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Acute Lymphoblastic Leukemia: Introduction

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Contemporary treatments for acute lymphoblastic leukemia (ALL) can cure more than 80% of children with this disease but fewer than 50% of adults.[1] Current risk-directed therapy is intended to improve not only the cure rates in ALL, but also the quality of life of the patients, in terms of decreased acute morbidity and long-term sequelae.[2] As we continue to learn more about the mechanisms of leukemic cell transformation and the development of drug resistance, as well as the germline genetic influences on a patient's responses to chemotherapy, the closer we are to an era of personalized therapy for ALL, in which common protocols for large groups of patients will be replaced by treatments based on the unique molecular targets and pharmacodynamics of individual patients.[3] In this issue of *Seminars in Hematology*, a group of distinguished investigators review the current and emerging concepts of leukemia pathobiology and therapy, emphasizing issues that must be addressed if we expect to eradicate ALL without undue side effects that may preclude a normal productive life.

Leukemia is caused by sequential alterations in proto-oncogenes, tumor-suppressor genes, and microRNA genes of hematopoietic stem cells or their committed progenitors.[3,4] These fundamental changes alter key regulatory processes in target cells by unleashing an unlimited capacity for self-renewal, subverting the controls of normal proliferation, blocking cell differentiation, and promoting resistance to death signals (apoptosis).[3,4] Despite remarkable progress in cataloging the molecular lesions that are common to ALL, our understanding of how such changes cooperate to produce overt ALL is still rudimentary at best. Mullighan and Downing address this problem by adroitly discussing recent advances in the use of high-resolution genome-wide platforms to detect DNA copy number abnormalities and regions of loss-of-heterozygosity. Together with transcriptional profiling, these studies can be used to determine interactions among tumor-suppressor genes and other oncogenic lesions that not only provide valuable mechanistic insights, but may also qualify as useful targets for therapy.[5,6] The authors have taken considerable care to highlight some of the technical aspects of data generation and analysis needed to generate optimal results and have pointed to reseach directions that are likely to pay dividends in the future. Meijerink, den Boer and Pieters succinctly review a series of new genetic abnormalities in ALL, many of which were discovered by state-of-the-art genome-wide screening techniques. These findings have begun to enlighten our understanding of ALL pathogenesis and prognosis and in some instances to stimulate the development of targeted therapy.[7]

Epigenetic changes, including hypermethylation of tumor-suppressor genes or microRNA genes, and hypomethylation of oncogenes, are common observations in cancer, including ALL.[8] These changes are reversible and do not alter the DNA sequence, yet they can alter gene expression in subtle ways that encourage malignant transformation and progression. Garcia-

Manero and colleagues describe recent applications of epigenetics to the development of new biomarkers for risk assignment or disease monitoring, and to the design of alternative treatments. Cancer stem cells have been clearly identified in a number of malignant diseases, including acute myeloid leukemia, and are thought to represent a central mechanism of treatment resistance and relapse. Although ALL appears to be propagated and maintained by a committed lymphoid progenitor with self-renewal capability, the clinical and biological relevance of leukemic stem cells in this disease remains controversial.[9,10] Bernt and Armstrong discuss current views and data on this contentious issue according to commonly recognized genetic subtypes of ALL, and point to specific areas for future research. The interplay of many gene products can influence the pharmacokinetics and pharmacodynamics (and hence the efficacy) of antileukemic drugs.[11] Cheok and Evans expertly summarize recent pharmacogenomic studies directed to the optimal use of existing drugs for individual patients and to the discovery new drugs, emphasizing the importance of validation for each therapeutic application, especially in different racial and ethnic groups.

The initial response to remission induction therapy has been recognized as one of the most important prognostic factors in ALL, as it encompasses leukemic cell genetics, host pharmacokinetics and pharmacogenomics, the host microenvironment of leukemic cells, and treatment efficacy.[1,12] Thus, the precise measurement of minimal residual disease affords a powerful tool for risk classification and treatment assignment, particularly in children. Campana succinctly reviews the methodologies required for accurate detection of residual leukemia, and describes efforts to identify new leukemia markers and to refine existing techniques that would increase the applicability of these measurements, ultimately extending them to clinical studies seeking to identify effective new agents. Careful assessment of the risk of relapse in individual patients ensures that very intensive treatment is given only for high-risk cases, thus sparing low-risk patients from undue toxic effects. In their comprehensive review, Stanulla and Schrappe discuss the rationale and principles of contemporary risk-directed treatment in pediatric ALL, raising several important issues that need to be addressed in future studies.

It has long been known that the pathobiology of ALL, and therefore its aggressiveness differs markedly between children and adults, requiring different approaches to clinical management. Gökbuget and Hoezler summarize recent advances in the treatment of adult ALL, which historically has had a much worse prognosis than childhood ALL. They attribute reports of improved outcome to better supportive care, optimal risk stratification, integration of hematopoietic stem cell transplantation into front-line therapy, and the development of targeted therapy, such as tyrosine kinase inhibitors for Philadelphia chromosome-positive leukemia and rituximab for CD20-positive B-cell precursor ALL. With improved understanding of fundamental cancer cell biology and mechanisms of drug resistance, a number of new therapeutic strategies have emerged.[7] Jeha describes new formulations of existing chemotherapeutic agents, new antimetabolites and nucleoside analogues, monoclonal anibodies against leukemia-associated antigens, and molecular therapies that target specific alterations in leukemic cells. Finally, attempts to harness the immune system to combat ALL have begun to yield promising results, to the extent that immunotherapy may soon earn a legitimate place in the armamentarium against ALL. Leung reviews the latest concepts in tumor immunology, focusing on immunotherapy with T cells, monoclonal antibodies and natural killer cells.

Impressive recent progress has been made in many areas of leukemia research not covered here, such as molecular epidemiology, molecular and cellular signaling networks, and DNA repair processes, to name only a few. I regret that space constraints did not allow me to include these advances in this monograph and, further, impose a severe limitation on the number of references that could be cited in the published reviews. Acute lymphoblastic leukemia is one

of the first human cancers that responded well to chemotherapy in a series of innovative clinical trials conducted more than four decades ago. The challenge now is to resist the natural tendency to become satisfied with the high cure rates that have been achieved in ALL, and instead begin to devise new approaches to treatment that will utilize the specificity of emerging molecular methods without compromising past gains in outcome. I can only hope that the next monograph on ALL in this series will demonstrate that this goal has been attained.

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