Current Issues in the Leukemias

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Monumental changes in the direction of hematology and oncology are upon us. Excluding childhood acute lymphoblastic leukemia (ALL), decades of stagnant survival data in chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), and acute myelogenous leukemia (AML) have now begun to disclose favorable gains. Skeptics will debate the impact of high costs, sophisticated technologies, new antineoplastic agents, biologics, growth factors, and stem cell transplantation in terms of overall patient survival. Melding of many laboratory findings with clinical leads has led to novel and remarkable diagnostic and therapeutic options in the leukemias. This section of the Journal reports some of these exciting findings.

Last year Henry Ford Hospital sponsored the symposium “Current Issues in the Leukemias” which featured some of southeastern Michigan’s finest laboratory and clinical researchers from the University of Michigan, Wayne State University, and Henry Ford Hospital, plus faculty from Roswell Park and the University of California, Los Angeles. The conference began with a fundamental report on the impact of bone marrow stroma and the microenvironment on stem cell growth. Subsequent presentations discussed the impact of cell markers by flow-activated cell sorting on diagnosis and prognosis correlating directly with childhood ALL. The role of cytogenetics and flow cytometric markers has favorably influenced treatment options. Comprehending the biology and natural history of B-cell malignancies such as CLL allows better understanding of novel agents in hairy-cell leukemia and CLL.

Bone marrow transplantation is employed in both conventional and experimental settings in parallel with current antineoplastic chemotherapy. Merits of each modality have been evaluated. CML, as the prototype leukemia, is discussed in terms of cell biology (Philadelphia chromosome) and molecular biology (gene rearrangement) with treatment responses, survival data, and results of bone marrow transplantation. Detection of residual disease after bone marrow transplantation, and its clinical significance, is a problem of growing importance.

Four key papers from this symposium are highlighted in this feature section. Dr. Gribbin reviews how adenosine deaminase, deficient in lymphocytes of children with Swiss-type severe combined immunodeficiency disease, exhibits abnormalities of both cellular and humoral immunity. T-cell dysfunction is generally the more profound defect (see pp. 98-102).

New purine nucleoside analogues have been developed for the treatment of chronic B-cell malignancy such as CLL and lymphomas. One of these, fludarabine, is now available for clinical use. The purine salvage pathway enzymes influence immunocompetence in both hairy-cell leukemia and CLL. While fludarabine may be the most effective drug in CLL, its impact upon overall survival is presently unknown.

Bone marrow transplantation, both allogeneic and autologous, is an option in a limited number of clinical settings. At best, only 10% of patients have suitable donors for transplantation. Efforts to increase the sources for allogeneic bone marrow transplantation by the Non-Donor-Related Bone Marrow Transplantation Registry may make transplantation more widely available. Autologous bone marrow transplantation, however, is increasingly available to all patients with lymphomas and AML. In certain conditions, peripheral blood stem cells, rather than bone marrow, is a means of obtaining stem cells. Dr. Janakiraman describes the concept and procedure of peripheral blood stem cell transplantation which she has implemented at Henry Ford Hospital (see pp. 103-107). This means of stem cell rescue may be used in conjunction with autologous bone marrow transplantation to enhance early engraftment. The real advantage to this form of stem cell transplantation may be as an option when bone marrow metastasis precludes harvest, or when prior pelvic irradiation to the stem cell pool limits adequate stem cell harvest marrow, or in patients who cannot risk general anesthesia for bone marrow harvest. The importance of this work lies in expanding the number of patients able to receive stem cell rescue after intensive chemotherapy/radiation therapy for relapsed or refractory disease. New AML patients deemed high-risk may especially benefit from this procedure.

Dr. Gale presents an intriguing discussion of CML (see pp. 108-111). Beginning with the association of the Philadelphia chromosome and CML, Dr. Gale discusses the clinical correlation of the chronic phase of CML with translocation of oncogenes, rearrangement of the break cluster region (BCR) gene, and secondary cytogenetic events leading to the accelerating or blastic phase of CML. Many of these fascinating points are still speculative. Dr. Gale also discusses bone marrow transplantation and alpha-interferon as therapeutic modalities.

Dr. Roth and Ms. Terry describe the technology of polymerase chain reaction (PCR) as a means of amplification of the BCR gene after bone marrow transplantation in CML (see pp. 112-116). The authors can detect minimum residual disease by PCR analysis despite normal bone marrow examination, flow cytometric markers, and karyotype. The significance of minimal residual disease detection by PCR analysis and clinical applica-
bility is unknown at this time, but this powerful tool markedly enhances our ability to study events at the molecular level.

In addition to these laboratory and clinical observations, present approaches have centered on ridding leukemia or lymphoma cells from marrow by a variety of techniques (purging, long-term bone marrow stem cell cultures). Hematopoietic growth factors (GM-CSF, G-CSF, IL-3) already have broadened the horizons for the future. However, there are major obstacles to overcome within the leukemias. One large issue centers on therapy of the elderly. Patients older than age 60 remain a therapeutic enigma for there is no evidence that present therapeutic options benefit this group. Perhaps some of the newer anthracyclines combined with cytosine arabinoside in limited, high doses may be more effective. Treatment strategies designed to deal with the differences in response to therapy and toxicity must be developed. Chemotherapy as a sole modality in CLL must give way to combinations with biologics or monoclonal antibodies. Finally, we must develop individualized therapy for patients, based on prognostic factors determined by clinical characteristics, cell markers, and karyotypes.

The last ten years have multiplied our options for therapy. Growth factors benefit vast numbers of patients beyond the neutropenic recipient. Oncogenes, molecular biology, and cytogenetics probe the level of cell cycle regulation in events of leukemogenesis. Biologics combined with chemotherapy are at the entry level for innovative therapies designed to enhance cell kill by cell synchronization. Finally, bone marrow transplantation, which makes possible increasing cell kill by means of a steep dose of chemotherapy/radiation therapy, is available to larger numbers of patients through allogeneic, autologous, and peripheral blood stem cell transplantation. The nihilistic approach, accepted by some, must now be reconsidered in light of the current positive trends.

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