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Idelalisib —targeting PI3Kδ in patients with B cell malignancies

Jan A. Burger and **Klaus Okkenhaug**
Department of Leukemia, MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, Texas 77030, USA (J. A. B.) and Laboratory of Lymphocyte Signaling and Development, The Babraham Institute, Cambridge CB22 3AT, United Kingdom (K. O.)

Abstract

Idelalisib, the first PI3Kδ inhibitor in clinical use, has excellent activity in patients with chronic lymphocytic leukaemia and indolent B cell lymphomas, heralding a new era of targeted therapy for these types of cancer. Idelalisib intercepts critical communications between B cells and the microenvironment, including B cell receptor signalling and chemokine networks.

After the introduction of monoclonal antibodies for the treatment of indolent lymphomas and chronic lymphocytic leukaemia (CLL) in the 1990s, kinase inhibitors that target B cell receptor (BCR) signalling are now emerging as the next breakthrough targeted therapy against these types of cancer. Chemo-immunotherapy (CIT), which combines anti-CD20 antibodies—such as rituximab—with chemotherapy, is currently the standard therapy for younger patients with these diseases, based on high efficacy and long remissions, especially in low-risk patients. However, elderly patients often cannot tolerate these treatments. Furthermore, CIT also becomes less effective after disease relapse and in patients with poor prognostic markers, such as disrupted function of the cell cycle regulator p53 due to mutations in *TP53* or deletions on the short arm of chromosome 17 [del (17p)]. These drawbacks, as well as short-term and long-term toxicities of CIT, fostered the development of alternative treatment approaches. Remarkably, kinase inhibitors targeting three different enzymes, the spleen tyrosine kinase (SYK),[1] Bruton's tyrosine kinase (BTK),[2] and the phosphatidylinositol-4,5-bisphosphate 3-kinase δ (PI3Kδ)[3, 4], have all been developed within the last six to eight years. Specifically, clinical trials evaluating fostamatinib[1], a SYK inhibitor, and ibrutinib,[2] a BTK inhibitor, have demonstrated high activity of these agents in patients with CLL, indolent B cell lymphomas, and mantle cell lymphoma (MCL). Now, two manuscripts by Gopal et al.[4] and Furman et al.[3] highlight the efficacy and safety of idelalisib, a PI3Kδ inhibitor, in patients with indolent non-Hodgkin's lymphoma (iNHL) and CLL.

Gopal and colleagues[4] published the results of an open-label Phase II trial that accrued 125 patients with relapsed iNHL who had failed a median of four previous treatments. Patients received idelalisib, as single-agent, continuously at a dose of 150 mg orally twice a day until disease progression or toxicity. The authors reported an objective response rate of 57%, with

Correspondence to: Jan A. Burger (jaburger@mdanderson.org).
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over 90% of patients showing a reduction in lymph node sizes. Responses were not affected by disease subgroups, and seemed to be relatively durable (median response duration was 12.5 months).[4] At the same time, Furman *et al.*[3] published the results of a randomized Phase III trial that enrolled 220 patients with CLL, who were randomly assigned to receive rituximab plus either idelalisib (150 mg) or placebo, orally twice a day on a continuous schedule.[3] Significantly higher overall response rates (81% versus 13%) and overall survival (92% versus 80% at 12 months of follow up) favoured the idelalisib arm.[3] The study was, in fact, stopped prematurely by the safety monitoring board owing to the overwhelming efficacy of idelalisib.[3] Particularly encouraging were the response rates in high-risk patients with the chromosomal alteration del (17p), which were similar to those observed in low-risk patients. Both studies established idelalisib as a highly attractive therapy for patients with relapsed iNHL and CLL. The safety profile of idelalisib seems to be relatively benign, with the appearance of few grade 3 or higher adverse effects compared with placebo. These adverse effects include diarrhea (idelalisib 4%, placebo 0%) and transaminitis (idelalisib 5%, placebo 1%).[3] Diarrhea could be an on-target effect of idelalisib, given that a mild inflammatory bowel disease was noted in previous experiments with PI3Kδ kinase-mutant mice.[5] Of note, most of these adverse effects could be managed with dose-adjustments or treatment interruptions; however, longer-term observations are needed to establish whether these or other adverse effects could become an obstacle for long-term treatment for a subset of patients.

Idelalisib (also known as CAL-101 or GS-1101) is a potent and selective inhibitor of the p110δ subunit of PI3Ks. The PI3Ks are divided into 3 classes; I, II, and III. Class I kinases contain 4 isoforms, designated PI3Kα, β, γ, and δ. PI3Ks integrate and transduce signals from various surface molecules, such as the BCR,[6] chemokine receptors, and adhesion molecules, thereby regulating key cellular functions, including growth, survival, and migration.[7] The PI3K pathway is commonly activated in human cancers, either by activating mutations of PI3K signalling modules, or by activation of upstream surface receptors.[7] Specifically, mutations in *PTEN, PIK3CA* (the gene encoding the PI3Kα catalytic subunit p110α), or *PIK3C1* (encoding the PI3K p85α regulatory subunit), commonly activate the PI3K pathway in solid tumours. By contrast, malignant B cells from patients with CLL and iNHL do not generally harbour activating PI3K pathway mutations. The activity of PI3K in malignant B cells is maintained through cellular and molecular interactions with the tumour microenvironment (Figure 1).[8] These interactions occur within secondary lymphatic tissues, and result in the activation of several signalling pathways—such as the PI3K/AKT axis—that are necessary for maintenance and expansion of B cells.[8] BCR signalling is a critical pathway in the pathogenesis of several B cell malignancies, including CLL.[9] PI3Kδ has an essential, non-redundant role in BCR signalling as demonstrated by the fact that PI3K signalling was able to rescue the survival of mature B cells in BCR-deficient mice.[6] PI3Kδ is the major PI3K isoform in B cells, and its expression is mainly restricted to hematopoietic cells, in which it is involved in B-cell homeostasis and function. Mice with inactivating PI3Kδ mutations have reduced numbers of B1 cells (a subclass of B cell lymphocytes involved in the humoral immune response) and marginal zone B cells, low immunoglobulin levels, poor responses to immunization, and defective BCR, CD40 and chemokine receptor signalling.[5] Correlative studies in patients with CLL demonstrated that treatment with

idelalisib thwarts BCR signalling, life support by nurse-like cells, and BCR-dependent secretion of the CCL3 chemokine, both *in vitro* and *in vivo*.[10] These findings are important for understanding the clinical activity of idelalisib. After beginning therapy with idelalisib, patients with CLL typically experience rapid resolution of enlarged lymph nodes, along with a transient surge in blood lymphocyte counts.[3]. These effects can be explained by the idelalisib-induced blockade of tissue anchors signals and chemokine receptor signalling, which normally retain CLL cells in lymph glands.[10] Remarkably, treatment with SYK[1] or BTK inhibitors[2] produce similar clinical effects (early, transient lymphocytosis and rapid lymph node shrinkage) in patients with CLL which suggests that these BCR-associated kinases have similar roles in CLL cell migration, tissue homing, and survival. On these bases, the redistribution lymphocytosis can now be considered as a benign target-related clinical outcome rather than an adverse event for this class of inhibitors.

Although there is much excitement about these new targeted treatments, durability of responses, risk of disease transformation and drug resistance, as well as long-term adverse effects will need to be carefully monitored. Pros and cons of combination therapy of idelalisib with cytotoxic drugs or antibodies is another issue that remains unanswered and will require further investigations. Responses to idelalisib in CLL can be accelerated and improved by combinations treatment with B cell-targeting antibodies, such as rituximab.[3] Moreover, the combination of idelalisib with cytotoxic drugs is expected to increase also the remission rates and depth of remissions, but likely at the expense of higher toxicity. Combination trials of idelalisib with various, older and newer, drugs are ongoing; the results of these studies will further guide us towards the optimal use of PI3K inhibition in B-cell malignancies.

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Key Points

- Idelalisib is an attractive alternative to chemotherapy-based regimen, especially for patients who cannot tolerate or who relapse after conventional chemo-immunotherapy
- Idelalisib blocks signal transduction pathways that lymphoma and CLL cells use for growth and maintenance in tissue microenvironments

"…kinase inhibitors that target B cell receptor (BCR) signalling are now emerging as the next breakthrough targeted therapy…"

"…durability of responses, risk of disease transformation and drug resistance, as well as long-term adverse effects will need to be carefully monitored"

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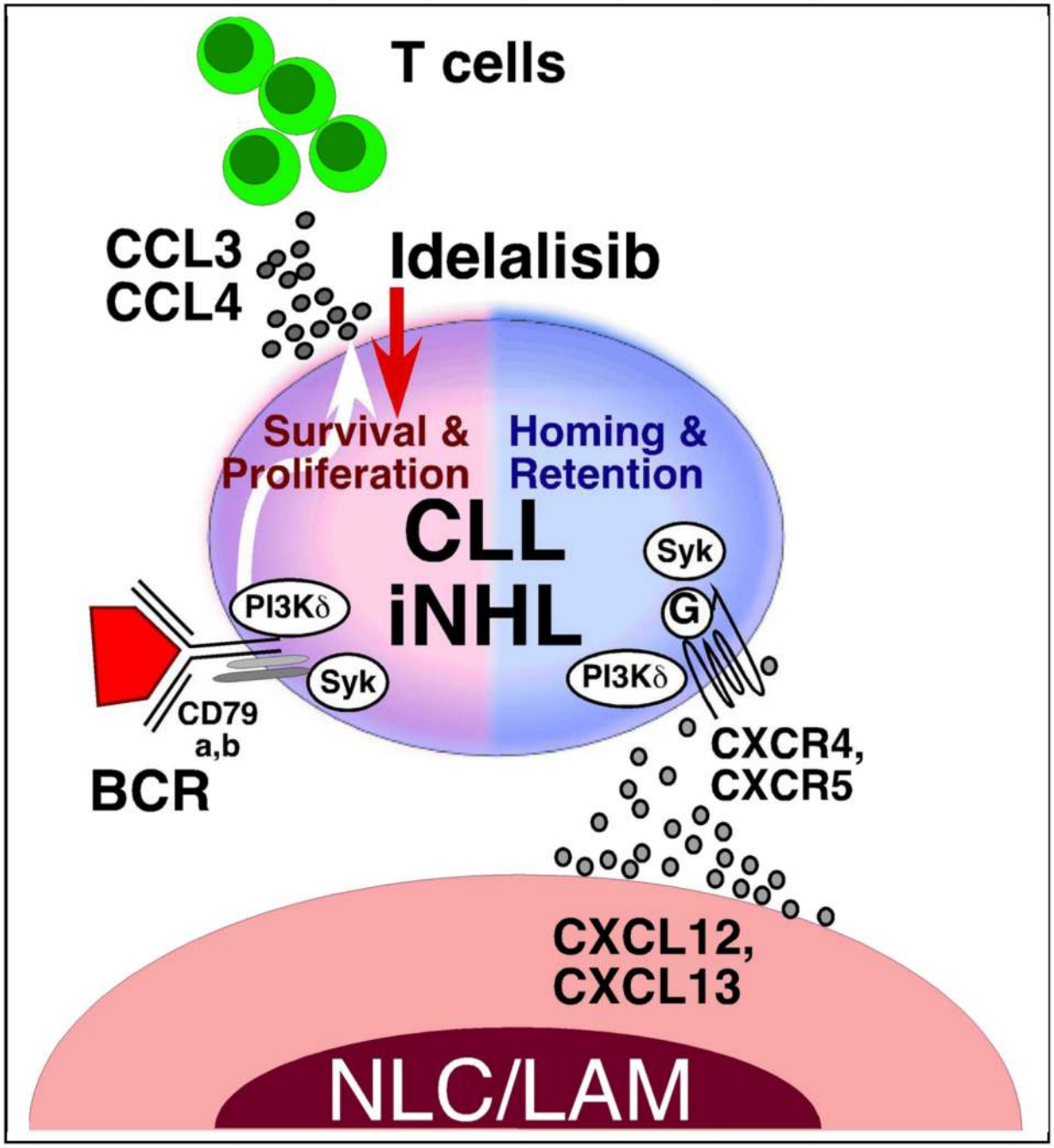

Figure 1. Effects of idelalisib on cross talk between malignant B cells and the microenvironment

CLL cells and indolent non-Hodgkin's lymphoma (iNHL) cells express B cell receptors (BCR) that are activated in the lymphoid tissues, leading to downstream signaling. PI3Kδ activation is a critical component of this signaling pathway, promoting survival and proliferation of the malignant cells (left). PI3Kδ activation also induces secretion of chemokines (CCL3, CCL4) by the malignant B cells, which in turn attract accessory cells, such as T cells, to the tissue microenvironment. These activation events are turned off by PI3Kδ blockade with idelalisib. In addition, idelalisib also interferes with tissue homing and

retention mechanism (right hand side). Tissue stromal cells, such as monocyte-derived nurselike cells (NLC) and lymphoma-associated macrophages (LAM) secrete chemokines (CXCL12, CXCL13) which cause homing and tissue retention of CLL and iNHL cells. Blockade of chemokine receptor (CXCR4, CXCR5) signaling by idelalisib explains the re-distribution of tissue-resident CLL cells into the peripheral blood during idelalisib therapy.

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