PREFACE

The impetus for *Treatment of Acute Leukemias: New Directions for Clinical Research* came from many conversations with colleagues and from my years of patient care experience at St. Jude Children's Research Hospital in Memphis, TN. The message was clear—too often we rely on discoveries in the laboratory to drive the next wave of treatment advances when, in fact, substantial progress can be made by identifying and discussing pivotal issues that might be resolved through better application of current methods of leukemia management. Although evolving insights from molecular biology studies are certain to translate into improved therapies directed at specific and unique targets, we still need to care for patients who cannot wait for these developments. Thus, I invited pairs of international experts to address 21 topics that continue to challenge clinical researchers who treat leukemia. These authors were asked to provide expert commentary in lieu of exhaustive descriptions of published studies. My hope is that these dual points of view have achieved a broad and balanced perspective on each topic.

A book of this type almost always contains some redundancies because of the need for completeness within single chapters, and the leukemia-related terminology tends to vary among subdisciplines and even among research groups. Nonetheless, I feel confident that such flaws have not detracted from the overall aim of the book, which was to compile the major debates that surround leukemia therapy at the beginning of the new millennium.

Part I focuses on the advantages and disadvantages of extant leukemia classification systems and the need for a single international system that incorporates the best features of each. Both chapters recognize the overriding importance of genetic risk factors, especially those that directly influence response to therapy, and devote considerable attention to how these emerging factors can be used to guide treatment selection and predict clinical outcome. Owing to the continuing rapid advances in technology and the development of more robust methods of microarray analysis, conventional immunophenotyping and genotyping may soon be replaced by gene expression profiling.

Part II, Chemotherapeutic Strategies, is the heart of the book and covers accepted and experimental treatments of the main forms of acute leukemia in children and adults. We learn in Chapters 3 and 4 that although acute lymphoblastic leukemia (ALL) in infants constitutes only 3% of childhood ALL cases, infant ALL warrants special consideration because of its unique constellation of features and resistance to standard therapy. Both authors agree that there is a need for "hybrid" treatment regimens for this leukemia variant and for greater international cooperation in evaluating such regimens in controlled clinical trials.

Three of every four cases of childhood acute leukemia are ALL; hence, this subtype is the focus of intense investigation by many independent research centers and cooperative study groups. Chapter 5 identifies six specific areas of controversy in the treatment of childhood ALL, including the relevance of residual disease measurements and the indications for stem cell transplantation during first complete remission. Chapter 6 adds alternative points of view to each of these debates and includes a final section on the true definition of treatment success, that is, whether a successful outcome should be defined solely on the basis of the long-held gold standard, event-free survival, or should include measures of quality-adjusted overall survival.

Adolescents and young adults are often treated arbitrarily on pediatric or adult protocols of chemotherapy, a fact that leads to diverse outcomes in these specific age groups. Chapters 7 and 8 argue convincingly that ALL cases in adolescents and young adults have a similar biology and tolerance to therapy, mandating more intensive chemotherapy than would generally be administered to older adult patients, as well as independent evaluation in multicenter clinical trials. In contrast to the high cure rates typically seen in childhood ALL, fewer than half of the adults with this disease achieve prolonged leukemia-free survival; this finding is mainly attributed to an increased frequency of the Philadelphia chromosome, a multidrug-resistance phenotype, and poor tolerance to therapy. As pointed out in Chapters 9 and 10, most of the controversial issues in adult ALL remain unresolved because of the lack of prospective, randomized multicenter trials. Nevertheless, the authors identify several promising strategies, such as wider use of high-dose cytarabine and stem cell transplantation, together with close monitoring of residual leukemia, which may lead to a better outcome in this historically poor prognostic group.

A decrease in the rate of central nervous system (CNS) relapse to 2% or lower in many recent studies has raised new questions about the CNS-directed treatment of childhood ALL, as adroitly outlined in Chapters 11 and 12. Most important, perhaps, is whether patients can be spared the hazards associated with cranial irradiation. The consensus opinion of these authors is that radiation-free treatments can be substituted in the vast majority of all newly diagnosed cases.

Chapters 13 and 14 focus exclusively on the challenges posed by the clinical management of relapsed ALL. The most urgent need, by far, is to identify methods that distinguish the subgroups that are likely to benefit from stem cell

transplantation from those who might be cured by intensive chemotherapy alone. The authors carefully evaluate numerous guidelines thought to be useful in this regard and suggest future directions, such as routine monitoring for residual leukemia, to discriminate among patients with a good, intermediate, or poor prognosis.

Mature B-cell ALL warrants separate coverage because of its distinctive features at diagnosis and unique treatment requirements. Despite the excellent cure rates achieved with high doses of cyclophosphamide, cytarabine, and methotrexate, for example, outstanding questions remain regarding the need for additional cytotoxic drugs, the optimal approach to CNS-directed therapy, and the role of supportive-care treatment such as uricolytic agents. Chapters 15 and 16 provide a critical analysis of these and other issues and remind us that the current therapy for B-cell ALL is both difficult to administer and highly toxic, justifying the efforts to devise new therapeutic strategies.

Although acute myeloid leukemia (AML) accounts for only 20% of cases of acute leukemia among children, it produces a disproportionate share of the leukemia-related mortality. Thus, the primary issue in the treatment of this disease concerns approaches that might improve historically inferior results. Chapters 17 and 18 evaluate strategies that hold the promise of optimizing available therapies, such as extending allogeneic stem cell transplantation to patients whose disease is not likely to respond to standard regimens of chemotherapy. These chapters also describe new directions that would avoid the excessive toxicity associated with many current protocols, including substitution of molecularly targeted agents. The even higher rates of relapse and death in cases of adult AML dictate innovative revisions of contemporary treatments. Chapters 19 and 20 call attention to the promising results of autologous and allogeneic stem cell transplantation in selected groups of patients, of antibody-based therapy, and of nonmyeloablative allogeneic transplantation in older patients with AML. Finally, Chapters 21 and 22 consider the unusual case of acute promyelocytic leukemia (APL). This AML subtype is exquisitely sensitive to all-*trans* retinoic acid, which induces benign differentiation of APL, and to arsenic compounds, which induce both apoptosis and differentiation. Retinoic acid-arsenic treatment of APL serves as a paradigm for the development of molecularly targeted therapy in acute leukemia and warrants the close scrutiny paid by these authors to mechanisms of drug action and optimal combinations of these agents within the context of standard APL treatment.

Only one in five children with acute leukemia who lives in underprivileged countries has access to adequate treatment, resulting in a long-term survival probability of less than 30% in these children. This sobering fact reminds us of the difficulty of translating therapeutic advances into protocols that benefit children worldwide. Chapters 23 and 24 describe how small but steady and consistent steps can be taken to remedy this situation and bring about dramatic change. The authors cite the successes gained by greater cooperation ("twinning") between pediatric centers in developing countries and those in developed countries and by stronger relationships between the medical staff members of hospitals in developing countries and their patients ("therapeutic alliances"). One remaining challenge is to define minimal treatments that will secure reasonable leukemia-free survival rates in nations with limited resources.

Part III examines the premise that many antileukemic drugs have unexploited potentials that could be harnessed to improve treatment outcome. Chapters 25 and 26 address issues that continue to impede optimal use of methotrexate. What are the most effective doses of "high-dose" methotrexate against specific cell lineages and genetic subtypes of ALL? What are the situations in which low doses of this drug are more effective than high doses? What are the clinically relevant mechanisms underlying resistance to methotrexate, and how can they be neutralized?

Although a mainstay of ALL therapy for over 20 years, L-asparaginase administration still has limitations, including the development of allergy, rapid clearance, induction of cellular resistance, and dose-limiting toxicity. Suggestions are made in Chapters 27 and 28 as to how these obstacles might be overcome. Particular emphasis is placed on the advantages of dose adaptations in individual patients, based on careful monitoring of pharmacologic end points. The drug 6-mercaptopurine and its analog 6-thioguanine have been used productively in so-called continuation therapy for nearly a half century, yet many questions remain concerning the optimal manner in which to incorporate these agents into multiagent protocols. As pointed out in Chapters 29 and 30, the results of pharmacogenetic studies can guide the optimal use of this class of agents.

The roles of etoposide and teniposide in acute leukemia therapy are highly controversial. Chapters 31 and 32 cast some doubt on the clinical utility of these compounds, citing their tendency to induce secondary AML and the lack of randomized trials to demonstrate that either epipodophyllotoxin can significantly improve outcome. The authors nonetheless identify the patients who appear to benefit most from these agents, as well as the drug dosages and schedules linked to acceptable levels of toxicity.

With the increasing range of donors and stem cell sources available to transplant specialists, one can look forward to wider use of hematopoietic stem cell transplantation in the treatment of acute leukemias. Thus, it is important to define the subgroups of patients for whom transplantation (but not chemotherapy alone) will provide a high likelihood of cure. Chapters 33 and 34 in Part IV offer expert opinions on this topic and on methods that can increase the efficacy and reduce the complications of this procedure.

Part V, Biologic Treatments, describes both the use of cytokines to rescue depleted bone marrow reserves and the administration of monoclonal antibodies, immunotoxins, donor lymphocytes, and activated T cells as antileukemic

therapy. In principle, treatment with the myeloid colony-stimulating factors G-CSF and GM-CSF could shorten the duration of neutropenia after intensive chemotherapy, leading to better protocol compliance and, possibly, to improvements in the long-term survival rates. However, as noted by the authors of Chapters 35 and 36, the results of clinical trials have not always supported this expectation, indicating limited applications of these growth factors in supportive care. There is much enthusiasm about the prospect of improving cure rates in acute leukemia through the use of immunotherapy. Chapters 37 and 38 critique recent studies of infusions of donor lymphocytes to enhance the graft-versus-leukemia effect of allogeneic transplantation, preliminary trials of antibody-based treatments, and experiments with activated syngeneic T cells in murine models.

Part VI takes a closer look at the assumption that a more complete understanding of drug resistance will lead to more effective treatments. All too often, it seems that cancer cells possess the ability to circumvent even the cleverest schemes of bypassing drug resistance. As discussed in Chapters 39 and 40, this conundrum results from the multifactorial nature of drug resistance and dictates a new focus on strategies that employ multiple agents to target specific pathways of growth, survival, and resistance. The direct corollary of drug resistance is minimal residual disease, whose clinical significance has been a topic of great interest and debate for at least 20 years. Thus, Part VII weighs the available evidence on the detection and monitoring of minimal residual disease and offers advice on the strategies that are best suited for use in the clinic.

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Chin-Hon Pui, ***MD***

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