

Preface
Chronic Lymphocytic Leukemia



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Guest Editors

The recent advances in chromosomal analyses have led to the precise definition of a number of genetic lesions that characterize lymphoproliferative disorders. These lesions, represented primarily by translocations, cause the deregulation and often overexpression of certain oncogenes. In many instances, the transfection or overexpression of the translocated gene in lymphoid cells *in vitro* or in transgenic mice provided formal proof that these translocations represented the causative agents of lymphoproliferative disorders. For example, several studies have determined that the translocation and up-regulation of *bcl-2* is responsible for the acquired resistance to apoptosis of the cells from follicular lymphoma. The excessive proliferation of B cells in mantle cell and Burkitt's lymphoma are caused by the translocation and deregulation of *bcl-1* and *c-myc* oncogenes, respectively.

In this scenario, B-cell chronic lymphocytic leukemia (B-CLL) represents a special and mysterious case. First, there are not recurrent chromosomal translocations that could facilitate the definition of gene(s) involved in B-CLL origin. Second, most of the recurrent chromosomal lesions (eg, deletions in 11q22-23 or 17p) are deletions that appear in a significant number of leukemic cells number late in the course of the disease. These likely contribute to the worsening of the clinical course, but are unlikely to be the cause of the disease. Third, the only deletion observed in a substantial number of cases in early stages of the disease (13q14-) has so far escaped molecular characterization. Although it is generally believed that this deletion causes the loss of a tumor suppressor gene, no such gene has been identified despite extensive and creative studies. Fourth, although

B-CLL has the highest familial incidence of all lymphoproliferative disorders, no indications regarding the genes involved was provided by linkage studies.

Despite these difficulties in determining the causative lesions, a wealth of data has accumulated in recent years that is important and relevant for understanding disease pathophysiology as well as for suggesting potentially novel approaches to management. This new information relates to the nature of the neoplastic B cells, their interactions with the micro-environment, the nature and the repertoire of the B-CLL cell's antigen receptor, and the potential signals that this receptor could convey to the cells leading to proliferation or apoptosis.

These studies have had a major impact on our perception of B-CLL as a disease. Thus, while in the past B-CLL was almost universally recognized as an accumulative disorder of slow proliferating cells with a defective apoptotic apparatus, at present a more dynamic interpretation is provided. Cell accumulation is now seen as the result of the balance between a relatively active cell proliferation and cell loss caused by apoptosis. Moreover, intrinsic apoptotic cellular defects need not be invoked any more. Furthermore, a potential excess in cell survival can be attributed to signals delivered by the stroma or other accessory cells to the neoplastic lymphocytes at particular sites such as bone marrow or lymphnodes. Therefore, B-CLL should no longer be viewed as a disease of immature, immuno-incompetent B cells but as a disease caused by mature antigen-experienced cells for which antigenic stimulation can still play a role in promoting growth. In addition, numerous studies have led to the identification of two subgroups of B-CLL, based on the presence or absence of somatic mutations of Ig V region genes, and CD38 on the surface and of ZAP-70 inside the malignant cells. These observations have in turn suggested new potential strategies for B-CLL management.

This issue of the *Hematology/Oncology Clinics of North America* is intended to convey this new information to clinicians interested in hemato-oncology. Topics have been selected to cover the new emerging issues. The new findings are not presented in isolation, but rather within the classical framework of well-accepted clinical concepts such as the pathologic classification of lymphomas and the clinical staging system of B-CLL. We hope that the final results are a useful blend of proven concepts of great clinical value and new ideas, based on cell and molecular biology observations, that may find their way into the clinical setting. We hope that readers will find this issue informative and will enjoy reading it as much we enjoyed editing the articles provided by our many distinguished colleagues.

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