Adult Acute Leukemia: A Need for Continued Translational Research

To the Editor:

Over the past 2 to 3 decades, the outlook for diverse types of acute leukemias has changed from rapidly fatal to potentially curable diseases. This gratifying change is mainly applicable to childhood acute lymphocytic leukemia (ALL) patients, where more than 70% enjoy greater than 5-year survival, but also holds true for some adults (in particular those under the age of 60) with acute myelogenous leukemia (AML) and ALL. However, even in the younger adult population, only about 30% are able to attain such long-term survival. Unfortunately, that degree of improvement has yet to be realized for older adults, those with therapy-induced (secondary) leukemias, or those whose leukemias have evolved from myelodysplastic syndrome (MDS). Thus, the leukemias continue to present a formidable challenge for which there is not yet a reliably curative standard approach for the majority of adults with this family of diseases. In this respect, clinical investigation—the design, implementation, and analysis of new strategies aimed at increasing the cure rate is necessary to provide state-of-the-art treatment and medical care in addition to measuring the efficacy of new approaches and validation of their widespread applications.

Most adult patients with newly diagnosed acute leukemia are able to achieve a complete remission (CR) in response to induction chemotherapy. Although the most appropriate form of potentially curative postremission therapy continues to be controversial, the long-term clinical results of both bone marrow transplantation (BMT) and dose-intensive chemotherapy in first CR continue to improve for several leukemia patient subgroups. The advances achieved to date in disease-free survival (DFS) are, in large part, attributable to the design and implementation of intensive cytoreductive therapies which, in turn, have been made possible only by aggressive support measures. There is no question that, in addition to increasing the DFS rate in these patient populations, intensive cytotoxic therapy is accompanied by a heightened risk for widespread mucosal and nonhematopoietic multi-organ toxicities as well as profound marrow aplasia. With an increasing ability to manage and in some instances circumvent diverse cytotoxic complications, the full antileukemic potential of aggressive cytoreductive therapy can be evaluated. Thus, patients receiving high-dose ara-C therapy in first CR have achieved a prolongation of DFS and cure compared with those patients receiving less intensive regimens. In addition, myeloablative therapy followed by either autologous or allogeneic BMT also results in substantial cure rates in patients able to tolerate this more aggressive approach. Yet, despite this progress, aggressive cytoreductive therapy with or without BMT is not curative for the majority of adults with acute leukemia.

The cornerstone of both present and future therapeutic advances for the curative treatment of adult patients with acute leukemia is an understanding of leukemia biology on both the molecular and clinical levels. As a result, continued progress will likely be linked to the exploitation of leukemia-associated molecular targets. For example, the concept of intensive therapy in the minimal residual disease state and the ability to monitor residual disease with molecular technology have been pioneered successfully in the leukemias, both in animal models and in the in vivo clinical situation. In this regard, detection of small numbers of residual malignant cells persisting after therapy is critical to overall therapeutic planning. There are certain molecular and biologic features that may prognosticate overall clinical outcome with regard to potential curability with specific treatment modalities such as allogeneic BMT, autologous BMT with novel purging regimens, aggressive chemotherapies using non-cross-resistant agents with unique mechanisms of action or newly developed strategies (gene-directed approaches such as antisense or gene therapy, immunonjugates, and agents aimed at abrogating drug resistance, eg).

Curability for increasing numbers of leukemia patients must be predicated on rationally designed clinical investigation testing specific hypotheses based upon fundamental leukemia pathobiology. The linkage of clinical protocols to basic investigation and the development of clinical-laboratory correlates using clinical materials that directly relate basic biologic studies of patients’ cells to the in vivo response to specific interventions is an integral part of such hypothesis-driven, translational research. Indeed, the ability to obtain clinically germane molecular correlates is critical to the management of acute leukemia from the moment of initial diagnosis. As a case in point, the discrimination of AML from ALL may be difficult on morphologic grounds alone, and specific tests such as cytochemistry and immunophenotyping must be performed immediately to assure that the appropriate treatment is initiated in a timely fashion. Furthermore, chromosomal analyses obtained at the time of initial assessment provide both crucial prognostic and diagnostic information that may have significant impact on clinical outcome in response to specific therapeutic modalities, as well as providing an important marker for detection of residual leukemia.

In addition to the ongoing molecular dissection and its translation into clinical practice, the successful outcome of antileukemic therapies can be linked directly to the creation of specialized nursing units with medical and nursing personnel dedicated to the unique clinical challenges presented by these patients and therapies. To this end, the development of BMT as a broadly applicable treatment modality for many hematopoietic malignancies has engendered the definition of guidelines for the clinical practice of this procedure. Both the American Society of Hematology and the American Society of Clinical Oncology have endorsed and published the acceptable minimum criteria for the development of a BMT nursing unit as well as the minimum qualifications for all members of the medical BMT team.12 Because of these guidelines and the attendant infrastructural requirements, most BMTs continue to be performed in university-based BMT programs. More recently, there has been an expansion to community hospital-based programs, primarily with the use of peripheral stem cell support, and with encouragement to maintain the criteria established for BMT.

Whereas most patients undergoing BMT begin their transplant procedure in CR with excellent performance status, patients with newly diagnosed acute leukemia often present with complex, multiorgan-system problems that demand immediate assessment and intervention and, thus, require an equally specialized nursing and medical environment. Even though many community hospitals have dedicated oncology units, few have the resources available for nursing units that focus on the intensive care required for the adult patient with active acute leukemia comparable with specialized BMT units. However, unlike the situation for BMT to date, there has been no formal attempt to develop similar guidelines for nursing units and medical teams dedicated to the care of patients with leukemia, either at disease presentation or relapse. In light of this, it is noteworthy that only about 8% of the more than 9,000 adults diagnosed annually with AML were entered onto National Cancer Institute (NCI)—sponsored clinical trials last year. Although this is a substantially greater percentage than the 1.5% of adults with common epithelial malignancies entered onto NCI-sponsored clinical trials, it is far less than...
the greater than 80% of children with leukemia who partake in clinical investigation. It is also noteworthy that the vast majority of such clinical investigations are spearheaded by academic physicians in university settings or NCI-supported cancer centers.

Currently, it appears that many community-based hematologists and/or oncologists believe that university-based referral programs should be used only for high-risked leukemia patients, e.g., elderly patients (≥60 years), patients who have relapsed, or those with a history of MDS or secondary AML. In such instances, younger patients with de novo AML would be referred only when they fail initial induction therapies or if they are considered appropriate BMT candidates and a decision has been made by the referring physician and the patient to consider BMT as a reasonable option. Such a trend toward initial treatment in the community of younger adults with acute leukemia has been evolving over the last decade. As a case in point, during a recent clinical trial of two cycles of intensive antileukemia therapy conducted on the Adult Leukemia Service of the Johns Hopkins Oncology Center between 1984 and 1988, about 35% of adults with newly-diagnosed AML had either a precedent MDS or secondary AML. However, in the preceding clinical trial of two-cycle therapy taking place from 1980 to 1982, less than 10% of newly diagnosed AML patients had such poor risk characteristics. This difference was not because of any change in protocol eligibility criteria, but could be explained only by a change in referral pattern or by an overall change in the characteristics of AML. Similarly, only 11 of the last 100 adult AML patients referred to The Emory University Hospital were under the age of 60 years and were newly diagnosed with de novo AML. The remaining 89 patients would be classified as high risk, based either on age or disease status (relapsed after a previous CR or considered refractory having failed at least one attempt at induction) or have a history of MDS or previous exposure to chemotherapy and/or radiation. Interestingly, 3 of the 11 younger patients with newly diagnosed de novo AML were referred to the leukemia service between December 24, 1993 and January 2, 1994, a time when staffing community hospitals is traditionally at a minimum. This pattern of referral to a university-based leukemia service is not unique to the Atlanta area.

If we hope to make a profound impact on the natural history of hematopoietic malignancies and eradicate death and suffering caused by these devastating diseases, we must adhere to the scientific method at both the bench and the bedside. The coupling of basic and clinical investigation in a fashion that fosters a bidirectional exchange of information and the translation of basic discoveries into clinical advances can only be performed in a research setting that is committed to the support of such integrated, multidisciplinary approaches. In this light, academically trained community clinical oncologists in community hospitals that are equipped with specialized nursing units are highly qualified to participate in the development and implementation of clinical investigative protocols. However, to fulfill the other crucial portion of the translational research equation, an intellectual and infrastructural commitment to basic laboratory investigation devoted to the study of human leukemia biology is also essential. Thus, in addition to providing an appropriate clinical milieu for the detailed care of the adult with acute leukemia, the clinical leukemia specialist in the community can contribute much expertise to the pivotal coordination of basic clinical investigation that serves as the foundation stone of progress if and only if that physician is able to provide pertinent clinical specimens before and throughout the entire clinical protocol (all cycles of therapy) for thorough molecular characterization, prognostication, and fundamental laboratory investigation.

Robert B. Geller
Emory University School of Medicine
Atlanta, GA
Judith E. Karp
National Cancer Institute
Bethesda, MD

REFERENCES
Adult acute leukemia: a need for continued translational research [letter]

RB Geller and JE Karp