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Role of Kinase Inhibitors in Treatment of Lymphoid Malignancies

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Deregulation or upregulated expression of specific oncogenic kinases has been implicated in the pathobiology of B-lineage lymphoid malignancies [1-4]. The intracellular signaling cascades that are active in maintaining the malignant phenotypes in B-lineage leukemias and lymphomas involve multiple potential therapeutic targets such as SYK, BTK, PI3K/AKT/mTOR, Src, Ras/Raf/MEK/ERK, JAK/STAT, and Aurora kinases. Inhibiting these kinases and their signaling pathways may result in significant clinical benefit especially for patients with relapsed or refractory B-lineage lymphoid malignancies.

Several kinase inhibitors (e.g. R788, PCI-32765, ASP3026, GS-1101, MK-2206, CCI-779, LY317615, R115777, SB1518, and MLN8237) have demonstrated promising activity in the treatment of aggressive and chemotherapy resistant B-lineage leukemias and lymphomas. The robust antitumor activity and tolerability of newer kinase inhibitors documented in multiple clinical trials suggest that kinase inhibitor therapy could be effective in selected malignancies and might be successfully combined with other drugs for optimal efficacy against relapsed or refractory lymphomas. Clinical success of targeting kinases will be dependent on the identification of reliable molecular and clinical biomarkers associated with response. Further insights into the signaling pathways should stimulate the identification of novel agents against specific oncogenic kinases and facilitate the development of new therapeutics selectively inhibiting these molecular targets.

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