Abstract

The successful introduction of the tyrosine kinase inhibitors (TKIs) has revolutionized the outcome of patients with chronic myeloid leukemia (CML). Imatinib mesylate therapy induced high rates of complete cytogenetic and major molecular responses and improved survival for patients with CML. A small proportion of patients in chronic phase CML and more patients in advanced phases are resistant to imatinib or develop resistance during treatment through BCR-ABL-dependent and BCR-ABL-independent mechanisms. Novel, more potent TKIs can overcome imatinib resistance, including dasatinib (a potent dual Src and Bcr-Abl inhibitor), nilotinib (a selective potent Bcr-Abl inhibitor), bosutinib and INNO406 (both Src-Abl inhibitors), among others. Other approaches are exploring combination therapy, agents affecting various oncogenic pathways, and immune modulation. This chapter reviews some of these targeted therapies, particularly those for which clinical data are already available.

Key Words: Chronic myeloid leukemia, Tyrosine kinase inhibitor, Resistance, BCR-ABL
1. INTRODUCTION

Chronic myeloid leukemia (CML) is an uncommon disease. Its incidence is low, but its prevalence is increasing. In the United States, approximately 4500 new cases of CML are diagnosed annually (1). The median age at diagnosis is 55 years. With an estimated survival rate of 90% at 5 years and an annual mortality rate of 2%, the prevalence of CML in 20 years may reach 200,000 to 300,000 cases in the United States.

The cytogenetic hallmark of CML is the Philadelphia chromosome (Ph), created by a reciprocal translocation between chromosomes 9 and 22 (t[9;22][q34;q11]). The molecular consequence of this translocation is the generation of a BCR-ABL fusion oncogene, which in turn translates into a Bcr-Abl oncoprotein. This most frequently has a molecular weight of 210 kDa (p210Bcr/Abl) and has increased tyrosine kinase activity. Such activity is essential for its transforming capability by activating multiple signal transduction pathways, including Ras/Raf/mitogen-activated protein kinase (MAPK), phosphatidylinositol 3 kinase, STAT5/Ianus kinase (JAK), and Myc. Bcr-Abl oncoprotein activity leads to uncontrolled cell proliferation and reduced apoptosis, resulting in the malignant expansion of the bone marrow-derived pluripotent stem cells (2,3).

CML normally progresses through three clinically recognized phases. Around 90% of patients are diagnosed during the typically indolent chronic phase, which is followed by an accelerated phase and a terminal blastic phase (2). Although progression through all stages is most common, 20% to 25% of patients progress directly from the chronic to the blastic phase. The mechanisms behind CML disease progression are not fully understood. The criteria for the CML accelerated phase and the CML blastic phase are defined hematologically based on blast cell and progenitor cell counts (2). The time course for progression can be extremely variable. As patients progress through the phases, cytogenetic abnormalities may be detected in addition to Ph chromosome perturbation (termed clonal evolution). Mutations and deletions in specific genes may also occur (e.g., p53, p16/INK4a, and RB) (4–6).

Historically, CML was treated with busulfan or hydroxyurea, and typically had a poor prognosis (2–7). Busulfan and hydroxyurea controlled the hematologic manifestations of the disease but did not delay disease progression. Treatment with interferon-α (IFNα) produced complete cytogenetic responses in 5% to 25% of patients with CML chronic phase and improved survival compared with previous treatments (5-year survival rates: IFNα 57% vs. chemotherapy 42%; p < 0.00001) (8). Combining IFNα with cytarabine (a DNA synthesis inhibitor) produced additional benefits (9,10). Hematopoietic stem cell transplantation (SCT) is curative in CML, but it is indicated after imatinib failure because it carries a significant risk of mortality. The 5-year survival with IFNα/imatinib was significantly superior to allogeneic SCT (11).

Imatinib mesylate, a potent and selective Bcr-Abl tyrosine kinase inhibitor (TKI), is now established frontline standard therapy in CML. A complete cytogenetic response to imatinib can be achieved in 50% to 60% of patients in the chronic phase after failing IFNα (12,13) therapy and in more than 80% of those receiving imatinib as first-line therapy (14,15). Responses are durable in most patients treated for early chronic phase CML, particularly among those who achieve major molecular responses (e.g., ≥ 3-log reduction in transcript levels) (16,17).

Despite the excellent results with imatinib in CML, resistance occurs at an annual rate of approximately 4% in newly diagnosed CML and more often in advanced disease (18,19).