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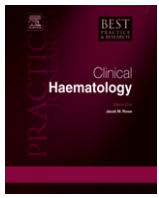

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Novel agents in mantle cell lymphoma

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Mantle cell lymphoma is a mature B cell neoplasm constituting 5–7% of all non-Hodgkin lymphoma. Overall prognosis with current therapeutics remains poor, thus numerous novel agents are currently under investigation. In this review we focus on early phase trials that have demonstrated promise in mantle cell. Constitutive activation of signaling components downstream of the B cell receptor play an important role in the pathobiology of mantle cell lymphoma. Targeting of this signaling pathway has become a focus with specific agents under development including inhibitors of spleen tyrosine kinase, phosphoinositide 3-kinase and Bruton's tyrosine kinase. Promising data also supports further development of BH-3 mimetics, a crucial component of anti-apoptotic signaling. Histone deacetylase inhibitors have an established role in cutaneous T-cell lymphoma and are now under investigation in mantle cell lymphoma as well. With further understanding of cellular signaling, the armamentarium of treatment options will be enhanced, with the hope of improving the prognosis of this disease.

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Introduction

Mantle Cell Lymphoma (MCL) is a mature B cell neoplasm first described in 1994 that constitutes 5–7% of all non-Hodgkin Lymphoma. This disease is characterized by the overexpression of cyclin D1 as a result of the translocation of t(11:14)(q13;q32) [1]. MCL can be viewed as an incurable disease. Historically, survival at the time of diagnosis was estimated to be 3–5 years, however recent data suggest that patients can live greater than seven years.

The standard of care has previously focused on aggressive upfront systemic chemotherapy with the option of autologous transplant, but recent literature has raised the question of an initial conservative approach with observation. Despite improved survival data in the younger population, therapy for the elderly or refractory/relapsed patient remains limited, and the prognosis quite poor. The role of proteasome inhibition and immunomodulatory therapy are well established, here we focus on novel agents recently identified as having a role in the treatment of mantle cell lymphoma.

At the crux of newer agents in MCL lie alterations of the B cell receptor (BCR). In normal B cell activation, initial antigen binding activates the SRC-family kinase LYN as depicted in Fig. 1. Spleen tyrosine kinase (SYK) is then activated via phosphorylation and autophosphorylation [2]. Once activated through association with B cell linker protein (BLNK), SYK facilitates downstream activation of Bruton tyrosine kinase (BTK) and subsequently phospholipase Cγ2 (PLC-γ2), in addition to activating phosphoinositide 3-kinase (PI3K). Downstream from these signaling molecules, second messenger activation generates release of intracellular calcium and activated protein kinase C, ultimately activating various transcription factors including NF-κB [2]. Other key downstream targets include mammalian target of rapamycin (mTOR) and AKT.

Current research in MCL indicates that BCR signal components are constitutively activated contributing to tumor proliferation and survival [3]. Modulation of this pathway has shown great promise in mantle cell, particularly in the otherwise refractory patient. A number of agents have been developed as logical targets for induction of apoptosis and will be addressed below, also highlighted in Tables 1 and 2.

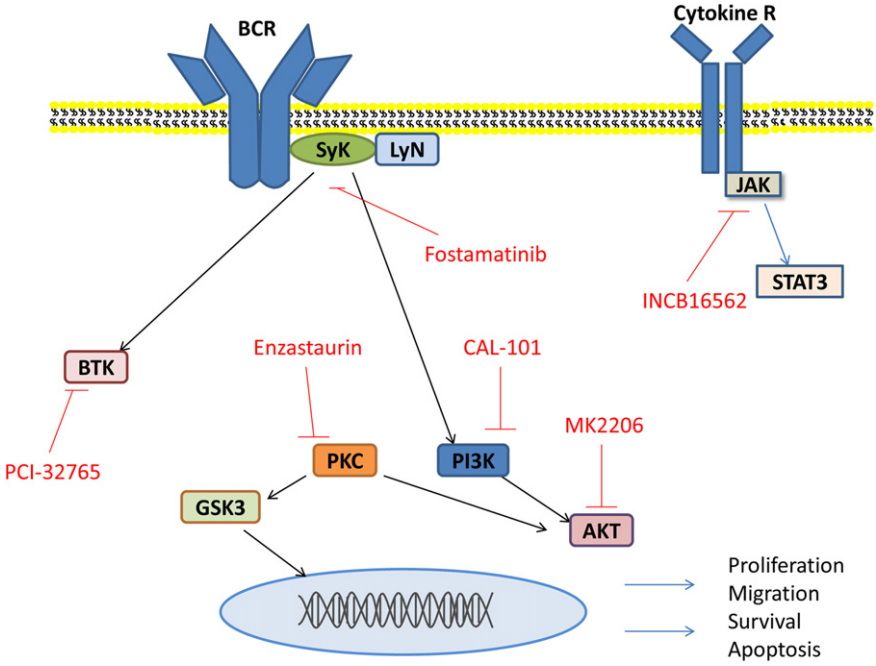

Fig. 1. Key signaling pathways in relation to the B cell receptor. Novel agents labeled in red are depicted at their particular focus of inhibition.