Current Approach to Treating Chronic Myeloid Leukemia

Series Editor:
Eric D. Jacobsen, MD
Instructor of Medicine, Harvard Medical School; Attending Physician, Dana-Farber Cancer Institute, Boston, MA

Contributors:
Jack W. Erter, III, MD
Fellow, Division of Hematology and Oncology, Department of Medicine and Comprehensive Cancer Center, Ohio State University, Columbus, OH

Ramiro Garzon, MD
Assistant Professor of Medicine, Division of Hematology and Oncology, Department of Medicine and Comprehensive Cancer Center, Ohio State University, Columbus, OH

Table of Contents

Introduction ..................................................... 2
Epidemiology and Risk Factors ............................ 2
Pathogenesis .................................................... 2
Clinical Evaluation ........................................... 3
Treatment ....................................................... 5
References ..................................................... 11

Cover Illustration by Nadja V. Frist
INTRODUCTION

Over the last 10 years, treatment of chronic myeloid leukemia (CML), a malignant clonal myeloproliferative disorder, has changed dramatically due to the introduction of targeted therapy with the tyrosine kinase inhibitor (TKI) imatinib. Imatinib, which received US Food and Drug Administration (FDA) approval for treatment of CML in 2001, provides a safe, highly efficacious treatment that has produced long remissions. Previously, immunomodulatory therapy with interferon alfa and hematopoietic stem cell transplantation (HSCT) were the main therapeutic options, with the former limited by lack of efficacy and the latter by well-known toxicities. Other TKIs were subsequently developed, and with these new treatments, a new paradigm for managing and following CML has emerged. Using an illustrative case, this manual will review the epidemiology, pathogenesis, clinical presentation, and evaluation of CML as well as discuss the modern consensus on its treatment in the TKI era.

EPIDEMIOLOGY AND RISK FACTORS

Worldwide, CML is a relatively rare disease. Approximately 4830 new cases of CML were diagnosed in the United States in 2008, with this disease accounting for approximately 10% of adult leukemia cases. The annual incidence has been reported at 1.5 cases per 100,000 adults, with a median age of 66 years and a slight predominance in males. There are no known hereditary, familial, geographic, ethnic, or economic associations for CML. An increased frequency of CML has been reported in various groups with high radiation exposure, including atom bomb explosion survivors in Japan circa 1945 and those with medical radiation exposures. Otherwise, the exact mechanisms leading to the development of CML remain obscured.

PATHOGENESIS

• How does the BCR-ABL oncogene induce leukemia?

The Philadelphia (Ph) chromosome is the result of a balanced translocation between the long arms of chromosome 9 and 22, t(9;22) (q34.1;q11.21), with the derivative chromosome 22 being significantly smaller. This translocation fuses the Abelson (ABL) protooncogene on chromosome 9 with the breakpoint cluster region (BCR) gene on chromosome 22 to produce a chimeric oncogene BCR-ABL. The ABL1 gene resides in the chromosome 9q34 and encodes for a nonreceptor tyrosine kinase that is involved in the regulation of cell cycle and in the cellular response to genotoxic stress. The breakpoint within the ABL1 gene can occur anywhere over a large area at its 5′ end but invariably includes the ABL exon a2 with all the sequences necessary for tyrosine kinase activity. In the t(9;22), the ABL gene segment is juxtaposed to the 3′ end of the BCR gene in chromosome 22. The BCR gene contains 25 exons and encodes for a 160-kilodalton protein that is ubiquitously expressed. Breakpoints in the BCR gene are located in 3 different sites, resulting in 3 specific Bcr-Abl chimeric proteins (p210, p230, and p190, depending on which breakpoint results from the translocation) with constitutive and aberrant tyrosine kinase activity, which has been shown to play a causal role in CML.

Previous research has established that the BCR-ABL oncogene is sufficient to produce a CML-like disease in mice. The Bcr-Abl hybrid protein acts on many pathways to induce and promote leukemia. Three main mechanisms have been implicated in this process: activation of mitogenic signaling, inhibition of apoptosis, and altered adhesion. Activation of MAP kinase, RAS, ERK, and Jun-kinases by BCR-ABL are critical for activating gene transcription, growth factor independence, and malignant transformation. Altered adhesion properties (caused by phosphorylation of substrate CRKL) and signaling...