when performed in the first year after diagnosis, so the decision to take that road must be made quickly. This puts us in a quandary: we cannot try interferon first and see what happens because the delay will reduce the likelihood of a successful transplantation.

Sokal score

The Sokal score can predict survival and can also be used to select patients for interferon therapy. The Sokal score rises with increasing age, larger spleen size, and rising numbers of blasts, eosinophils, basophils, and platelets.[10] Patients with high Sokal scores do not respond well to interferon-cytarabine therapy and should be targeted for bone marrow transplantation. One study shows that interferon therapy works very well for patients with a low Sokal score, and in fact after 7 years of follow-up, survival in the interferon group was similar to survival in the bone marrow transplantation group.

Deciding on treatment

The algorithm for deciding on treatment for newly diagnosed patients with CML is evolving. Clear indications for allogeneic transplantation include advanced CML and failure to achieve remission on imatinib mesylate therapy. Whether younger patients should receive a trial of imatinib mesylate before transplantation is considered is uncertain. Only through well-designed, prospective clinical trials will these answers be forthcoming. Until then, shared decision-making between patient and clinician should guide treatment recommendations.

Patients with high Sokal scores do not respond well to interferon therapy

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