EDITORIAL

Treatment of Chronic Myeloid Leukemia by Marrow Transplantation

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Patients with newly diagnosed chronic myeloid leukemia (CML) who have suitable marrow donors need all the help they can get in deciding when to undergo the reputedly dangerous treatment of marrow transplantation. Since 1983 the Seattle transplant team has recommended transplantation as soon as possible after diagnosis for two reasons. Transplantation before the disease accelerates is important because the results during chronic phase are much better than in accelerated or blast phase. Secondly, the Seattle experience has consistently shown that, even when transplants are performed in chronic phase, delay has an adverse effect on survival.1,2

Our recommendation has not gone unchallenged. Sokal et al3 reported that patients less than 45 years old have a 95% chance of remaining in chronic phase for 1 year after diagnosis. Seattle does not report its results to the International Bone Marrow Transplant Registry (IBMTR), and repeated analyses of experience reported to this registry failed to demonstrate benefit from transplantation earlier rather than later in chronic phase.4 The demonstration that treatment with interferon can produce complete cytogenetic (and even molecular) remission in a small proportion of patients has provided an additional rationale for delay, adding to the difficulties in counselling patients.5 A report from the IBMTR in this issue of BLOOD6 removes some, but not all, of the uncertainty that surrounds this problem. This report now shows a significant benefit for patients with CML in chronic phase when they are transplanted within 1 year of diagnosis compared with later, with an improvement in survival as well as a lesser incidence of relapse when the delay from diagnosis to transplant is short. The negative effect of delay on survival in this analysis was not a consequence of an increased risk of relapse because patients often survive for long periods after relapsing. Thus, the advantages of early transplantation should become even more obvious as the relapsed patients ultimately succumb.

One can devise explanations for an increased risk of post-transplant relapse in patients who have had CML longer before being transplanted, but we do not know why patients who remain in chronic phase without obvious physical, hematologic, or cytogenetic change have an increased risk of dying of the complications of marrow transplantation. No single cause of death accounts for the difference. The IBMTR report shows that treatment with busulfan before transplantation has an adverse effect on the outcome of marrow transplantation. Busulfan was the standard treatment for CML until a few years ago when most physicians began to use hydroxyurea instead. Consequently, until recently patients with a long interval between diagnosis and transplantation were much more likely to have been treated with busulfan than with hydroxyurea. This has made it difficult to examine separately the effect of delayed transplantation and the effect of pretreatment with busulfan. Now, however, the IBMTR report shows that delay was detrimental even in patients who did not receive busulfan. It may well be that treatment with hydroxyurea is also detrimental, which could only be recognized if there were a comparative series of patients who had received no treatment before transplant.

The only situations in which allogeneic marrow transplantation has been widely used in adults without a history of intensive treatment with cytotoxic chemotherapy are aplastic anemia and early transplantation in the chronic phase of CML. In each of these situations the survival after transplantation is extremely good. Thus, in Seattle 189 adult patients with chronic phase CML receiving transplants less than 1 year from diagnosis using our current regimens had a 90% probability of survival for 1 year and an 81% probability of survival to 5 years (Fig 1), whereas patients with aplastic anemia receiving transplants without previous transfusions had a 90% probability of survival for 3 years.7 Clearly, allogeneic marrow transplantation need not be very hazardous, and most of what is currently called transplant-related mortality is not an inevitable consequence of allogenicity, but is heavily influenced by the disease itself and its previous treatment. The message here is that 100% 1-year survival is a reasonable objective in most transplant situations. Although more understanding is needed of the mechanisms by which prior therapy influences transplant-related toxicity, the association is already strong enough to suggest that physicians should always consider how the early treatment of patients with acceptable marrow donors may affect later transplantation.

In the most recent Seattle analysis, the results of transplantation between 1 and 2 years after diagnosis were not worse than when the delay was less than 1 year, whereas delay beyond 2 years had a major adverse impact on survival. It is not known whether this change from the original observation was a consequence of the almost universal substitution of hydroxyurea for busulfan as the drug of choice for controlling chronic phase CML. Presumably an extra year of delay still carries the cost of a higher proportion of patients developing accelerated disease, but it is important to determine whether this is the only cost. It would be useful to analyze the IBMTR data for an answer to this question and to determine whether treatment with interferon and the delay which this occasions has an effect on survival after transplantation.

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CML TREATMENT BY MARROW TRANSPLANTATION

While the IBMTR report advises younger patients with CML and matched family donors to undergo transplantation early after diagnosis, this recommendation applies to only a minority of CML patients because of the age structure of CML and the lack of suitable family member donors. The median age at diagnosis of CML is relatively high. Reports from individual referral centers usually indicate a median age at diagnosis of less than 50 years. However, the National Cancer Institute Report of Surveillance, Epidemiology and End Results for the United States lists the median age at death of patients with CML as 65.8 years, indicating that the median age at diagnosis for patients not selected by referral is close to 60 years. Because increasing age is known to exert a powerful adverse influence on the outcome of allogeneic marrow transplantation, most patients with newly diagnosed CML are never offered the option of marrow transplantation even if they have suitable donors. However, the Seattle experience using current regimens suggests that patients over the age of 50 with newly diagnosed CML in chronic phase can derive substantial benefit from transplantation from HLA identical related donors. Thirty-three patients 50 years of age or older (10 were aged 56 through 60 years) have received transplants in chronic phase within 2 years of diagnosis using one of the two current regimens. The survival of these patients is presented in Fig 2. There have been 5 deaths (4 in the first 100 days posttransplant), all due to pulmonary complications (2 idiopathic pneumonitis, 1 cytomegalovirus pneumonitis, 1 pulmonary fibrosis, and 1 adult respiratory distress syndrome). There is obviously a strong case for marrow transplantation in older patients with CML. The IBMTR report does not refer to the effect of age on survival, and perhaps the number of patients older than 50 years transplanted in centers other than Seattle is too small to permit useful study.

Most patients do not have HLA-identical siblings to serve as marrow donors. The excellent results of marrow transplantation for CML have encouraged the search for alternative marrow donors for patients who would otherwise be denied the benefits of this treatment. Early experience suggested that the results of using one-antigen mismatched family members (about 50% long-term survival) were not much worse than with fully matched donors. However, the marked improvement in the results of matched family member transplants that has resulted from the use of newer regimens for GVHD prophylaxis has not been equalled in these partially matched transplants. In any case such recipient-donor combinations are not common. Another alternative is provided by the higher probability of finding matched unrelated donors in the data banks of the large multinational registries. The patient with newly diagnosed CML is particularly well placed to benefit from such searches because the slow initial progression of the disease accommodates the delays involved in searching for, and arranging the logistics of harvesting marrow from, unrelated donors. Preliminary results of unrelated transplants in CML have been published and more studies are in progress. At present there are insufficient numbers of patients receiving transplants within the first year to determine whether the advantage seen in matched family transplants with early transplantation will be seen with matched unrelated donors.

The IBMTR report advises patients less than age 50 with newly diagnosed CML and matched family member donors to avoid treatment with busulfan and to undergo marrow...

Fig 1. Kaplan-Meier probabilities of survival and relapse-free survival for 189 patients receiving transplants before 1993 from HLA-identical family members for the treatment of CML in chronic phase within 1 year of diagnosis. The conditioning regimens were cyclophosphamide 120 mg/kg followed by 6 daily exposures each of 2.0 Gy of 60Co total body irradiation or busulfan 16 mg/kg followed by cyclophosphamide 120 mg/kg. All patients received methotrexate and cyclosporine for graft-versus-host disease (GVHD) prophylaxis. The patient who died at 9 years had relapsed at 2 years.

Fig 2. Kaplan-Meier probabilities of survival for 33 patients, 50 years of age or older, receiving transplants before 1993 from HLA-identical family members for the treatment of CML in chronic phase within 1 year of diagnosis. The conditioning regimens were cyclophosphamide 120 mg/kg followed by 6 daily exposures each of 2.0 Gy of 60Co total body irradiation or busulfan 16 mg/kg followed by cyclophosphamide 120 mg/kg. All patients received methotrexate and cyclosporine for GVHD prophylaxis. Twenty-three patients were aged 50 through 55 years, and 10 patients were aged 56 through 60 years.
transplantation "relatively early" after diagnosis. Similarly, the Seattle recommendation is that marrow transplantation should be undertaken as soon as possible after diagnosis. The Seattle experience strongly suggests that the upper age at which transplantation is recommended could be raised to 60 years. Patients without HLA-identical sibling donors should be offered treatment with interferon and a search for unrelated donors should be initiated for younger patients.

REFERENCES


Treatmen of chronic myeloid leukemia by marrow transplantation [editorial; comment] [see comments]

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