To the Editor:

Higano et al have recently communicated their experience with interferon-α (IFN-α) treatment in 14 chronic myeloid leukemia (CML) patients with cytogenetic relapse after unmanipulated allogeneic bone marrow transplantation (BMT). Eighty percent of their patients obtained complete cytogenetic responses, and the authors suggest that the response to IFN-α may be related to tumor burden after having found a twofold difference in durable complete cytogenetic responses between the group with cytogenetic relapses and their previous experience using IFN-α in hematologic relapses (57% vs 29%).

Given the small size of the series, it would be interesting to see if these results are concordant with the published data on that topic. For that purpose, we have reviewed the data of 106 relapsing CML patients that have been previously reported in the literature, including 9 patients treated in our institution. Hematologic and cytogenetic relapses have been analyzed separately. The results are summarized in Tables 1 and 2.

Since 1988, we have offered IFN-α as initial therapy for CML patients who relapse after BMT. Out of nine patients treated in our institution (seven with hematologic relapses and two with cytogenetic relapses) three patients have obtained complete cytogenetic responses (CGR) at 11, 15, and 51 months of IFN-α treatment. One of these patients lost the response after 16 months of continuous CGR, and the other two continue in CGR 33 and 98 months after having obtained it. The clinical evolution of the last patient has been previously described. Among these two patients, a molecular remission with polymerase chain reaction (PCR) negativity has been obtained both in blood and bone marrow in the patient with the longest CGR, but RNA bcr-abl has been continuously present in the bone marrow of the other patient, whereas it has been undetectable in blood reverse transcription (RT)-PCR sensitivity, 10^-5 cells. Six patients are alive with a median of 54 months after IFN (range, 6 to 113 months). Two of the not-responding patients have received donor lymphocyte infusions plus IFN-α. One of them obtained CGR and has extense chronic GVHD, and the other one has had grade III acute GVHD. The response has not yet been evaluated. Three patients have died, two because of transformation and one because of hepatic cyrtosis. The literature review shows that 43 patients with isolated cytogenetic relapse have been reported (Table 1). Genetic responses have been obtained in 26 of them (58%), and they have been complete in 19 (43%). The time for obtaining CGR has been between 2 and 51 months. Duration of CGR has been quite prolonged, and several patients remained in CGR more than 5 years after having obtained it.

The results have been poorer in patients with hematologic relapses (Table 2). Out of 63 patients treated in this disease status, genetic responses have been obtained in 46%, but CGR has been achieved in 18 (28%). Most responses occurred in the first year of treatment, but later CGR has been described.

Complete genetic responses have been more frequently reported in patients with non-T-depleted BMT (Tables 1 and 2). Although a recent analysis of the French Group has not detected influence of type of GVHD prophylaxis on response to IFN, the rate of CGR was slightly higher in non-T-depleted grafts (7 out of 16 v 4 out of 17; J. Reiffers, personal communication, 1996). A European Bone Marrow Transplantation group survey has found that among patients with cytogenetic relapse, partial or complete disappearance of Ph-positive cells occurred in 40% of untreated patients and in 42% of those treated with IFN. However, the IFN group contained significantly more patients with T-deplete grafts (22 out of 24). This point merits further consideration. If response to IFN-α is influenced by the status of T repletion of the graft, it can be argued that IFN may exert its effect not only directly but also by its immune actions.

We feel that these studies confirm those obtained by Higano et al and indicate that IFN-α can induce CGR in more than 40% of the patients with CML in isolated cytogenetic relapse. We think that the results using IFN-α as front-line therapy of relapsing CML after BMT warrant a randomized comparison with the use of donor lymphocyte infusions.

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Response

Dr Steegmann et al have provided additional data supporting the efficacy of interferon-α IFN-α for the treatment of cytogenetic relapse of chronic myelogenous leukemia (CML) after allogeneic marrow transplantation. They propose a randomized trial of interferon versus donor lymphocyte infusion (DLI) based on the encouraging cytogenetic response rates of each modality.

With respect to IFN therapy of posttransplant cytogenetic relapse, Steegmann et al underscore several points that have been previously observed1 (1) patients with less tumor burden (ie, cytogenetic versus hematologic relapse) appear to have a greater cytogenetic response rate to IFN; (2) patients who have received T-depleted marrow do not seem to have the same response rate to IFN as those who received unmanipulated marrow, presumably because in the former fewer T-cells are available to participate in the graft versus leukemia effect, and (3) the complete cytogenetic response rate to IFN alone in nontransplant patients is lower than after transplantation, suggesting that, in addition to its direct effects on the malignant clone, interferon has an immunomodulatory role following allogeneic bone marrow transplantation (BMT).

The need for IFN maintenance, the cost of the therapy, and the unknown long-term side effects of IFN drive the search for more permanent solutions. DLI, which presumably works strictly through immunomodulatory mechanisms, results in a very significant proportion of complete cytogenetic responses (70% to 100%), often accompanied by complete disappearance of the BCR/ABL rearrangement as determined by polymerase chain reaction (PCR). Usually no maintenance therapy is required, although some patients require short-term IFN treatment, either before or after DLI. The immediate problem is that in many series, the treatment-related mortality rate, usually due to complications of graft-versus-host disease or aplasia, may be as high as 20%. Most series have not been updated with respect to long-term morbidity and mortality rates or durability of complete response. Porter et al just presented such data in 37 patients with complete response after DLI with a median follow-up of 39 months3: 22% had relapsed and 35% had died with a treatment related death rate of 13.5%.

Given the current enthusiasm about DLI based on the high percentage of both cytogenetic and molecular responses (but the paucity of long-term data) and the significant proportion of patients with durable long-term cytogenetic responses to IFN, the time is right for a randomized trial in patients with isolated cytogenetic relapse after marrow transplantation. However, this is a formidable endeavor requiring a large sample size and a long follow-up period to show a survival difference between the groups. To be successful, such trials require the enthusiastic support of the referring physicians and collaboration between transplant centers to meet accrual goals in a timely fashion.

Moreover, in designing such a trial, it is crucial to establish adequate outcome measures. It is very important that the PCR test not be used as a surrogate end-point for persistent disease, cytogenetic relapse, or survival because the significance of a positive PCR test is not clear in this setting. Because the chromosomal rearrangement can be present in nonleukemic cells (such as lymphocytes) in CML, the PCR test does not necessarily indicate the persistence or relapse of CML. Alternatively, very low levels of the malignant clone may be detectable by PCR, but this may not translate into inferior survival in the setting of either interferon or DLI therapy. For these reasons, the PCR test should not be viewed as a definitive indicator of the success or failure of interferon or DLI therapy.

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Treatement of Chronic Myeloid Leukemia Relapsing After Allogeneic Bone Marrow Transplantation: The Case for Giving Interferon

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