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EDITORIAL

New Strategies for the Treatment of Chronic Myeloid Leukemia

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CHRONIC MYELOID LEUKEMIA (CML) is relatively easy to diagnose, not only because of the increased number of clonally derived myeloid cells but also because of the characteristic reciprocal translocation between chromosomes 9 and 22. This results in the formation of the Philadelphia (Ph) chromosome that is found in the malignant hematopoietic cells of 95% of the patients. However, in the chronic phase of CML the phenotypic differences between karyotypically normal and Ph+ myeloid cells are quite subtle and, unlike most other hematopoietic malignancies, the Ph cells are not blocked in their ability to undergo differentiation and the mature cells that are produced show few, if any, morphologic differences or functional deficiencies. What, then, is responsible for the pathogenesis of the disease? The preferred candidate is a constitutively activated protein tyrosine kinase that arises from a fusion gene, bcrlabl, formed as a consequence of the 9:22 translocation. Indeed, transfer of this gene into murine hematopoietic cells can reproduce most of the pathology seen in human CML. However, recent studies using cell lines have shown that when an activated abl tyrosine kinase is expressed in multipotent hematopoietic cells, only subtle effects are produced; but these effects are nonetheless compatible with the changes in myeloid cell populations seen in CML. For example, in such cells there is a delay in maturation resulting in increased amplification, a small increase in the ability of the cells to respond to suboptimal concentrations of growth factor, and a delay in apoptosis in the absence of growth factor, particularly when the cells are grown at a high cell density. However, the finding that CML is incurable by conventional chemotherapy emphasizes how difficult it has been to exploit the modest cytogenetic responses and that, if this response reaches greater than 65% Ph− metaphases, the actuarial survival at 5 years is probably in the region of 90%. Unfortunately, however, only a small percentage of patients respond in this way (in the order of 13%) and only some of these become totally Ph−. Furthermore, even in post-IFN Ph− patients, the bcrlabl gene can still be identified. In other words, although IFNα can control the disease in many patients, cures are expected to be rare if defined as a permanent Ph− and bcrl abl-negative state.

What further improvement can be made? For the relatively few patients who have matched sibling donors, allogenic transplantation can produce long-term disease-free survival (DFS) (possibly cure) in about 45% of cases, but the mortality and morbidity increases with age. For patients between the ages of 30 to 50 years, bone marrow transplantation (BMT) may not improve the overall survival when compared with current conventional nontransplant treatment schedules. It is likely that the patients in this age group who survive allogeneic BMT may be cured, but many still die from complications associated with the procedure. Furthermore, matched unrelated donor transplants are restricted to the young and achieve a poorer overall survival rate than seen after matched sibling transplants. In this case, the increased mortality is related to pneumonic complications, although hematologic relapse rates are similar. It remains to be seen whether cord-blood-derived grafts may be more useful in this respect.

Should autografts be considered if allogeneic donors are not available? At least patients would then be spared the debilitating effects of graft-versus-host disease. The data indicate that cure (the persistence of Ph− and bcrlabl-negative cells) is unlikely to result from unmanipulated autografted BM or peripheral blood cells that are collected at presentation, although a reduction of the tumor burden may allow the expression of residual Ph− hematopoiesis in some patients.

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However, there may be some benefits in terms of survival because one unrandomized study has shown 56% of patients living 5 years after the autograft. Because it has been shown that contaminating leukemic cells present in the autograft can contribute toward subsequent relapse in acute leukemia, it is likely (although not formally shown in the majority of autografted patients) that disease recurrence from autografted leukemic cells is a major constraint to the widespread use of unmanipulated hematopoietic cells from patients with CML.

How can these contaminating leukemic cells be removed from hematopoietic cells collected for autografting? Several approaches are currently under investigation, one of which is reported in this issue of Blood (Barnett et al, page 724) and is based on the Vancouver group’s previous characterization of the behavior of CML cells in long-term stroma-associated BM cultures. In a series of elegant in vitro experiments, this group first showed in 1983 that Ph+ cells are compromised in terms of their ability to survive in long-term BM culture (LTBMC). They later showed that, in the same conditions, the survival of normal long-term culture initiating cells (putative stem cells) was undiminished—at least over 10 days of culture—whereas the leukemic cells were reduced by 30-fold. Presumably this time frame was chosen based on our previous report showing the successful use of LTBMC in autografting patients with acute myeloid leukemia after myeloblastic therapy: so far, 26 patients with AML in first complete remission have received transplants with autologous cells maintained in LTBMC and show an actuarial DFS of 80% (unpublished data, June 1994). As with CML, our interpretation of the data is that the culture conditions conserve normal hematopoietic stem cells and at the same time restrict the survival of the leukemic cells.

What are the mechanisms underlying the differential survival of the normal cells? Unfortunately the answer is not clear and, although there are some data showing that leukemic cells are deficient in their ability to adhere to marrow stromal cells, more work is required to resolve this issue to provide a more rational basis for developing further ‘purging’ strategies.

The present Vancouver studies now show that the in vitro purging procedure of LTBMC may be advantageous for those patients with CML who show adequate in vitro numbers of normal long-term culture initiating cells (LTCIC) and concurrent loss of leukemic cells when maintained in vitro. However, based on these parameters only a proportion of CML patients may be suitable for LTBMC and subsequent autografting. What happens in these patients after transfer of cultured cells? The results are particularly intriguing in that a majority of patients initially regenerate with Ph− hematopoietic cells. In some patients, this is maintained for 2 or more years before Ph+ cells make a reappearance; in other patients, the Ph+ cells occur earlier. However, in most cases the Ph+ cells appear to respond well to treatment with IFNα. One firm conclusion is that the conditioning of the patient and subsequent rescue with cultured cells led to a very substantial reduction of the tumor burden, but not total elimination of leukemic stem cells. Although the relative contribution of leukemia in situ versus leukemia in the cultured cells is not known (and gene marker studies may be useful here), the precedent of leukemia recurrence even after allogeneic transplantation strongly indicates that more effective myeloablative regimens need to be developed (perhaps based on cytokine-mediated sensitization of target cells). In terms of the graft itself, Barnett et al correctly point out that several strategies for purging leukemic cells are worth exploring, although our own experience of antisense oligonucleotides against bcr/abl have not been encouraging and we have been unable to confirm the data reported thus far. In addition, we are intrigued about the possibility of using macrophage inflammatory protein-1α (MIP-1α) as part of a treatment regime for CML. This is based on the Vancouver group’s study showing that the primitive Ph+ clonogenic cells are not growth inhibited by this cytokine, and our own20 and other1,2,22 data showing that primitive normal multipotent cells respond to MIP-1α by exiting the cell cycle. Such a differential response of normal versus leukemic cells seems open to therapeutic intervention and also fetches us back to the opening paragraph of this editorial: because a major difference between normal and Ph+ cells appears to lie in the response of cells to MIP-1α, it is tempting to suggest that bcr/abl has a role to play in this growth-regulation pathway.

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