Ibrutinib as a Bruton Kinase Inhibitor in the Management of Chronic Lymphocytic Leukemia: A New Agent With Great Promise

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Abstract

The recent discovery of the role of the B-cell antigen receptor (BCR) signaling pathway in the propagation and maintenance of both normal B-cell function and in B-cell malignancies has highlighted the importance of many protein kinases involved in BCR signal propagation. Considerable research attention has focused on the Bruton tyrosine kinase (BTK) as a potential therapeutic target in B-cell malignancies. Treatment paradigms including ibrutinib, a potent inhibitor of the BTK recently approved by the US Food and Drug Administration, have significantly improved disease outcome among high-risk and relapsed/refractory cases of chronic lymphocytic leukemia. This has provided additional treatment options, especially among the elderly, where improved disease response has been accompanied by more manageable treatment-associated toxicity than commonly found with chemoimmunotherapy. In this review, we provide a synopsis of the current data on the efficacy and clinical utilization of ibrutinib and management of its resistance in the treatment of chronic lymphocytic leukemia.

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western world, with an estimated incidence of 14,620 new cases expected in the United States in 2015.[1] It is characterized by mature functionally defective B lymphocytes, and it is usually diagnosed when the absolute lymphocyte count is persistently greater than 5000 cells/mL with immunophenotypic expression of CD5, CD23, CD19, and dim CD20 markers on the defective lymphocytes by flow cytometry.[2]

The past decade had witnessed a significant improvement in the management of CLL after the introduction of chemoimmunotherapy involving various combinations of purine nucleoside analogues (fludarabine), alkylating agents (cyclophosphamide, chlorambucil), and anti-CD20 monoclonal antibodies (rituximab,[3] obinutuzumab,[4] ofatumumab[5]). Despite the favorable clinical response reported with these agents, chemoimmunotherapeutic treatment is usually not curative, and clinical utilization is limited, especially among elderly patients, as a result of treatment-associated toxicity such as prolonged immunosuppression and treatment-related neoplasm.[6] However, the discovery of the Bruton tyrosine kinase (BTK) as a therapeutic target has opened a window of opportunity in overcoming these limitations in the treatment of CLL.

The BTK was first described in 1993 as a nonreceptor protein tyrosine kinase found to be defective in X-linked agammaglobulinemia (XLA), an inherited immunodeficiency disease that affects males, in which B lymphocytes and immunoglobulin are almost absent from the circulation as a result of failure of B-cell development.[7,8] BTK was named after Ogden Bruton, who first described XLA in 1952.[9] Shortly after the discovery of BTK, the effects of stimulation of the B-cell antigen receptor (BCR) in mature B cells were shown to be mediated by phosphorylation of the BTK, which caused up-regulation of BTK activity in the BCR signaling pathway.[10-12]

The roles and fate of the B cell as part of the immune system are largely controlled by the BCR signaling pathway through the regulation of cellular selection, maturation, proliferation, migration, survival, and antibody production.[13] This pathway is potentiated in normal B cells by antigen binding, which stimulates the recruitment of the SRC-family kinases tyrosine protein kinase (LYN) and spleen tyrosine kinase (SYK). Signal transduction proceeds downstream via the signaling components phospholipase Cγ2 (PCL-γ2), phosphoinositide-3-kinase (PI3K), and the BTK.[14]

Because of the expression of the BTK in many B-cell leukemias and lymphomas,[15,16] targeting BTK to develop new therapeutic modalities for B-cell malignancies became attractive. The first rationally designed small-molecule BTK inhibitor (LFM-A13) was

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shown to have activity against leukemia in vitro in 1999, only a few years after the identification of the BTK.[17] More selective BTK inhibitors were subsequently developed, such as the irreversible inhibitor ibrutinib (formerly known as PCI-32765), which was shown to induce objective clinical responses in dogs with spontaneous B-cell non-Hodgkin lymphoma.[18] Ibrutinib's inhibitory effect was also shown in the human activated B-cell–like subtype of diffused large B-cell lymphoma, demonstrating the importance of the BTK in oncogenic BCR-signaling control of cell survival.[19] Ibrutinib is now approved for the management of previously treated CLL,[20,21] all CLL patients with the T53 tumor suppression protein deletion 17p13.1 (del(17p)),[22] mantle-cell lymphoma,[20] and Waldenstrom macroglobulinemia[23] by the US Food and Drug Administration (FDA).

This review provides a summary of the latest data on efficacy in the current indication of ibrutinib in the management of CLL.

B-Cell Receptor Signaling and BTK Activity and Regulation

The BCR consists of a surface transmembrane immunoglobulin (Ig) associated with CD79α and CD79β chains.[24] Antigenic binding to the BCR in normal B cells leads to receptor aggregation and subsequent phosphorylation of the receptor's cytoplasmic tyrosine-based SH activation domains by the SRC-family kinase LYN (signalosome formation).[14] Initial signaling events are mediated by spleen tyrosine kinase (SYK) via association with the adaptor molecule B-cell linker protein (BLNK) and BTK, and binding and activation of the p85 subunit of PI3K.[25] Downstream signaling involves the activation of additional distal signaling molecules. PI3K induces the conversion of phosphatidylinositol 4,5 bisphosphate (PIP2) to phosphatidylinositol 3,4,5 triphosphate (PIP3).[14] Recruitment of PIP3 to the plasma membrane is required for the optimal activation of the BTK as well as recruitment of 3′ phosphoinositide-dependent kinase (PKP) and protein kinase B (PKB or AKT).[26] The induction of these signaling molecules leads to further propagation and amplification of the signal via the phosphorylation of phospholipase C-γ 2 (PLC-γ2), responsible for the recruitment of calcium secondary messengers and activation of protein kinase C. PCL-γ2 is also involved in mobilization of mitogen activated kinase (MAP) pathways, nuclear factor of activated T cells (NFAT), and nuclear factor kappa B (NF-κB).[27] These factors ultimately lead to regulation of the pattern of gene expression necessary for cell survival and proliferation, and alterations of any of the potentiating pathways may result in oncogenic phenotypes.[13,24,26]

Antigen-independent signaling, also called tonic signaling, has been shown to exist in normal B cells in addition to the antigen-dependent BCR signaling cascade, albeit to a lesser extent.[25,28] It is believed that an overactive antigen-independent pathway is a contributing factor in the development of those B-cell malignancies characterized by constitutively or abnormally active BCR signaling.[29,30] This overactivity is believed to promote a supportive tumor microenvironment by modulating chemokine-controlled migration and integrin-mediated adhesion of surrounding stromal cells, while the absence of such support leads to rapid apoptosis of B cells.[24,28] On the basis of this observed mechanism, several inhibitors of protein kinases involved in BCR signaling such as the LYN inhibitor bafetinib, SYK inhibitor fostamatinib, and PI3K inhibitor idelalisib have been developed for clinical use and have shown notable beneficial clinical results.[31]

BTK as a Therapeutic Target

The BTK is a member of the Tec kinase family, a group of nonreceptor kinases with the 4 additional members TEC, IL-2-inducible T-cell kinase (ITK), redundant resting lymphocyte kinase (RLK), and bone marrow–expressed kinase (BMX).[32] While only B cells express BTK, ITK and RLK are expressed in the T-cell lineage. BMX is expressed in myeloid cells, where it regulates the secretion of proinflammatory cytokines, epithelial cells, endothelia cells, and fibroblast.[33]

Loss of gene function mutations of the BTK in humans results in XLA, characterized by complete absence of B cells, low serum Ig levels, and recurrent infections. This observation in XLA suggested that BTK is required in B-cell development and immunoglobulin production[34] and thus provided a unique therapeutic target for inhibition of the BCR signaling pathway, as illustrated in Figure 1.

Inhibition of the BTK results in lack of NF-κB DNA binding, impaired integrin-mediated cell adhesion and migration, reduced cell production of chemokines, and diminished cellular response to chemotactic factors, and ultimately induces B-cell apoptosis.[28,35,36] Dubovsky et al[37] have also demonstrated that ibrutinib exerts a selective inhibition on ITK by skewing CD4 T-cell populations isolated from CLL patients from a Th2-dominant immunity to a Th1 and $CD8^+$ cytotoxic population. It was also shown that ibrutinib induces a compensatory mechanism mediated by RLK, which remains uninhibited in Th1 cells. Both of these observations confirmed the immune-modulatory effects of ibrutinib on the CLL microenvironment.

Ibrutinib as a Single-Agent Therapy in the Management of Treatment-Naive and Relapsed/Refractory CLL

Honigberg et al[18] reported in 2010 that ibrutinib demonstrated promising preclinical and early clinical activity in CLL as part of the first-in-human dose-escalation study in multiple B-cell lymphoid malignancies. This was corroborated by the work of Herman et al[35] in 2011, which showed similar activity in B-cell malignancies. In 2013, Advani et al[38] showed that ibrutinib had significant activity in patients with relapsed/refractory (R/R) B-cell malignancies, while Brown[39] reported an overall response rate (ORR) of 67% and progression-free survival (PFS) of 88% at 15 months' follow-up in R/R CLL patients, and a median PFS at 15 months of 96% in treatment-naive (TN) patients older than age 65.

On the basis of these study reports, a subsequent phase 1b/2 study of ibrutinib (PCYC-1102) in R/R and symptomatic older TN patients with CLL showed a high response rate, sustained remissions, and acceptable toxicity. In this trial,[40] the authors showed that ibrutinib monotherapy was capable of inducing a high response rate of 71% and a PFS rate of 75% at 2 years among patients with R/R CLL/small lymphocytic lymphoma who had received a median of 4 previous therapies. It also showed that toxic effects were limited, and responses were often durable with prolonged therapy. The study further reported an associated initial lymphocytosis that