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Bruton tyrosine kinase inhibition in chronic lymphocytic leukemia

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia and remains incurable outside of the setting of allogeneic stem cell transplant. While the standard therapy for both initial and relapsed CLL has traditionally included monoclonal antibody therapy in combination with chemotherapy, there are patients with high-risk disease features including unmutated IgVH, del(11q22) and del(17p13) that are associated with poor overall responses to these therapies with short time to relapse and shortened overall survival. Additionally, many of these therapies have a high rate of infectious toxicity in a population already at increased risk. Targeting the B-cell receptor (BCR) signaling pathway has emerged as a promising therapeutic advance in a variety of B-cell malignancies, including CLL. Bruton agammaglobulinemia tyrosine kinase (Btk) is a tyrosine kinase in the BCR pathway critical to the survival of both normal and malignant B cells and inhibition of this kinase has shown to block the progression of CLL. Ibrutinib, a first in class oral inhibitor of Btk, has shown promise as a very effective agent in the treatment of CLL—in both relapsed and upfront therapy, alone and in combination with other therapies, and in patients of all-risk disease—which has led to its approval in relapsed CLL and as frontline therapy in patients with the high-risk del(17p13) disease. Several studies are ongoing to evaluate the efficacy and safety of ibrutinib in combination with chemotherapy as frontline treatment for CLL and investigation into newer-generation Btk inhibitors is also underway.

1. Introduction

Chronic lymphocytic leukemia (CLL), the most common adult leukemia, is characterized by leukemic mature B cells accumulating in the blood, bone marrow, lymph nodes, and spleen secondary to survival and proliferation signals delivered to the cells from various receptors and ligands. CLL is now recognized as a heterogeneous disease; while many patients have a more indolent course and are observed without therapy upon initial diagnosis, some patients with high risk disease features characterized by unmutated immunoglobulin heavy chain variable (IgHV) gene regions, overexpression of ZAP70 and CD38, and high-risk interphase cytogenetic abnormalities (including del(11q22) and del(17p13)) progress rapidly to requiring therapy and relapse within a short time following initial therapy. The standard initial therapeutic approach to CLL has been treatment with chemoimmunotherapy which combines chemotherapy (fludarabine, pentostatin, bendamustine) with anti-CD20 monoclonal antibody (rituximab) therapy. While these regimens have shown high efficacy in younger patients with low-risk CLL, they are associated with shortened remissions in patients with high-risk disease features and increased toxicities in the elderly population. The recent emergence of oral kinase inhibitors targeting the B-cell receptor (BCR) signaling pathway is significantly changing the treatment paradigm for CLL patients.

Signaling through the BCR is critical for B-cell development, differentiation, and migration, as well as for B-cell proliferation and survival. BCR antigen-driven activation leads to phosphorylation of tyrosine kinases, including spleen tyrosine kinase (SYK), phosphatidylinositol 3-kinase (PI3K), and Bruton tyrosine kinase (Btk) activating downstream signaling pathways critical to the survival of mature B cells (Fig. 1). The BCR signaling pathways plays a significant role in the proliferation and survival of malignant B cells in the different B-cell non-Hodgkin lymphomas (B-NHLs), including CLL, through chronic activation of the pathway [1]. This has led to significant interest in targeting inhibition of these pathways for treatment of the B-cell malignancies.

2. Targeting the BTK pathway

Btk is a tyrosine kinase in the Tec family of tyrosine kinases. The Tec family of tyrosine kinases is expressed on hematopoietic cells,

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