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Pharmacological targeting of PI3K isoforms as a therapeutic strategy in chronic lymphocytic leukaemia

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ABSTRACT

PI3Kδ inhibitors such as idelalisib are providing improved therapeutic options for the treatment of chronic lymphocytic leukaemia (CLL). However under certain conditions, inhibition of a single PI3K isoform can be compensated by the other PI3K isoforms, therefore PI3K inhibitors which target multiple PI3K isoforms may provide greater efficacy. The development of compounds targeting multiple PI3K isoforms (α, β, δ, and γ) in CLL cells, in vitro, resulted in sustained inhibition of BCR signalling but with enhanced cytotoxicity and the potential for improve clinical responses. This review summarises the progress of PI3K inhibitor development and describes the rationale and potential for targeting multiple PI3K isoforms.

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1. Introduction

B cell receptor (BCR) activation and subsequent downstream signalling is pivotal for maintenance and proliferation of chronic lymphocytic leukaemia (CLL) leading to tumour progression [1]. Therefore targeting the BCR and associated pathways is attractive for CLL and other BCR driven B cell malignancies. These BCR signals are mediated via a series of key kinases including SYK, BTK and PI3K, and inhibitors such as entospletinib (SYK inhibitor), ibrutinib (BTK inhibitor) and idelalisib (PI3Kδ inhibitor) are showing clinical efficacy, and are likely to replace standard chemotherapy regimens for the treatment of CLL. So far, with limited follow up, ibrutinib and idelalisib have shown clear efficacy in suppressing tumour progression but have not been curative. A minority of treated patients who go on to develop resistance to ibrutinib have extremely poor outcomes with a median survival of 3.1 months after discontinuation [2]. However once resistance to ibrutinib occurs, PI3K inhibitors may still be therapeutically effective [3]. This review will therefore focus on PI3K inhibitors in CLL.

PI3K, via phosphorylation of the inositol lipid phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$), forms the second messenger molecule phosphatidylinositol (3,4,5)-trisphosphate ($PI(3,4,5)P_3$) which recruits and activates pleckstrin homology domain containing proteins, leading to downstream signalling events crucial for proliferation, survival and migration. Class I PI3K enzymes consist of four distinct catalytic isoforms, PI3Kα, PI3Kβ, PI3Kδ and PI3Kγ. The PI3Kδ and PI3Kγ isoforms are expressed predominantly

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in leucocytes, whereas the PI3Kα and PI3Kβ isoforms are ubiquitously expressed [4].

PI3K becomes activated upon ligation of a number of chemokine and cytokine receptors expressed by CLL cells and following BCR ligation [5,6]. PI3K mediated signalling is known to be constitutively activated in CLL [6] and patients with more progressive disease [*IGHV* unmutated (U-CLL)] show significantly greater PI3K expression compared to less progressive disease [*IGHV* mutated (M-CLL)] [7].

2. Pharmacological inhibition of PI3Kδ in CLL

The crucial role of PI3Kδ in normal B cell biology was identified using genetic and pharmacological studies [4] and its haematopoietic restricted expression has made it an attractive target for therapeutic intervention in haematological malignancies (Fig. 1A).

Idelalisib preferentially inhibits PI3Kδ and has recently gained approval for the treatment of relapsed/refractory CLL. It has been evaluated in a phase I clinical trial in 54 CLL patients with relapsed/refractory disease; nodal shrinkage and overall survival were obtained in 81% and 72% patients respectively [8]. In a phase III clinical trial, idelalisib combined with the anti-CD20 antibody rituximab significantly improved progression free survival (81%) and overall survival (91%) in relapsed CLL patients ($n=220$) compared to placebo plus rituximab [9]. Commonly observed adverse events in patients taking idelalisib included pneumonia, rash and diarrhoea [8], however idelalisib and rituximab demonstrated an acceptable safety profile with no significant increase overall in adverse events compared to placebo plus rituximab [9].

Idelalisib demonstrates a dual mechanism of action by inhibiting pro-survival signalling pathways [6], and, like other kinase inhibitors, leads to re-localisation of tumour cells by blocking ingress into and promoting egress out of the lymph node into the blood. Release from the protective lymph environment into blood renders CLL cells more susceptible to apoptosis. PI3Kδ is expressed by all leucocytes including T cells, raising the possibility that the therapeutic effect of idelalisib may, at least in part, be due to effects on the surrounding immune cells in addition to direct effects on CLL cells [10]. Intriguingly, IL-4 protects against idelalisib induced apoptosis in vitro [6], indicating that microenvironmental influences may protect CLL cells against PI3K inhibitors and that co-inhibition of the function of surrounding cells may be an important factor in successful treatment.

Ongoing clinical trials with idelalisib are examining the combination with other agents; including rituximab, ofatumumab, obinutuzumab and bendamustine. Furthermore, a recent publication showed that combination of idelalisib with ibrutinib is synergistic, indicating potential benefit from combined or sequential therapy [11]. In addition to idelalisib, development of other PI3Kδ inhibitors for the treatment of lymphoid malignancies is ongoing including TGR-1202, a novel PI3Kδ inhibitor with significant differences in its chemical structure compared to idelalisib and with lower reported incidences of colitis in patients. TGR-1202 is currently in phase I clinical trials, with significant nodal responses observed in 88% of relapsed/refractory CLL patients to date (clinicaltrials.gov, NCT01767766).

Duvelisib (IPI-145) targets both PI3Kδ and PI3Kγ isoforms [12] and induced apoptosis in CLL samples in vitro, abrogated bone marrow stromal cell-mediated survival, inhibited BCR mediated signalling and chemotaxis in response to CXCL12 [13]. Importantly, duvelisib also killed CLL cells that were resistant to ibrutinib [3], this may hold true with other PI3K inhibitors, and could form an important strategy for treating patients refractory to ibrutinib. Duvelisib has completed phase I clinical trials in which 89% of patients showed a reduction ($\geq 50\%$) of enlarged lymph nodes and 47% patients showed an overall response to the drug [14]. Duvelisib is now in a number of clinical trials for CLL, including in combination with anti-CD20 antibodies and in patients refractory to ibrutinib (clinicaltrials.gov, NCT02292225, NCT01871675).

Although these results are extremely promising, the long term effects of PI3Kδ inhibition in patients are unknown. Will the disruption of regulatory T cell function over a number of years lead to increased risk of developing autoimmune disorders? Furthermore, increased incidences of colitis have been reported in patients treated with idelalisib, and although the exact cause is unknown, increased colitis also occurred in a murine model where PI3Kδ kinase activity was disrupted. Moreover, the PI3Kδ isoform is expressed by epithelial cells and is known to have a crucial role in lumen formation [15]. This challenges the concept of restricted usage of PI3Kδ to haematological cells and therefore raises potential concerns for the effect of PI3Kδ inhibitors on epithelial tissues; however patient responses to these agents in the short term may outweigh any potential long term effects.

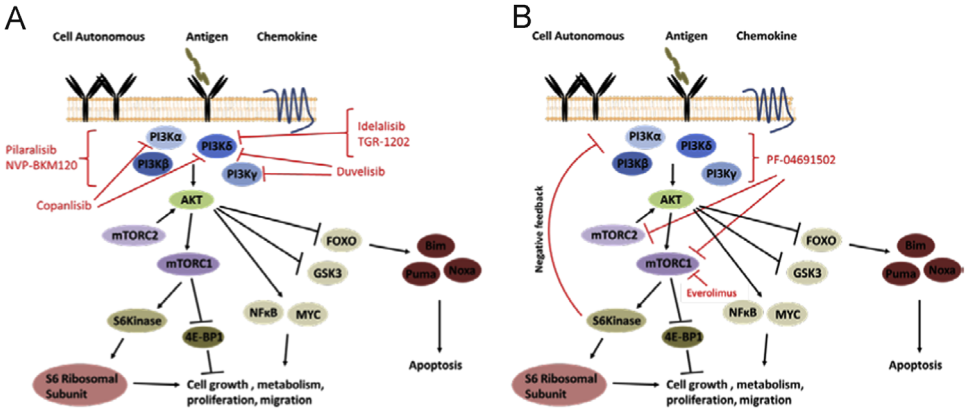

Fig. 1. Schematic representation of the PI3K/mTOR signalling pathway with pharmacological agents in pre-clinical/clinical development for CLL indicated. (A) PI3K activation by receptor ligation induces re-localisation and activation of AKT (amongst other proteins not shown) which in turn initiates downstream signalling events crucial for CLL survival and proliferation. PI3K inhibitors in pre-clinical development, clinical trials or approved for CLL treatment are indicted. mTOR exists in two complexes; mTORC1 which phosphorylates S6 kinase and 4E-BP1 (eukaryotic translation initiation factor 4E-binding proteins) thereby promoting translation and protein synthesis and mTORC2 which phosphorylates and thus enhances the activation of AKT. (B) S6 kinase is activated downstream of PI3K and mTORC1 and promotes ribosomal translational activity. S6 kinase also acts in a negative feedback loop to constrain further PI3K mediated signalling. Selective inhibition of mTORC1 (for example by everolimus as indicated) abrogates S6 kinase mediated negative feedback mechanisms and leads to enhancement of PI3K mediated signalling and AKT activation. This effect is thought to have limited the efficacy of mTOR inhibitors alone in the clinic for various cancers. Use of a dual PI3K/mTOR inhibitor (for example PF-04691502 as indicated) prevents this amplification of PI3K signalling by preventing the phosphorylation of AKT by mTORC2 and by directly inhibiting PI3K.