Targeting B-Cell Receptor Signaling for Anticancer Therapy: The Bruton’s Tyrosine Kinase Inhibitor Ibrutinib Induces Impressive Responses in B-Cell Malignancies

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Ibrutinib (PCI-32765) is an orally active inhibitor of Bruton’s tyrosine kinase (BTK) that covalently binds to the cysteine Cys-481 of BTK and thereby irreversibly inactivates the kinase.1,2 In the report accompanying this article, the results of the first clinical study of ibrutinib in patients with relapsed/refractory B-cell malignancies are presented.3 Objective responses were observed in an impressive 60% of patients, including 16% complete responses, and adverse effects were minimal. This article provides an overview of the role of BTK for B-cell receptor (BCR) signaling and the importance of the BCR in B-cell malignancies.

BTK is a cytoplasmic tyrosine kinase of the Tec family that is essential for BCR signaling.1 Loss-of-function BTK mutations cause X-linked agammaglobulinemia, which is characterized by the virtual absence of B cells and immunoglobulins and results in recurrent bacterial infections.4 BTK is expressed in B cells and myeloid cells but not in plasma cells or T lymphocytes. Moreover, its essential functions seem to be limited to B cells. BTK is required for BCR-induced calcium release, cell proliferation, and activation of the nuclear factor κB (NF-κB) pathway.1,4

The BCR consists of a surface transmembrane immunoglobulin (Ig) receptor associated with the Igα (CD79A) and Igβ (CD79B) chains.5 The BCR serves as the receptor for antigen and promotes cell growth, proliferation, and survival of normal and malignant B cells.5,6 On antigen binding, the tyrosine kinases LYN and SYK initiate a signal transduction cascade that involves several kinases, adapter molecules, and the generation of second messengers (Fig 1). Of the surface Ig isotypes, IgM is of particular importance for antigen-dependent signaling and is the isotype expressed by most mature B-cell malignancies.6

BCR signaling is increasingly implicated in the pathogenesis of some B-cell malignancies. Definitive experimental evidence comes from studies in the activated B-cell–like (ABC) subtype of diffuse large
of MCL. Furthermore, this signaling pathway is also been appreciated in mantle-cell lymphoma (MCL), suggesting the importance of BCR and NF-κB-dependent BCR signaling as a mechanism of disease progression. However, these mutations are insufficient to initiate BCR signaling, suggesting that antigen-dependent activation is also required.

Chronic stimulation of B cells by microbial or viral antigens contributes to the oncogenesis of some lymphomas. Classic examples include mucosa-associated lymphoid tissue lymphoma and splenic marginal zone lymphoma arising in response to infections with Helicobacter pylori or hepatitis C, respectively. In some cases, eradication of the infection leads to regression of the lymphoma, indicating an antigen-dependent state. In contrast, in chronic lymphocytic leukemia (CLL), antigenic drive seems to be provided by autoantigens. A role of antigen is inferred from the observations that CLL cells use a restricted repertoire of Ig heavy chain variable (IGHV) genes and that in many cases of CLL, virtually identical BCRs—so-called stereotyped BCRs, which could recognize shared antigens—are expressed. Ongoing antigen-dependent BCR signaling as a mechanism of disease progression is suggested by the recent demonstration of inducible activation of the BCR and NF-κB pathways in CLL cells in the lymph node. The specific antigens recognized by the BCR expressed on CLL cells remain incompletely defined, but in many cases, they may be autoantigens expressed by dying cells. Most recently, a bias for certain IGHV genes and the expression of stereotypic receptors has also been appreciated in mantle-cell lymphoma (MCL), suggesting that response to antigen may also play a role in the pathogenesis of MCL.

Clinical trials with the BTK inhibitor ibrutinib and the SYK inhibitor fostamatinib report objective responses across different B-cell malignancies. Interestingly, CLL is the entity with the highest response rates at 79% and 55%, respectively. Follicular lymphoma and MCL are also highly responsive to ibrutinib but not to fostamatinib. Response rates in DLBCL were 28% with ibrutinib and 22% with fostamatinib. A possible explanation for the lower response rate in DLBCL is the inclusion of patients irrespective of molecular subtype. However, only the ABC subtype depends on chronic active BCR signaling and is expected to respond to these inhibitors. Conceptually, B-cell malignancies that depend on BCR signaling can be targeted by ibrutinib, whereas tumors that rely on other, BTK-independent pathways or have genetic lesions that activate the BCR signal transduction cascade downstream of BTK are likely to be resistant.

Whether all the therapeutic effects of ibrutinib can be attributed to the inhibition of BCR signaling is impossible to ascertain, given that many pathways with important roles in B-cell biology, including B-cell activating factor, CD40, Toll-like receptors, and several cytokines and chemokines, can activate BTK. Regardless, it may be that BTK inhibition is efficacious exactly because BTK is involved in many pathways that promote B-cell survival. Similar considerations apply to the P13Kδ inhibitor GS-1101, which reportedly also has significant clinical activity.

Prolonged use of ibrutinib might interfere with normal B-cell function and lead to hypogammaglobulinemia. Although this aspect needs to be further explored, the absence of a decrease in IgG levels during administration of ibrutinib, as reported by Advani et al, is good news. Equally encouraging is the median progression-free survival of 13.6 months. However, progression-free survival seems short in DLBCL, which could be the result of activation of BTK-independent survival pathways. Thus, the most effective use of ibrutinib may differ between different B-cell malignancies. In CLL, for example, chronic suppression of the disease may be possible and sufficient, especially for elderly or frail patients. In contrast, combination with chemotherapy to enhance cytotoxicity may be particularly warranted for ABC-DLBCL, which has a high failure rate with conventional chemotherapy and in which there is a strong biologic rationale for the use of targeted agents that inhibit BCR and NF-κB pathways. Although much remains to be learned about the use of kinase inhibitors in B-cell malignancies, the good news is that potent novel treatment options targeting pathogenic mechanisms in these diseases have arrived.

The author(s) indicated no potential conflicts of interest.

REFERENCES


DOI: 10.1200/JCO.2012.44.4281; published online ahead of print at www.jco.org on October 8, 2012