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TREATMENT OF LEUKEMIA AND LYMPHOMA

VOLUME EDITORS

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ADVANCES IN
PHARMACOLOGY

TREATMENT OF LEUKEMIA AND LYMPHOMA

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PHARMACOLOGY

VOLUME 51

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ACADEMIC
PRESS

AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

Elsevier Academic Press
525 B Street, Suite 1900, San Diego, California 92101-4495, USA
84 Theobald's Road, London WC1X 8RR, UK

This book is printed on acid-free paper. ♾

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ISBN: 0-12-032952-2

PRINTED IN THE UNITED STATES OF AMERICA
04 05 06 07 08 9 8 7 6 5 4 3 2 1

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Preface

In recent years, we have witnessed a paradigm shift in cancer treatment. Greater understanding of signaling pathways that regulate cell growth, cell cycle progression, and programmed cell death has provided new insights into the molecular mechanisms of disease. While traditional cytotoxic agents still form the backbone of cancer therapy, advances in molecular biology and immunology have led to the identification of novel therapeutic targets and treatment strategies. This volume highlights many of the major developments in biologically targeted, immunologic, and chemotherapeutic approaches to the treatment of leukemia and lymphoma over the past decade.

The remarkable activity of imatinib mesylate, an inhibitor of the ABL kinase of the BCR/ABL fusion protein that causes chronic myeloid leukemia (CML), provides "proof of concept" that molecularly targeted therapies will become an important new class of cancer therapeutics. In addition to describing the development and use of imatinib, Levis and Small (Chapter 1) examine other kinases, such as flt-3, that may be clinically useful targets. The success of imatinib in CML, however, has been difficult to translate to other malignancies. Unlike CML, where BCR/ABL is the causative molecular abnormality and may be the sole leukemogenic event early in the disease, single pathogenetic abnormalities do not exist for the vast majority of malignancies. For small-molecule inhibitors to achieve broader success, it is likely that the most useful agents will target early oncogenic events and that blocking multiple pathways critical for cell survival will be required for clinically meaningful responses. Estey (Chapter 4) provides a framework for investigating these new agents by addressing issues regarding patient selection, efficacy endpoints, and the need for comparative studies.

Like CML, acute promyelocytic leukemia (APL) has become an ideal model for the study of molecularly targeted therapies. In contrast to the development of imatinib, however, which represents a rationally designed compound targeting specific molecular lesions, the success of empiric therapies in APL has led to a new biological understanding of the disease. Differentiation therapy with all-trans retinoic acid that directly targets PML-RARα, the underlying molecular abnormality in APL, has produced complete remissions in up to 90% of patients. Similarly, arsenic trioxide, which degrades PML-RARα and leads to non-terminal differentiation and apoptosis, has shown significant activity. Soignet and Maslak (Chapter 2) outline the current role of these agents in the treatment of APL.

Until the widespread application of molecularly targeted therapies proves more clinically useful, new chemotherapeutic agents will be required. An expanding knowledge of cancer biology has led to the development of a large number of novel drugs, including inhibitors of multi-drug resistance, angiogenesis, farnesyltransferase, and proteosomes, all comprehensively reviewed by Cortes (Chapter 3). Among the most promising therapeutic approaches, hypomethylating agents such as 5-azacitidine and decitabine, capable of activating silenced genes, have shown significant activity in myelodysplastic syndromes and acute myeloid leukemia (AML). Additionally, inhibition of histone deacetylases by phenylbutyrate, SAHA, and depsipeptide, among others, may reverse transcriptional repression caused by histone binding to DNA. In combination, hypomethylation and histone deacetylase inhibition provide an attractive therapeutic strategy for APL and other core binding-factor leukemias, where transcriptional block may play a particularly important role in leukemogenesis. Lamanna and Weiss (Chapter 5) focus on the purine analogs that have shown activity in lymphoid malignancies and the more recent clinical evidence leading to their use in a variety of applications, including non-myeloablative stem cell transplantation and treatment of graft-versus-host disease.

Monoclonal antibodies have now become an important therapeutic modality for cancer, but the overly optimistic view of the early 1980s that they were "magic bullets" has now been replaced by a more realistic understanding of their therapeutic potential. The intrinsic immunologic activity seen with the anti-CD20 antibody rituximab against low-grade lymphoma has provided a foundation for further development of native antibody therapy. Lin and Byrd (Chapter 6) outline recent advances using this approach for the treatment of chronic lymphocytic leukemia (CLL), including new therapeutic targets and chemoimmunotherapy combinations; Weiner and Link (Chapter 10) discuss similar applications for lymphoma.

In an effort to enhance potency, antibodies may be used as vehicles to deliver radioisotopes, drugs, and toxins directly to tumor cells. Weiner and Link discuss radioimmunotherapeutic approaches for lymphoma, including iodine-131-tositumomab and yttrium-90-ibritumomab tiuxetan. In

examining the radioimmunotherapy of leukemia, Burke and Jurcic (Chapter 8) highlight the use of α particle-emitting isotopes, which may allow for more specific tumor cell killing compared to β-emitters. Sievers (Chapter 7) details the development of the anti-CD33-calicheamicin construct gemtuzumab ozogamicin for AML, while Rosenblum (Chapter 9) reviews various strategies for targeting toxins to tumor cells, including cytokines and growth factors, in addition to monoclonal antibodies.

While passive treatment with antibody-based therapies has shown potent anti-tumor effects, it represents only one immunotherapeutic approach. In addition to eliciting antibody responses, vaccine strategies may also produce T-cell responses that allow ongoing surveillance against tumor cells. Lu and colleagues (Chapter 11) review the biological basis of antileukemia immunity and highlight potential leukemia-associated target antigens. Timmerman (Chapter 12) focuses on therapeutic vaccines targeting lymphoma "idiotype." Farag and Caligiuri (Chapter 13) examine the use of cytokines to harness effector cells, including natural killer (NK) cells and monocytes, against autologous leukemia and lymphoma.

Passive cellular therapy has also gained a role in the management of hematologic malignancies, as demonstrated by the ability of donor lymphocyte infusions (DLIs) to induce durable complete remissions in CML. Ho and Alyea (Chapter 14) discuss the biological basis for a graft-versus-tumor effect, current clinical applications of DLI, and the development of nonmyeloablative approaches for allogeneic stem cell transplantation. Finally, Brentjens and Sadelain (Chapter 15) explore the use of gene transfer techniques to engineer tumor cells capable of activating host immune cells, to modify dendritic cells to express tumor antigens, and to alter patient T-cell specificity to recognize antigens present on tumor cells.

The comprehensive reviews in this volume reflect our rapidly expanding knowledge of hematologic malignancies and should provide an exceptional resource for clinicians caring for patients with leukemia and lymphoma as well as clinical or laboratory researchers. In closing, we would like to thank all those who contributed to this collection and Tom August for the invitation to edit this volume.

Joseph G. Jurcic
David A. Scheinberg
April 26, 2004

Contents

Investigational Agents in Myeloid Disorders

Methodologic Issues in Investigation of Targeted Therapies in Acute Myeloid Leukemia

Purine Analogs in Leukemia

Antibody Therapy of Lymphoma

Vaccines in Leukemia

Therapeutic Idiotype Vaccines for Non-Hodgkin's Lymphoma