

HOSPITAL PHYSICIAN®

HEMATOLOGY BOARD REVIEW MANUAL

STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Hematology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

PUBLISHING STAFF

PRESIDENT, GROUP PUBLISHER

Bruce M. White

EDITORIAL DIRECTOR

Debra Dreger

SENIOR EDITOR

Bobbie Lewis

ASSOCIATE EDITOR

Rita E. Gould

EDITORIAL ASSISTANT

Farrowh Charles

EXECUTIVE VICE PRESIDENT

Barbara T. White

EXECUTIVE DIRECTOR OF OPERATIONS

Jean M. Gaul

PRODUCTION DIRECTOR

Suzanne S. Banish

PRODUCTION ASSOCIATE

Kathryn K. Johnson

ADVERTISING/PROJECT MANAGER

Patricia Payne Castle

SALES & MARKETING MANAGER

Deborah D. Chavis

NOTE FROM THE PUBLISHER:

This publication has been developed without involvement of or review by the American Board of Internal Medicine.



Endorsed by the
Association for Hospital
Medical Education

Chronic Lymphocytic Leukemia

Series Editor:

Eric D. Jacobsen, MD

Instructor in Medicine, Harvard Medical School, Department of Medical Oncology, Brigham & Women's Hospital and Dana-Farber Cancer Institute, Boston, MA

Contributing Editor:

Arthur T. Skarin, MD, FACP, FCCP

Medical Director, Thoracic Oncology Program, Department of Adult Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital; Associate Professor of Medicine, Harvard Medical School, Boston, MA

Contributor:

Yi-Bin Chen, MD

Fellow in Hematology/Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Table of Contents

Introduction	2
Pathogenesis	2
Approach to the Patient with CLL	2
References	10

Cover Illustration by Christine Armstrong

Copyright 2007, Turner White Communications, Inc., Strafford Avenue, Suite 220, Wayne, PA 19087-3391, www.turner-white.com. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, electronic, photocopying, recording, or otherwise, without the prior written permission of Turner White Communications. The preparation and distribution of this publication are supported by sponsorship subject to written agreements that stipulate and ensure the editorial independence of Turner White Communications. Turner White Communications retains full control over the design and production of all published materials, including selection of appropriate topics and preparation of editorial content. The authors are solely responsible for substantive content. Statements expressed reflect the views of the authors and not necessarily the opinions or policies of Turner White Communications. Turner White Communications accepts no responsibility for statements made by authors and will not be liable for any errors of omission or inaccuracies. Information contained within this publication should not be used as a substitute for clinical judgment.

Chronic Lymphocytic Leukemia

Yi-Bin A. Chen, MD

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common type of adult leukemia in the Western world, with approximately 10,000 new cases diagnosed each year in the United States.¹ CLL is often an indolent disease and is an incurable entity for the majority of afflicted patients. Each year, approximately 4600 patients die from complications of CLL,¹ most commonly from infection, bleeding, and gradual cachexia. CLL exhibits a 2:1 male to female predominance, and the usual age of diagnosis is between 65 and 75 years.^{2,3} The incidence of CLL has increased in the last several decades, which is most likely due to several factors such as the aging of the general population, increased utilization of laboratory tests, and increased awareness among practitioners. There are no clearly identifiable risk factors for developing CLL, and it is the only adult leukemia that has not been linked with increased exposure to radiation.⁴ Although family members of CLL patients do have a slight genetic predisposition to develop CLL and other lymphoproliferative disorders, no defined mechanisms have been elucidated.⁵

Under the most recent World Health Organization (WHO) classification, CLL (a B-cell neoplasm) and the entity formerly labeled T-cell CLL have been classified as separate disorders, with the latter now being called T-cell prolymphocytic leukemia (PLL). In addition, no distinction is drawn between CLL and small lymphocytic lymphoma (SLL), an indolent non-Hodgkin's lymphoma (NHL), as they are considered to be different manifestations of the same entity.³ The term SLL is reserved for nonleukemic cases, when the characteristic cells are absent from the peripheral blood.

In the last few years, significant progress has been made in understanding the pathogenesis of CLL, in predicting patient prognosis with molecular markers, and in the development of more effective treatment regimens. This article will review the current understanding of CLL, including the common clinical presentation, diagnostic work-up, indications for treatment, prognostic tests, and current choices for treatment.

PATHOGENESIS

Traditionally, CLL was viewed as a disease of slowly proliferating naive B cells that accumulated mainly due to a defect in apoptosis. Currently, it is theorized that CLL involves the acquisition of one or more specific genetic changes coinciding with an environment of appropriate stimulation that allows a normal CD5-expressing B cell to gain an advantage in proliferation and survival.⁶ The actual triggers for stimulation are unclear, although they have been hypothesized to be of microbial or autoimmune origin. In addition, immunophenotypic analysis has shown that most leukemic cells are not naive B cells but actually possess the expression profile of antigen-exposed activated lymphocytes.⁷

The actual leukemic clone in CLL may or may not possess somatic hypermutation of the variable region of the immunoglobulin heavy chain (IgV_H). Cells without IgV_H mutations (< 2% sequences change from germline) are thought to arise from a pregerminal center B cell, whereas cells with somatic hypermutation of IgV_H are thought to arise from a postgerminal center B cell.⁶ Two candidates for the normal counterparts are separate subsets of CD5-expressing B cells: one engaged in autoantibody production⁸ and the other predominantly present in the inner layer of the mantle zone of secondary follicles.⁹ Interestingly, recent studies have identified phenotypic clones consistent with the CLL phenotype in 3.5% of the asymptomatic normal population.¹⁰ Whether these phenotypic clones represent a normal population or true indolent CLL is unclear, but these patients may offer an opportunity to observe the development of CLL at its earliest stages.

APPROACH TO THE PATIENT WITH CLL

CASE STUDY

Initial Presentation and History

A 69-year-old woman is referred to an oncologist for further evaluation of an enlarged lymph node. The patient reported to her primary care physician after