Bone Marrow Transplantation for Cancer Today

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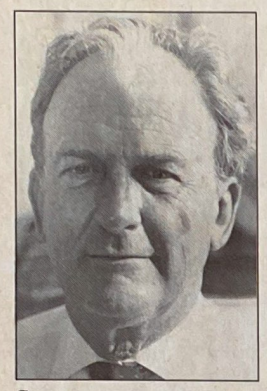

Santos

Bone marrow transplants for malignancy are performed as highly intensive treatments to eliminate every possible malignant cell, particularly in leukemia and lymphoma. With this approach, we rescue patients from the toxicity to the bone marrow induced by cancer treatment. For example, in patients with acute lymphocytic leukemia who are in second remission, we can expect a 50% to 60% disease-free survival, with patients surviving from 15 to 16 years after the transplant. In patients with acute myelogenous leukemia who are in first remission, our data suggest a disease-free survival of close to 65% of patients thus treated. With chemo-therapy in first remission, however, results vary, with long-term survival ranging from 20% to 40%. Most physicians obtain only about a 20% long-term survival with chemotherapy alone.

In subsequent remissions in patients with acute myelogenous leukemia, the results with transplantation, while still encouraging, are not quite as good. In patients with chronic myelogenous leukemia, if the transplant is done during the chronic phase of the disease, one may expect from 50% to 65% disease-free survival, with patients in some series surviving 10 or 15 years. More recently, patients with non-Hodgkin's lymphoma or Hodgkin's disease, who are not curable by conventional methods, have had disease-free survival of from 50% to 60% with bone marrow transplants.

We have been using family members for donors of bone marrow; unfortunately, however, donors are not available for most patients. We are now trying another approach, that of using the patient's own bone marrow, first purging it of any tumor cells. With this approach in acute myelogenous leukemia, we have done relatively well in patients in second and third remissions, achieving a 30% disease-free survival in over 60 patients.

The most exciting application of this approach has been in the treatment of the lymphomas. We have treated from 30 to 40 lymphoma patients (about 1,000 patients worldwide have been treated by this method), with the results suggesting that from 50% to 60% of patients will have long-term, disease-free survival, with a good number being cured.

As to the extension of bone marrow transplantation to the treatment of other types of malignancies, early results in multiple myeloma are encouraging. This is also true with myelodysplastic syndrome, a condition often leading to leukemia. Other tumors likely to be responsive to this treatment are breast carcinomas that are metastatic and not responsive to other forms of therapy. Early work indicates that ovarian carcinoma seems to be a likely candidate for this approach, with first results highly encouraging. Small cell carcinoma of the lung is also responsive to this approach. Some investigators have used autologous transplantation in patients with small cell carcinoma of the lung and have been encouraged by their early findings. Also, there have been some studies of testicular tumors, not curable with other therapies, that have shown good results with bone marrow transplants. Along with these exciting applications of this treatment, it has been found that in pediatric neuroblastomas, autologous bone marrow transplants done early have given good results.

With the good results obtained in treating the leukemias with bone marrow transplants, and the availability of platelets and superior antibiotics, we can expect a useful extension of bone marrow transplantation for more intensive treatment of common malignancies.

The Regulation of Hematopoiesis in Chemotherapy for Cancer

By Saul J. Sharkis, PhD
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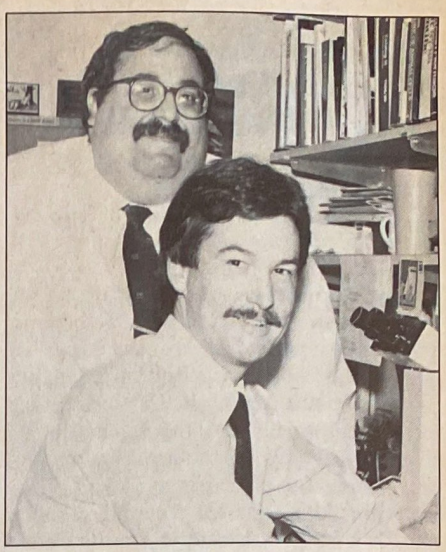
Our interest is in investigating the regulation of hematopoiesis as it relates to bone marrow failure caused by chemotherapy for oncologic disease. Our special concern is stem cell physiology. We are questioning particularly how cells of the hematopoietic system increase through self-renewal processes and how they differentiate along the various cell lineages of the blood system. We are attempting to grow hematopoietic stem cells in the laboratory so that we can provide them to patients who are deficient in such cells. For this purpose, we are trying to discover the steps necessary in stem cell renewal. We provide in vitro specific growth factors that allow such renewal under stress. We are also seeking to understand the interaction of hematopoietic stem cells with other cells in the hematopoietic system, such as lymphocytes and macrophages. Clearly, in the case of malignancies such as the lymphomas, similar regulatory processes, although



May (front), Sharkis (rear)

abnormal in nature, are responsible for the malignant hematopoietic growth and the failure of the cells to differentiate.

The research interests of one of us (May) lies in the signals transmitted within a cell that cause it either to grow or stop growing, or to grow too much. We are particularly interested in how normal, regulatory, signal-producing substances, such as hematopoietic growth factors, can stimulate cells to grow normally. We also are asking why or whether such processes are interrupted in a disease such as leukemia. We have been working with multipotential growth factors, such as interleukin-3, which can stimulate bone marrow stem cells to produce mature white cells, platelets, and red cells. We have concentrated on this agent's role in interaction with the stem cell and on the interaction of IL-3 with its receptor as well as the biochemical changes resulting from the receptor interaction.

Primarily, we are interested in the early signals transduced after an agent/cell interaction, including signals generating secondary messengers within the cell. In other words, these signals may cause direct effects, such as the secretion of a hormone and the aggregation of platelets, or they may stimulate the formation of subsequent signals in the cell nucleus, depressing certain genes necessary for cell differentiation.

In addition to studying these growth factors, we have been investigating an antineoplastic agent, bryostatin,[1] derived from bryozoa, which are marine organisms. Bryostatin[1] mimics the effects of hematopoietic growth factors. The bryostatins are macrocyclic lactones that can directly stimulate bone marrow progenitor cells to form colonies in vitro and functionally activate neutrophils. We are unaware of any other set of compounds that have both antineoplastic activity and a stimulatory effect on the hematopoietic system. This is why we are so excited about it. This unusual molecule, which was isolated by Dr G. Robert Pettit of Arizona State University, has a potential clinical advantage over many other chemotherapeutic agents in that it may not