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New Approaches to the Treatment of Chronic Myelogenous Leukemia *

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A number of therapeutic strategies have been introduced for the management and treatment of the benign phase of CML. Eighty years ago, radiation therapy was the only available treatment and splenic irradiation was continued for a period in excess of 20 years when in 1924, Minot and colleagues published the now classic paper demonstrating that, although therapy could reduce morbidity of the disease, the median duration of survival with or without therapy was the same. Because of symptomatic relief, radiation therapy or ^{32}P were the methods of choice until the introduction of busulfan in the early 1950s. The initial study with busulfan showed median survival of 42 months and did not appear to be a significant improvement over radiation therapy, although symptomatic improvement was again seen and this is still true today. A number of other agents have been used in an attempt to delay the onset of blast crisis and prolong survival, the most commonly used being hydroxyurea, dibromomannitol, melphalan, and 6-mercaptopurine. In addition, nitrogen mustard, cyclophosphamide, and vinca alkaloids have been used in an attempt to manage the disease.

Because of the relatively prolonged nature of the disease and the ease of administering an oral single agent medication, very little progress has been made in its management. More recently, however, with the introduction of newer chemotherapeutic agents and combination chemotherapy, attempts have been made to treat the benign phase of the disease aggressively, particularly in an attempt to eradicate the Philadelphia chromosome and the abnormal neoplastic clone. Although more than 50% of patients can get a significant reduction in the number of abnormal chromosomes identified after aggressive combination chemotherapy, the majority of the patients have recurrent Philadelphia chromosome within 3–12 months from the discontinuation of this form of aggressive therapy. Preliminary reports suggest, however, that with this aggressive therapy there has been an associated prolongation of median duration of survival.

Other modalities of therapy include bone marrow transplantation: isogeneic, allogeneic and autologous. However, transplantation performed in the later stages of the disease, particularly in the blast phase, has been almost uniformly unsuccessful because of the resistant nature of the underlying disease and recurrence is almost inevitable in spite of the regimen used. Investigators are now looking at the possibility of transplantation in the benign phase of the disease and preliminary data, particularly from identical twins, is encouraging with disease-free survivors in excess of 24 months without evidence of a recurring Philadelphia-positive clone.

In addition to allogeneic transplantation, autologous transplantation in the benign phase of the disease has been attempted and although engraftment does occur, the abnormal clone is not eradicated and the

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disease makes recurrence almost inevitable. More recently, a number of institutions have adopted the approach of aggressive chemotherapy in an attempt to eradicate the Philadelphia chromosome and store the bone marrow of these patients for use in transplantation in the early phase with normal hemopoietic stem cells without the Philadelphia chromosome.

We previously demonstrated that leukocyte interferon (HuIFN-α) had a significant antiproliferative effect on in vitro colony proliferation. In addition to its antiproliferative effect, it appeared to block differentiation. In search of new modalities of treatment of chronic granulocytic leukemia, a pilot study was embarked on to investigate the potential of using HuIFN-α prepared in the State Serum Institute of the Finnish Red Cross Center, Helsinki, Finland. This material was partially purified to a specific activity of $1-3\times10^6$ U per milligram protein. The initial pilot study was performed on seven patients with Philadelphia-positive chronic myelogenous leukemia utilizing a schedule of 3×10^6 U/day up to a maximum 9×10^6 U/day. Following hematologic remission, the patients were maintained on doses of 3×10^6 U/day or every other day. Five of the initial patients responded to interferon, judged by a reduction in the white cell count, platelet count, normalization of serum B12 and LDH, and a reduction in the bone marrow cellularity for pretreatment values of 100% –70%, or less. ME ratios returned to normal and there was a modest reduction of 10%–35% in Philadelphia chromosome-positive cells in the bone marrow aspirate.

With these encouraging results, the phase II program was developed utilizing the same doses of HuIFN-α and a further 25 evaluable patients have been entered. A majority of these were previously untreated and the remainder had minimal treatment with a single agent. Of the 25 patients, 22 responded with normalization of the peripheral blood, and a decrease in the mean white cell count from 112 000 to 5000 µl. There was a decrease in marrow cellularity and serum B12 levels returned to normal, as did serum LDH. One patient developed blast transformation after 2 months on HuIFN-α. Of 11 patients who have been treated for months or more, 7 show a modest decline in the Philadelphia-positive cells in the bone marrow from 100% to a median of 65% (range 10–92% diploid cells). Human interferon is effective in causing a block in myeloid proliferation in the chronic phase of chronic granulocytic leukemia, with normalization of the peripheral blood and reduction in marrow cellularity and return of other parameters to normal. These changes can be maintained with reduced doses of HuIFN-α.

It is clear in this pilot study that the possibility of combining HuIFN-α with intensive chemotherapy is worthwhile, using the intensive chemotherapy to reduce the complement of Philadelphia-positive cells toward zero and maintaining this status with HuIFN-α maintenance therapy. Further activity and significantly more biologic effect may be obtainable with the more purified forms of interferon now becoming available, utilizing cell lines and recombinant techniques.

References

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