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Invited review

BCR-ABL tyrosine kinase inhibitors in the treatment of Philadelphia chromosome positive chronic myeloid leukemia: A review

Xin An[a,b,c,1], Amit K. Tiwari[a,1], Yibo Sun[a,1], Pei-Rong Ding[a,b,c,1], Charles R. Ashby Jr.[a], Zhe-Sheng Chen[a,*]

[a] Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, St. John's University, 8000 Utopia Parkway, Jamaica, NY 11439, USA
[b] Department of Medical Oncology, Cancer Center, Sun Yat-Sen University, Guangzhou, China
[c] State Key Laboratory of Oncology in South China, Sun Yat-Sen University, Guangzhou, China

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ABSTRACT

Chronic Myeloid Leukemia (CML) is a clonal disease characterized by the presence of the Philadelphia (Ph+) chromosome and its oncogenic product, BCR-ABL, a constitutively active tyrosine kinase, that is present in >90% of the patients. Epidemiologic data indicates that almost 5000 new cases are reported every year and 10% of these patients eventually succumb to the disease. The treatment of CML was revolutionized by the introduction of imatinib mesylate (IM, Gleevec®), a BCR-ABL tyrosine kinase inhibitor (TKI). The clinical use of specific BCR-ABL inhibitors has resulted in a significantly improved prognosis, response rate, overall survival, and patient outcome in CML patients compared to previous therapeutic regimens. However, the complete eradication of CML in patients receiving imatinib was limited by the emergence of resistance mostly due to mutations in the ABL kinase domain and to a lesser extent by molecular residual disease after treatment. The second-generation BCR-ABL TKIs nilotinib (Tasigna®) and dasatinib (Sprycel®), showed significant activity in clinical trials in patients intolerant or resistant to imatinib therapy, except in those patients with the T315I BCR-ABL mutation. Identifying key components involved in the CML pathogenesis may lead to the exploration of new approaches that might eventually overcome resistance mediated to the BCR-ABL TKIs. Here, we present an overview about the current treatment of Ph+ CML patients with the TKIs and the obstacles to successful treatment with these drugs.
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* Corresponding author. Tel.: +1 718 990 1432; fax: +1 718 990 1877.
E-mail address: chenz@stjohns.edu (Z.-S. Chen).
[1] These authors contributed equally to this work.

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1. Introduction

Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder due to an acquired mutation affecting hematopoietic stem cells. CML accounts for ~20% of all leukemias diagnosed in adults and occurs at approximately the same frequency in countries around the world. The annual incidence is 1.6 cases per 100,000 adults, with a male-to-female ratio of 1.4/1.3. The median age at diagnosis is approximately 55 years, with less than 10% of patients under the age of 20 years [1]. There are three distinct phases of CML: chronic, accelerated and blast phase. CML is usually diagnosed in the chronic phase (CML-CP), which is characterized by an increase in granulocytes and is primarily asymptomatic. However, CML-CP ultimately progresses to the accelerated phase (CML-AP), with a rapid expansion of granulocytes and blast crisis (CML-BC) that resembles acute leukemia, leading to metastasis, organ failure, and death [2].

Two pathologists, Drs. Rudolf Virchow and John Hughes Bennett, first described CML in 1845 [3,4]. However, in 1960, Drs. Peter Nowell and David Hungerford, who worked in Philadelphia, described a consistent chromosomal abnormality in patients with CML; the chromosome was subsequently called the Philadelphia (Ph) chromosome [5]. More than 90% of adults with CML are shown to be Ph chromosome positive (Ph+) [6]. In 1972, Rowley discovered that the Ph chromosome is generated by a reciprocal translocation [t(9;22)(q34;q11)] and fusion between abelson (ABL) tyrosine kinase gene at chromosomes 9 and break-point cluster (BCR) gene at chromosome 22 [7]. The resulting chimeric BCR-ABL oncogene encodes a 210 kDa protein (in >90% Ph+ CML and approximately 30–35% acute lymphocytic leukemia (ALL) patients) with constitutive and aberrant ABL tyrosine kinase activity, and this has been shown to play a causal role in CML [8,9]. A subset of CML patients are associated with variable 185–230 kDa BCR-ABL oncoprotein depending on the site of the breakpoint in the *BCR* gene [10]. This subtle difference in the cell context and intrinsic tyrosine kinase activity arising from each BCR-ABL isoform governs the final leukemia type [11]. The BCR-ABL fusion protein mediates the development and maintenance of CML through interaction with multiple downstream signaling partners, resulting in altered cellular adhesion, activation of mitogenic signaling, and inhibition of apoptosis, leading to the transformation of hematopoietic stem cells [12]. BCR-ABL-mediated signaling is also associated with defective DNA repair, resulting in additional chromosomal alterations and mutations, which may partly explain the aggressive nature of advanced CML [13].

The therapeutic options for CML before the discovery of BCR-ABL included cytotoxic drugs such as busulfan and hydroxyurea [14]. Although effective chemotherapy could normalize the elevation in white blood cell count, prevent complications due to hyperleukocytosis, and control the clinical manifestations of the disease, it did not change the natural history of CML, as most patients would ultimately progress to the blast phase [2]. The introduction of recombinant interferon-alfa (rIFN-α) provided a significant survival advantage when compared with cytotoxic drugs [15]. The majority of patients using rIFN-α monotherapy could achieve hematologic remission; however, only a minority of patients achieved a complete cytogenetic remission (ranging from 13% to 27%) [16]. Moreover, most patients were unable to tolerate rIFN-α because of its adverse effects [13,17]. Allogeneic hematopoietic cell transplant (HCT) remains the only established curative approach for CML [18]. However, significant morbidity and mortality rate, in addition of lack of human leukocyte antigen (HLA) matching donors only allows a small percentage of CML patients to use HCT [19].

As the intricate mechanisms of CML are being detailed, research is now directed towards developing compounds that selectively inhibit the aberrant BCR-ABL tyrosine kinase. Imatinib mesylate (IM, STI-571 or Gleevec), is the first BCR-ABL tyrosine kinase inhibitor (TKI) to be used for the treatment of CML [20]. However, several subsequent studies reported that point mutations within the ABL kinase domain or overexpression of BCR-ABL could lead to imatinib resistance in patients with advanced disease [21,22]. Therefore, to surmount imatinib resistance, several other novel TKIs were developed and tested in patients with BCR-ABL positive CML, such as dasatinib (BMS-354825, Sprycel), nilotinib (AMN-107, Tasigna) and bosutinib (SKI-606) [23–25]. The development of these TKIs significantly changed the prognosis and treatment algorithms of patients with newly diagnosed CML. Currently, BCR-ABL TKIs are the initial choice of treatment for most patients with CML. Consequently, the use of any type of HCT in patients with CML has experienced a substantial decline. This manuscript will review the clinical use of BCR-ABL TKIs for the treatment of CML. The mechanisms of action and resistance of TKIs (especially for imatinib) will be discussed along with possible treatment options for patients with imatinib resistance or intolerance.

2. Mechanism of action of BCR-ABL TKIs

As described above, cytogenetic abnormalities produce a constitutively active BCR-ABL tyrosine kinase, and this has been implicated in the pathogenesis of CML. BCR-ABL TKIs can inhibit the BCR-ABL pathway and significantly reduce the proliferation of BCR-ABL positive CML cells [26]. Imatinib, a 2-phenylamino pyridine-based ATP competitive inhibitor, binds to the inactive conformation of the ABL protein tyrosine kinase and competitively blocks the ATP binding site and prevents its conformational switch to the active form (Fig. 1) [20]. Imatinib inhibits cellular proliferation and tumor formation without the induction of apoptosis [27]. An *in vitro* study reported that imatinib produced a 92–98% decrease in CML colony growth without significantly inhibiting normal colony growth [27]. Imatinib also inhibits the platelet-derived growth factor receptor (PDGFR), Arg, and c-kit, but not the Src family kinases [28] (Table 1). Imatinib could also reverse bone marrow angiogenesis and decrease the plasma concentration of vascular endothelial growth factor (VEGF) in CML patients [29,30]. Moreover, increasing evidence has emerged indicating that imatinib exerts profound immunomodulatory effects on T cells and antigen-presenting cells, such as dendritic cells (DC) [31]. However, the exact nature of the effects of imatinib (activation or suppression) on immune cells remains controversial. Some reports show that imatinib inhibits CD4+ or CD8+ T cell proliferation and activation, as well as downregulates the Ag-presenting function of DC [32,33]. In contrast, other studies have shown that imatinib enhances the Ag-presenting function of DC and fosters DC-NK reciprocal activation, thereby promoting the antitumoral function of NK cells [34,35].

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