New perspectives with PI3K inhibitors in B-cell malignant hemopathies

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Phosphoinositide 3-kinase inhibitors represent a new group of promising targeted therapies for malignant hemopathies and primarily lymphoproliferative disorders. This short report summarises recent knowledge on the mechanism of action, the rationale to use it in humans bearing malignant hemopathies and preliminary clinical trials' data that led to the Food and Drug Administration approval of one of these compounds (idelalisib).

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Introduction

Phosphoinositide 3-kinases (PI3Ks) are a family of lipid kinases that control many physiological functions and cellular processes, which include cell proliferation, growth, survival, motility and metabolism. Activation of PI3K is found in a variety of malignant hemopathies. The PI3K inhibitors represent a new group of promising targeted therapies for acute myeloid leukaemia (AML) and lymphoproliferative disorders.

In this short report, we summarise recent knowledge on the mechanism of action, the rationale to use it in lymphoproliferative disorders and preliminary clinical trials' data that recently led to the Food and Drug Administration (FDA) approval of one of the compounds (idelalisib) in combination with rituximab for the treatment of patients with relapsed chronic lymphocytic leukaemia (CLL) and granted accelerated approval to idelalisib for relapsed follicular B-cell non-Hodgkin lymphoma (FL) or relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies.

The PI3K signalling pathway

PI3Ks are a family of lipid kinases that catalyse the phosphorylation of plasma membrane phosphoinositides resulting in phosphatidylinositol 3, 4, 5-trisphosphate (PI(3,4,5)P3/PIP3).[1] In short, PIP3 binding results in full activation of Akt. Active Akt then phosphorylates an array of proteins that control cell survival, growth and cell cycle progression.[2]

PI3Ks are subdivided into three classes (I-III).[3] Class I PI3Ks is further subdivided into class I_A and I_B, based on the type of cell surface receptor that activates PI3Ks: class I_A PI3Ks (comprising the catalytic isoforms p110α, p110β and p110δ) are activated by receptor tyrosine kinases (RTKs), while the class I_B PI3K (comprising the catalytic isoform p110γ) is activated by G-protein-coupled receptors (GPCRs).[2]

Deregulation of PI3K/Akt/mTOR signalling in cancer

Constitutive activation of the PI3K/Akt/mTOR pathway has been reported in many different human cancers.[4,5] Intriguingly, somatic mutations that activate catalytic class I PI3K isoforms are mostly restricted to PIK3 class I_A. However, it should be noted that p110β, p110δ and p110γ have the ability to induce oncogenic transformation.[6] Another type of genetic alteration are mutations in the phosphatase and tensin homolog deleted on chromosome ten (PTEN).[7] PTEN is a phosphatase that de-phosphorylates PIP3 thus antagonising PI3K activity.[8] Similarly, deregulated activation of the PI3K/Akt/mTOR pathway has been reported in leukaemia and lympho-

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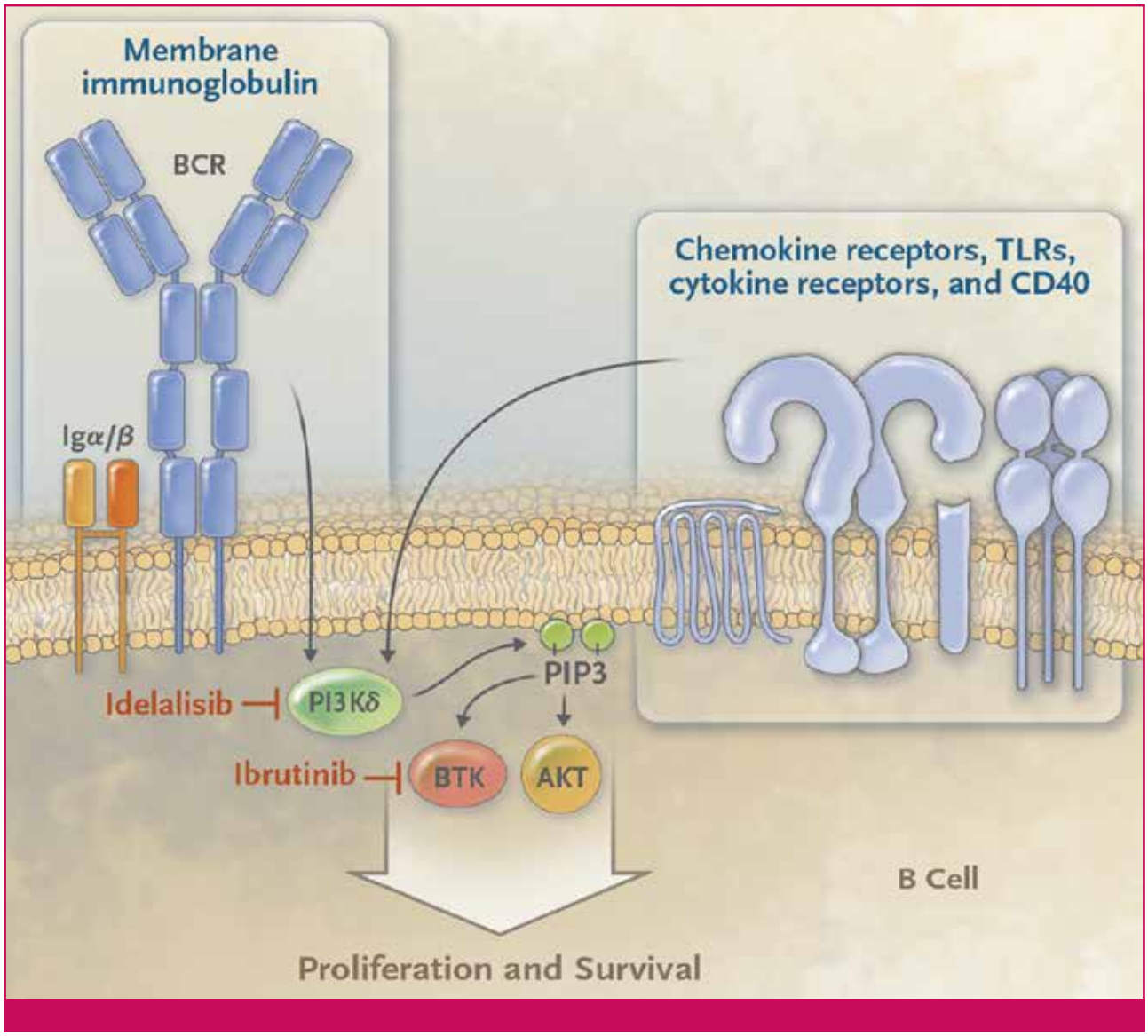

Figure 1. Mechanism of Action of Idelalisib and Ibrutinib. B-cell receptor (BCR) signaling activates phosphoinositide 3-kinase (PI3K) to produce the second messenger, phosphatidylinositol 3,4,5-trisphosphate (PIP3), which activates Bruton's tyrosine kinase (BTK) and AKT, a prosurvival kinase that binds PIP3 and plays a key role in many solid tumors. Idelalisib, a selective inhibitor of the delta isoform of PI3K, targets signal transduction downstream of the BCR in malignant B cells, whereas ibrutinib targets BTK. PI3K and BTK are also activated downstream of numerous other receptors on B cells, including CD40, cytokine receptors, chemokine receptors, and toll-like receptors (TLRs). The BCR is composed of antibody heavy and light chains associated with two signaling chains, Igα and Igβ. *Source: Fruman DA, Cantley LC. N Engl J Med 2014;370:1061-1062.*

ma.[9,10] In general, PIK3CA mutations are not believed to be the major cause of PI3K/Akt/mTOR pathway activation in leukaemia and lymphoma.[11] In contrast, PTEN inactivation has been reported in AML and non-Hodgkin's lymphoma (NHL).[12] The hyper-activation of the PI3K/Akt/mTOR pathway has been linked to increased cell growth and proliferation, survival and chemoresistance in leukaemia and lymphoma and thus represents an attractive target for the development of anti-cancer drugs in these malignancies.[2,10,13]

PI3K/Akt/mTOR pathway inhibitors in leukaemias and lymphomas

A wide array of small molecules has been developed.[14] These can be broadly subdivided into different classes: pan-PI3K inhibitors (BKM-120), isoform-specific PI3K inhibitors (idelalisib, IPI-145), PI3K/mTOR inhibitors (BEZ-235, VS-5584), Akt inhibitors (MK-2206, perifosine), allosteric mTOR inhibitors (rapamycin analogs, rapalogs: sirolimus, everolimus, temsirolimus, ridaforolimus) and mTOR kinase inhibitors (OSI-027, CC-223).

Table 1. Class 1 PI3K isoforms.

PI3K Isoforms	Cellular expression	Primary Physiological role
ALPHA (α)	Broad	Insulin signaling/angiogenesis
BETA (β)	Broad	Platelets function
GAMMA (γ)	Leucocytes	Neutrophils and T cell function
DELTA (δ)	Leucocytes	B cell signaling, development and survival

Single agent PI3K/Akt/mTOR pathway inhibitor treatment has been reported to produce incomplete responses in different cancers.[15] Therefore combining these targeted agents is a promising approach. In contrast to the situation in other cancers, B-cell malignancies appear to be uniquely responsive to PI3K inhibitors, in particular to isoform-specific PI3K inhibitors targeting the class I_A isoform p110δ.[3,15-17] This PI3K isoform is mostly expressed in leukocytes and plays a crucial role in intracellular signalling by the B- and T-cell receptors.[3,6,18-23] Accordingly, small molecule inhibitors of p110δ (*Figure 1*), in particular idelalisib, were shown to be active in several pre-clinical models of leukaemia and lymphoma.[3,22,24-26]

PI3K/AKT/mTOR inhibitor in clinical trials

The most advanced drug in terms of clinical data is idelalisib (inhibition of PI3K Δ). The phase I trial revealed a very well-tolerated drug with minimal side-effects up to 350mg BID but the dose of 150mg BID was recommended for phase II trials. Phases Ib trials studied combinations with rituximab, bendamustine, ofatumumab, fludarabine and chlorambucil without major intolerance.

The combination of idelalisib (150mg BID) and rituximab (375 mg/m^2/week x8) was chosen for the phase II trial in 64 patients with CLL or SLL; the OR was 96% with 19% CR . CR was observed even in 17p- CLL patients. The median time to response was two months. The most common adverse events were: diarrhoea (55%), pyrexia (42%), nausea (38%), rash (38%), chills (36%), cough (33%), fatigue (31.%), increased ALT (28%), increased AST (27%), pneumonia (27%), dyspnoea (23%), headache (23%), vomiting (20%), insomnia (20%), constipation (17%), pruritus (17%), and arthralgia (17%).

The phase III study of idelalisib and rituximab in CLL patients demonstrated improved rates of overall response and overall survival at twelve months, compared to rituximab and placebo.[20]

The phase II study of idelalisib in patients with NHL (follicular lymphoma, small lymphocytic lymphoma, marginal-zone lymphoma, and lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinaemia), showed a response rate of 57%, with 6% of patients having complete responses.[17] Idelalisib had an acceptable safety profile in NHL patients.[17]

These clinical trial results with idelalisib led to its approval by the FDA in July 2014 for relapsed CLL (in combination with rituximab), for relapsed follicular B-cell NHL and for relapsed small lymphocytic leukaemia.[16,17,27] Idelalisib is currently undergoing further clinical testing in additional indications, as a single agent or in combination with other drugs. A phase III trial is ongoing in Belgium comparing bendamustine/rituximab +/- idelalisib in naive CLL patients.

Other PI3K inhibitors are currently being studied in leukaemia and lymphoma. IPI-145 (duvelisib), a dual specificity p110δ and p110γ inhibitor was shown to be active in pre-clinical studies in CLL.[28] This compound is currently being evaluated (25mg BID 21d/28d p.o.) in clinical trials in lymphoma (phase III, IPI-145 combined with rituximab) and CLL (phase III, IPI 145 compared with the anti-CD20 monoclonal antibody ofatumumab).

BKM-120 (buparlisib) is a pan-class I PI3K inhibitor which is currently undergoing clinical testing in B-cell lymphoma and CLL.[29,30]

Conclusion

The approval, in 2014, of the first PI3K inhibitor demonstrating activity in CLL and B-cell NHL strongly supports the further development of PI3K pathway inhibitors in leukaemia and lymphoma. The most advanced drugs are PI3K δ inhibitors (idelalisib).

Multiple clinical trials are ongoing with these agents in haematological malignancies and it is likely that further drugs will be approved in different indications in the

Key messages for clinical practice

1. Idelalisib and others PI3K inhibitors represent a new group of promising targeted therapies for malignant hemopathies.
2. Adverse effects – generally mild – are gastrointestinal disturbances and fatigue. Abnormal liver function and pneumonia are also reported.
3. The Food and Drug Administration recently approved the compound idelalisib in combination with rituximab for relapsed CLL.

near future. To optimise the use of these agents, the combinatorial approaches involving PI3K inhibitors and other drugs (BTK inhibitor, mTOR inhibitor, etc. or standard chemotherapy), are major developments for the future.

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