Haematology and Blood Transfusion Vol. 31
Modern Trends in Human Leukemia VII
Edited by Neth, Gallo, Greaves, and Kabisch

Biologic Agents for the Management of Hematological Disorders: Chronic Myeloid Leukemia

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Biological materials, either alone or in combination with cancer chemotherapeutic agents, have been used in treatment for almost 20 years. Initially, agents such as BCG, pseudomonas vaccine, and MER were used in the hopes of enhancing normal immunity and retarding the proliferation of neoplastic cells. In addition, it was felt that these agents might enhance the production of normal hematopoiesis, allowing for early bone marrow recovery and thus enabling increasing doses of chemotherapy to be administered with lower toxicity and a consequent reduction in morbidity and mortality. A number of studies from many institutions using this approach showed a prolongation of complete remission, particularly in leukemia, but there was no clearcut increase in the percentage of patients cured. Additional studies of solid tumors, particularly breast cancer and small-cell carcinoma of the lung, produced similar but less convincing data. No long-term benefit was obtained as related to freedom from disease and eventual survival.

The 1980s have been associated with a rapid increase in the development of naturally occurring compounds that control different aspects of proliferation, differentiation, and immunity (biological response modifiers).

Interferon has long been recognized as the body's front-line defense against viruses. Commercially, it was initially prepared from leukocytes by the Finnish Red Cross for clinical trial. The success of the osteogenic sarcoma program in Sweden led in the early 1980s to a more widespread investigation of human leukocyte interferon. Responses were seen particularly in patients with hairy cell leukemia, renal cell carcinoma, and chronic granulocytic leukemia.

Developed in parallel with the use of the crude interferon preparations, a number of companies, using cloning techniques, have been able to produce purified preparations of alpha, beta, and gamma interferon, and these materials are undergoing extensive clinical trials throughout the world (Table 1).

A number of other materials are now becoming available for clinical testing. Tumor

Table 1. Results of clinical investigations of alpha interferon

Sensitive Tumors
Remission rate 75%–90%
Hairy cell leukemia
Cutaneous T-cell lymphoma
Chronic myeloid leukemia
Remission rate 40%–50%
Kaposi's sarcoma
Nodular poorly differentiated lymphoma
Moderately sensitive tumors
Remission rate 20%–30%
Renal cell carcinoma
Multiple myeloma
Relatively resistant tumors
Lung cancer

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necrosis factor has advanced to combination clinical trials in a number of centers. Future use of these materials either singly, in combination, or in combination with chemotherapy or other modalities of therapy would add a significant number of new methods for better biological control of tumor proliferation over the next few years. Following is a list of biological agents that are currently used in clinical practice:

Human leukocyte interferon
Alpha recombinant interferon
Gamma recombinant interferon
Tumor necrosis factor
Interleukin 2
Granulocyte-macrophage colony-stimulating factor
Pluripoitin and pluripoitin A
Antidiotypic antibodies

For a number of years we have been investigating the use of the various interferons as a modality of therapy for patients with chronic granulocytic leukemia. The initial studies were done [1] with human leukocyte alpha interferon given intramuscularly to a series of seven patients. Hematological remission obtained in five patients was associated with reduction of their white cell count from an average of 97 to an average of $4.2 \times 10^3/ml^3$. Associated with this fall in peripheral white cell count was normalization of the platelet count and the serum B-12 and LDH levels. Enlarged spleens, seen in half the patients, became smaller again. These patients continued to respond to treatment and showed reduction in the number of cells containing the Philadelphia (Ph) chromosome.

These studies were subsequently extended to use the human recombinant interferon alpha-A in chronic myeloid leukemia (CML) in 17 patients [2]; of these, eight showed hematological remission with cytogenic improvement, five showed hematological remission without cytogenic improvement, and one patient had a partial hematological improvement. Three patients were considered treatment failures, either because of toxic reactions to interferon or because the interferon failed to control the disease [1]. The disappearance of cells containing the translocation and the return of cells of normal karyotype was encouraging. Results of preliminary studies with probes related to the abnormal protein production seen in the Ph-positive leukemias suggest that the abnormal protein and abnormal gene expression disappeared in patients who became Ph negative.

The study has now been extended to 51 patients with previously untreated or minimally treated benign-phase chronic granulocytic leukemia. Eighty percent of the patients demonstrated a response; 71% obtained a complete hematological remission as judged by the criteria previously reported. More than half of the patients showed a reduction in the number of chromosomes. These changes have persisted for periods of 30 or more months, and there appears to be continuing reduction in the Ph-positive metaphases seen over time in these patients. They have been followed up for longer than 2 years, and 28 remain in continued disease-free control on the therapy. The current projected 3-year survival rate is 74% [2].

Risk factors have been defined from our past experience in treating patients with chronic granulocytic leukemia, and these include such adverse blood and bone marrow parameters as anemia with thrombocytosis or thrombopenia, a high proportion of peripheral blasts and promyelocytes or basophils, a high proportion of marrow blasts or basophils, a decrease in bone marrow megakaryocytes, and cytogenetic abnormalities in addition to the Ph chromosome [3]. In a multivariant regression analysis of these features we found that age, blood and marrow basophilia, and additional cytogenetic abnormalities had a strong predictive relationship to survival. Patient groups could be divided into low-, intermediate-, and high-risk groups according to these prognostic factors, their median survivals being 53, 39, and 25 months respectively. As defined by this multivariant prognostic model, patients on alpha interferon did significantly better than those in the control groups.

Ten patients developed blastic transformation without clonal evolution, and of these, six were of lymphoid origin and two had an undifferentiated morphology, which suggests a suppression of the myeloid clone and reversion to the more primitive lymphoid disease. In the blastic phase, this has

been easier to treat with intensive chemotherapy.

The use of intensive chemotherapy for the treatment of chronic granulocytic leukemia has been previously reported, and in younger patients it shows a significant advantage over treatment with conventional or single-drug therapy. This type of therapy [3] is now being combined with interferon in an attempt to combine a biological response modifier with intensive chemotherapy and in the hope of substantially prolonging the survival of these patients. In addition to intensive chemotherapy, attempts are being made to render these patients Ph negative for prolonged periods, during which marrows are harvested for use substantially in autologous transplantation, as the disease progresses from the more benign to the accelerated phase.

In an attempt to look at the mechanisms of resistance to interferon, we have correlated interferon receptor binding and induction of 2′,5′-oligoadenylate synthetase. A study of 14 patients treated with partially purified human interferon suggested an association between the absence of clinical response to interferon therapy and a failure of induction of 2′,5′-oligoadenylate synthetase activity. In the sensitive patients, enhancement of enzyme activity was seen during the responsive phases despite reduction of interferon receptor density on the cell surface. The absence of clinical response may in fact be initiated by events subsequent to receptor binding, and thus result in a failure of induction of the enzyme activity which activates interferon and leads to control of proliferative activity [4].

The initiation of new therapies with combinations of interferons and tumor necrosis factor, the use of factors that control proliferation and differentiation of granulocytes and macrophages, and an understanding of the role played by the rearranged chromosome at the *ber-abl* region and its associated production of an abnormal protein may increase our ability to control CML.

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