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editorial

TREATMENT OF THE INDIVIDUAL PATIENT WITH CHRONIC MYELOGENOUS LEUKEMIA

A young lady has a routine blood examination which shows a WBC of 15x10^9/L with absolute neutrophilia and a few metamyelocytes and myelocytes. She was fine before this check, but her life now changes dramatically. In fact, when patients with chronic-phase CML are fully informed about the natural history of their disease, they view the blast crisis as a sort of sword of Damocles hanging over their head. A median survival of 5-6 years can be viewed as a success by physicians, but it is death sentence to the patient's eyes and clearly he/she desires a treatment that may remove this impending threat.

In this issue, a group of distinguished CML experts reviews the state of art on biology and treatment of CML.[1] The pathogenesis of chronic myelogenous leukemia has been reviewed in this journal by Santucci *et al.*,[2] who emphasized the following concepts: a) normal and clonal hematopoiesis coexist in CML. Based on the assumption that normal and malignant stem cells may coexist in CML, several studies have been directed toward the characterization and in-vitro selection of benign progenitors within CML hematopoiesis;[3] b) p210 bcr/abl has multiple effects on signal transduction and influences the adhesion properties of clonal hematopoiesis; c) immunological tolerance of p210 bcr/abl rearranged progenitors favors the expansion of clonal hematopoiesis. This knowledge will hopefully translate into therapeutic achievements in the next future. At the present moment, however, the only therapeutic options available are: conventional chemotherapy, interferon-α, allogeneic stem cell transplantation and autologous stem cell transplantation (this latter being still considered an experimental procedure).

Carella *et al*.[1] conclude their through review by proposing an interesting therapeutic algorithm for the individual patient with CML. We will submit this critical pathway to the judgment of our Internet readers in order to evaluate to which extent they agree with the proposed approach. Basically the major points to be discussed are as following:

1. *Stem cell collection and preservation at diagnosis.* It is not clear how many hematologists are currently routinely doing this procedure. Additional questions are: a) should peripheral blood stem cell collections be studied for the presence of normal residual stem cells? b) should multiple collections be made in order to allow more than one use during the course of the disease? c) when should autografting be planned?
2. *Hydroxyurea treatment.* The natural history of CML is not altered by conventional therapy with hydroxyurea: median survival ranges from 4 to 5 years in the overall population, but is only about 3 years in the high-risk group that includes about one third of the total patients. Is this true? Which is the optimal dose of hydroxyurea?[4] Is there convincing evidence that a suppressing hematopoiesis considerably (WBC $\leq 4\times10^9$/L) may in some way prevent the events leading to blast crisis and prolong survival?[4] It is tempting, in fact, to speculate that the longer the Ph-positive clone is fully expressed in the bone marrow and peripheral blood, the higher the probability that molecular lesions responsible for transforming chronic phase CML into blast crisis will occur in one or more leukemia clonogenic cells.[5]
3. *Interferon-α.* The prolongation of life provided by interferon-α is absolutely mediated by restoration of Ph-negative polyclonal hematopoiesis?[6] Which criteria should be used to decide IFN-α treatment? Should cost-effectiveness be taken into account? Kattan *et al.*[7] have provided evidence that, compared with hydroxyurea, interferon-α is, in most clinical scenarios, a cost-effective initial therapy for patients with chronic-phase CML who can tolerate the drug. However, Liberato *et al.*[8] analyzed the same topic with a very similar model and obtained that in the most frequently used protocols, IFN for treating CML is expensive. The marginal cost-effectiveness with respect to hydroxyurea ranges from $50,000 to $100,000 per quality adjusted life years gained. This difference is due to the different cost of the drugs between United States and Italy.
4. *Allogeneic stem cell transplantation.* Is 50 years a reasonable age cut-off? Should the patient's opinion (his/her feeling of the sword of Damocles) taken into account in this respect? Is

there any substantial difference between allogeneic transplantation from an HLA-identical donor and that from a MUD?

5. *Autologous stem cell transplantation*. When should autologous transplantation be considered? When the patient is not eligible for allogeneic BMT from a family donor and interferon alpha does not provide a major cytogenetic remission within 6-12 months? When no MUD is available? Which is the best source of autologous cells? The initial stem cell collection or mobilized progenitors?

We will ask our Internet readers to discuss these points and any single step ot the therapeutic algorithm for CML proposed by Carella *et al*.[1]

References

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