Ibrutinib (PCI-32765) in Chronic Lymphocytic Leukemia

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KEYWORDS

• B-cell receptor inhibitor • Bruton tyrosine kinase inhibitor • Ibrutinib • PCI-32765
• Chronic lymphocytic leukemia

KEY POINTS

- B-cell receptor (BCR) signaling plays a crucial role in pathogenesis of chronic lymphocytic leukemia (CLL).
- Many kinases in the BCR signaling pathway are being explored as therapeutic targets such as Src family kinases, spleen tyrosine kinase, phosphoinositide 3 kinase, and Bruton tyrosine kinase (BTK).
- Ibrutinib (PCI-32765) is a selective, irreversible, and oral inhibitor of BTK.
- Preclinical data suggest that ibrutinib affects both CLL cell survival/proliferation as well as CLL cell migration/homing.
- Preliminary clinical data in patients with CLL is encouraging, with a 67% response rate in the 420-mg dose cohort in the relapsed/refractory CLL setting.
- Combination of ibrutinib with monoclonal antibodies and chemoimmunotherapy has also shown favorable early results.
- BCR inhibitors will likely become an important component of CLL therapeutics in the near future.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults in the Western world, with approximately 16,060 men and women expected to be diagnosed with CLL in year 2012 in the United States.[1] Most patients with CLL do not need treatment at diagnosis; however, most patients need CLL-directed therapy in their life time. Chemoimmunotherapy is the current standard of care for patients with CLL needing treatment.[2] One of the commonly used regimens is FCR (fludarabine, cyclophosphamide, rituximab). Tam and colleagues[3] reported long-term follow-up of the FCR regimen for frontline treatment of CLL with a complete remission (CR) rate of 72%

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and median progression-free survival (PFS) of 80 months. Despite these impressive results, certain subgroups of patients treated with chemoimmunotherapy have less than optimal outcomes. These patients include older adults (>65 years old), those with poor-risk cytogenetics (del[17p], del[11q]), and patients with relapsed/refractory disease.[2–4] Many approaches have been undertaken to improve the outcome of patients with CLL, including incorporation of drugs such as lenalidomide, ofatumumab, alemtuzumab, and bendamustine.[5–11] These treatment strategies offer options after relapse after chemoimmunotherapy, but outcomes are still less than satisfactory, with approximately 4500 patients expected to die from CLL in the United States in the year 2012.[2] This situation underscores the need to develop better therapeutics for patients with CLL.

B-cell receptor (BCR) activation signaling plays a crucial role in the pathogenesis in CLL.[12–15] The BCR signaling pathway consists of immunoglobulin bound to the cell membrane, which attaches to a heterodimer consisting of CD79a and CD79b.[15–17] Binding of a ligand to the membrane immunoglobulin leads to recruitment and phosphorylation of spleen tyrosine kinase (SYK) and Src family kinases (LYN), which in turn recruit and phosphorylate many kinases and adapter proteins, including Bruton tyrosine kinase (BTK). BTK is a nonreceptor tyrosine kinase of the Tec kinase family and plays a crucial role in BCR signaling.[18,19] BTK is expressed in non–T-cell hematopoietic cell lineages.[20,21] The BTK gene is located on chromosome Xq21.33-q22, and mutations in this gene result in X-linked agammaglobulinemia, a condition characterized by marked reduction in mature B cells, severe hypogammaglobulinemia, and increased susceptibility to infections.[22] BTK activates downstream molecules such as nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) kinase (MEK)/extracellular signal regulated kinase (ERK), which are involved in many cellular processes, including proliferation, survival, differentiation, apoptosis, and metabolism. Gene expression profiling has shown that BCR signaling is the most expressed signaling pathway in patients with CLL.[14] BCR signaling is enhanced in patients with poor prognostic markers such as ZAP-70 overexpression and those with unmutated immunoglobulin heavy chain gene (*IGHV*) rearrangement.[23,24] Activated BCR signaling has also been shown to be required for cell survival in the activated B-cell subtype of diffuse large B-cell lymphoma (DLBCL).[25] Thus, multiple lines of data point to the crucial role of BCR signaling in CLL and other B-cell lymphoid malignancies. Many kinases in the BCR signaling pathway are being pursued as therapeutic targets in CLL, including LYN,[26] SYK,[27–29] phosphoinositide 3 kinase (PI3K),[30–32] and BTK.[16,17]

Ibrutinib (formerly PCI-32765, Pharmacyclics, Sunnyvale, CA) (**Fig. 1**) is an oral, selective, and irreversible inhibitor of BTK and is the focus of this article. Ibrutinib was initially developed by Celera Genomics (now Quest Diagnostics, Madison, NJ) and acquired by Pharmacyclics in 2006. Ibrutinib forms a specific bond with the cysteine-481 of BTK.[33] It leads to highly potent BTK inhibition with an IC_{50} (half maximal inhibitory concentration) of 0.5 nM (**Table 1**).[34] Ibrutinib is orally administered with daily dosing and has no cytotoxic effect on T cells.[35]

PRECLINICAL STUDIES

Honigberg and colleagues[34] showed that in a B-cell lymphoma cell line (DOHH2), ibrutinib irreversibly inhibited autophosphorylation of BTK (IC_{50} 11 nM) and phosphorylation of downstream kinases such as ERK. Phosphorylation of upstream kinases such as SYK was not affected. These investigators also showed that ibrutinib blocked the transcriptional upregulation of B-cell activation genes in primary cultures of human peripheral B cells.[34] In a mouse model for lupus nephritis, ibrutinib reduced

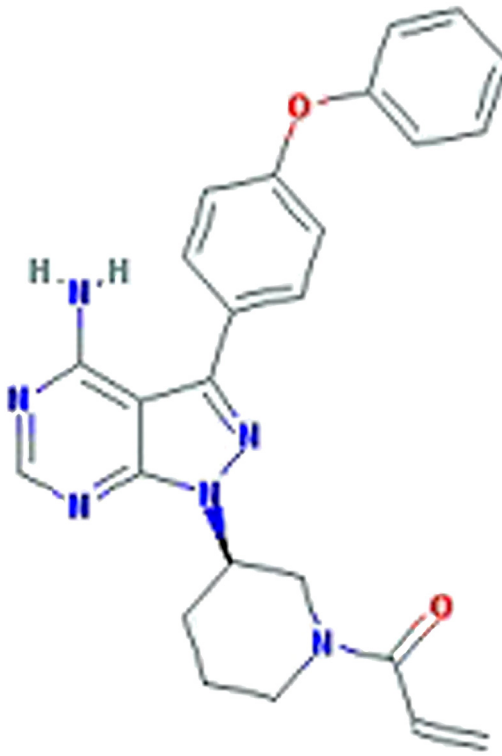

Fig. 1. Chemical structure of PCI-32765 (ibrutinib), a BTK inhibitor.

proteinuria, lowered anti-dsDNA antibody levels, and improved glomerular function, indicating the potential role for ibrutinib in autoimmune diseases.[34] Clinical activity of ibrutinib with once daily oral dosing was also seen in naturally occurring B-cell lymphoma in dogs.[34]

Herman and colleagues[35] reported that BTK mRNA expression was significantly higher in CLL (CD19+) cells compared with normal B cells. These investigators also noted that baseline BTK protein expression was highly variable in the CLL cells and protein expression did not correlate with known prognostic markers such as age, cytogenetics, *IGHV* status, and ZAP-70 expression. Treatment of CLL cells with ibrutinib induced apoptosis in a dose-dependent and time-dependent manner, which was independent of baseline cytogenetics, *IGHV* mutational status, or baseline BTK protein expression but dependent on caspase-pathway activation.[35] Ibrutinib also induced apoptosis in normal B cells, but this was significantly less than that seen in CLL cells, indicating that CLL cells are more sensitive to ibrutinib than normal B cells. Ibrutinib treatment of CLL cells inhibited downstream signaling pathways, including ERK1/2 phosphorylation, CD40L-induced AKT phosphorylation, and CD40L-induced NF-kB DNA binding.[35]

Ponader and colleagues[36] evaluated the role of the tissue microenvironment of CLL cells and its effect on treatment with ibrutinib. They reported that ibrutinib treatment significantly inhibited CLL cell migration and survival in a nurselike cell coculture assay. In this model, ibrutinib treatment significantly decreased the levels of CCL3 and CCL4 and inhibited chemotaxis toward CXCL12 and CXCL13. In an adoptive transfer TCL1 mouse model, ibrutinib treatment was reported to delay CLL disease

Table 1
Inhibition of selected kinases by ibrutinib

Kinase	IC_{50} (nM)	Fold Selectivity for BTK Inhibition
BTK	0.5	—
BLK	0.5	1
BMX	0.8	1.6
CSK	2.3	4.6
FGR	2.3	4.6
EGFR	5.6	11.2
ErbB2	9.4	18.8
ITK	10.7	21.4
JAK3	16.1	32.2
RET	36.5	73
FLT3	73	146
TEC	78	156
ABL	86	172
c-SRC	171	342
LYN	200	400
PDGFRα	718	1436
JAK1	>10,000	>10,000
JAK2	>10,000	>10,000
PI3K	>10,000	>10,000
PLK1	>10,000	>10,000
SYK	>10,000	>10,000

Abbreviations: ABL, Abelson tyrosine-protein kinase; BLK, B lymphoid tyrosine kinase; BMX, Bone marrow kinase on chromosome X; BTK, Bruton Tyrosine Kinase; c-SRC, Src oncogene; CSK, c-Src tyrosine kinase; EGFR, Epidermal growth factor receptor; ErbB2, v-erb-b2 erythroblastic leukemia viral oncogene homolog 2; FGR, Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog; FLT3, fms-related tyrosine kinase 3; ITK, IL2-inducible T-cell kinase; JAK1, Janus kinase 1; JAK2, Janus kinase 2; JAK3, Janus kinase 3; LYN, v-yes-1 Yamaguchi sarcoma viral related oncogene homolog; PDGFRα, platelet-derived growth factor receptor alpha; PLK1, Polo-like kinase 1; PI3K, phosphatidylinositol 3-kinase; RET, Rearranged during Transfection; SYK, spleen tyrosine kinase; TEC, transient erythroblastopenia of childhood.

Data from Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl Acad Sci U S A 2010;107(29):13075–80.

progression.[36] Overall, the preclinical data suggest that ibrutinib is a selective, irreversible BTK inhibitor with effect on both CLL cell survival/proliferation and CLL cell migration/homing.[15]

CLINICAL STUDIES

Clinical studies with ibrutinib have been published only in abstract form. Ibrutinib was evaluated in a phase 1 study in patients with CLL and lymphoma (small lymphocytic lymphoma (SLL), follicular lymphoma, mantle cell lymphoma [MCL], DLBCL, marginal zone lymphoma, Waldenstrom macroglobulinemia) with a 28-day-on/7-day-off schedule in 5 dose-cohorts (1.25–12.5 mg/kg orally daily) and once daily continuous dose in 2 dose cohorts (8.3 mg/kg and 560 mg fixed dose).[37] Fifty-six patients with relapsed/refractory disease (median 3 previous regimens [range 1–10]) were enrolled.

No dose-limiting toxicity was observed. Maximum tolerated dose was not reached. Of the 50 evaluable patients, 30 (60%) patients achieved an objective response rate (ORR) (23% CR, 77% partial response [PR]). Responses were seen in all non-Hodgkin lymphoma (NHL) subtypes and irrespective of the dose levels. A unique pattern of response was noted, with a transient lymphocytosis lasting a few months. Transient lymphocytosis was also noted by Ponader and colleagues[36] in an adoptive transfer TCL1 mouse model after treatment with ibrutinib. Transient lymphocytosis is postulated to be caused by an initial compartment shift of CLL cells from lymphatic tissues into the peripheral blood.

In a phase 1B/2 study (PCYC-1102), patients with relapsed/refractory CLL and older adults (≥65 years) with untreated CLL were treated with 2 fixed doses of ibrutinib (420 mg daily and 840 mg daily).[38] Ibrutinib was given orally once daily for 28-day cycles until disease progression. Patient enrollment occurred from May 2010 to July 2011. Sixty-one patients were enrolled in the relapsed/refractory cohort (420-mg cohort, n = 27; 840-mg cohort, n = 34). The median age was 64 years (range, 40–81 years). The median number of previous therapies for the 420-mg cohort was 3 (2–10), and for the 840-mg cohort, it was 5 (1–12). High-risk molecular features were present in most of the patients (unmutated *IGHV*: 79%; del[17p]: 36%; del [11q]: 39%). The median follow-up for the 420-mg cohort was 12.6 months, and for the 840-mg cohort, it was 9.3 months. Seventy-five percent of the patients were still on the study at the time of last follow-up. Treatment was well tolerated, with most adverse events being grade 1/2 (diarrhea, fatigue, and nausea). Six patients needed dose reduction (2 in the 420-mg cohort, 4 in the 840-mg cohort). Grade 3/4 hematologic toxicity (neutropenia, anemia, thrombocytopenia), irrespective of attribution, was seen in 8%, 7%, 7% (420-mg cohort) and 21%, 12%, 9% (840-mg cohort), respectively. ORR was noted to be 67% (63% PR, 4% CR) in the 420-mg cohort and 68% (all PR) in the 840-mg cohort. An additional 22% (420-mg cohort) and 24% (840-mg cohort) of patients achieved nodal PR (>50% reduction in aggregate lymph node size) with residual lymphocytosis. Maximum change in tumor burden is shown in **Fig. 2**. Clinical responses were independent of the high-risk molecular

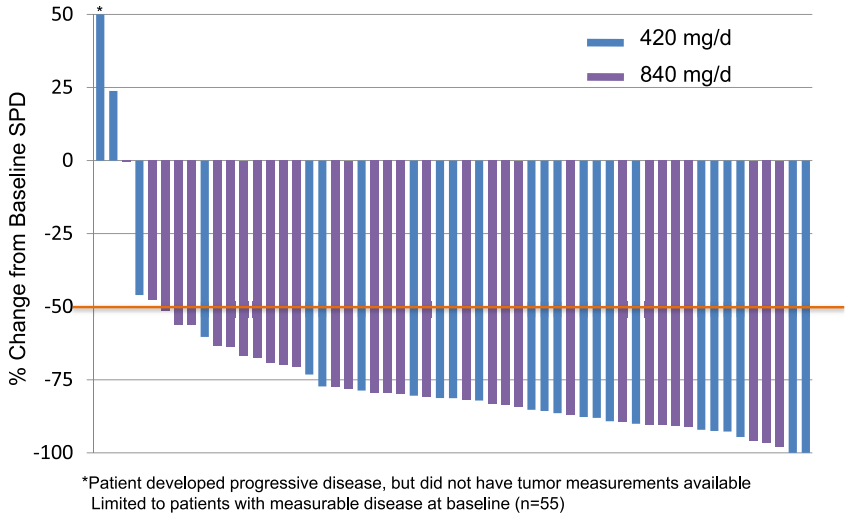

Fig. 2. Maximum change in tumor burden in patients with relapsed/refractory CLL treated with single-agent ibrutinib (PCYC-1102 trial).

features. Seventy-four percent of the patients with unmutated *IGHV*, 65% with del(17p), and 73% with del(11q) responded. Most clinical responses were nodal responses in the first 4 to 5 months of therapy, which then improved to PR/CR with continued treatment over the next few months. Estimated 18-month PFS was 87.7% in the 420-mg cohort.[39] A transient lymphocytosis typically peaking within the first 2 months of treatment, followed by gradual resolution over the next 6 to 8 months, was noted (**Fig. 3**).

In the update of the data presented at the European Hematology Association meeting in June 2012, O'Brien and colleagues[39] reported the outcomes of 31 treatment-naive older patients (420 mg, n = 26; 840 mg, n = 5). Enrollment in the 840-mg cohort was terminated after similar results were noted between the 420-mg and 840-mg cohort in the relapsed/refractory cohort. Median age was 71 years (range, 65–84 years), with 75% of patients being older than 70 years. Forty-three percent of patients had unmutated *IGHV* and 6% had del(17p). Most of the adverse events (AE) were mild (grade 1–2) and included diarrhea, nausea, and fatigue. Grade 3 nonhematologic AE potentially related to the drug were seen in 6 (19%) patients (diarrhea, 4 patients; hyponatremia, 2 patients; hemorrhagic enterocolitis, 1 patient). No grade 4 nonhematologic toxicity was seen. Hematologic toxicity of grade 3 or higher was seen in 4 (12%) patients and included 2 patients each with anemia and thrombocytopenia. Neutropenia was not observed. In the 420-mg cohort, only 4 of the 26 patients have discontinued therapy, and only 1 patient for disease progression. With a median follow-up of 14.4 months on the 420-mg cohort, 81% achieved a response (69% PR, 12% complete response) by the International Workshop on Chronic Lymphocytic Leukemia criteria. An additional 12% of patients achieved a nodal response. Fifty percent of patients with baseline thrombocytopenia or anemia noted sustained improvement in blood counts. The responses were independent of high-risk features. Ninety-two percent of patients with unmutated *IGHV* responded. There were 2 patients with del(17p), and both responded. The estimated 15-month median PFS for the 420-mg cohort was 96%.

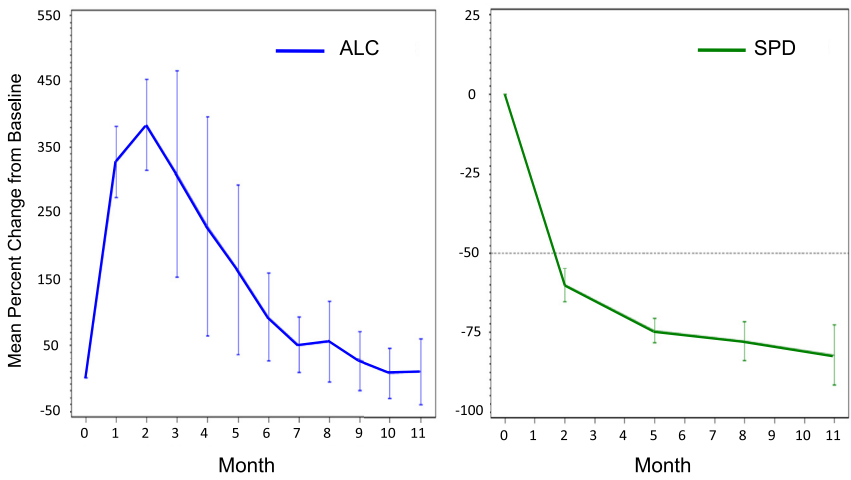

Fig. 3. Characteristic response pattern with transient lymphocytosis typically peaking within the first 2 months of treatment, followed by gradual resolution over the next 6 to 8 months. Decrease in lymphadenopathy was consistent from the beginning. Data derived from patients with relapsed/refractory CLL treated with single -agent ibrutinib (PCYC-1102 trial).

Given the impressive single-agent activity of ibrutinib in patients with CLL, trials exploring combinations of ibrutinib with either monoclonal antibodies (rituximab or ofatumumab) or with chemotherapy (bendamustine or FCR) have been initiated. Some of these trials have been reported in abstract form. Preliminary data have been reported for ibrutinib in combination with ofatumumab (PCYC-1109-CA trial).[40] Patients with relapsed/refractory CLL following 2 or more previous therapies, including a purine-nucleoside analogue, were treated with ibrutinib 420 mg daily with addition of ofatumumab from cycle 2 onwards. Twenty-four patients with CLL/prolymphocytic leukemia (PLL) and 3 with Richter transformation were treated. The median age was 66 (range 51–85). High-risk cytogenetics were seen in most patients (10 patients with del[17p] and 9 patients with del[11q]). Most AE were grade 1 to 2. All patients with CLL/PLL and 2 of the 3 patients with Richter transformation achieved PR.

Brown and colleagues[41] reported preliminary data on the combination of ibrutinib with bendamustine/rituximab (PCYC-1108-CA) in relapsed/refractory patients with CLL. Thirty patients were enrolled, with a median age of 62 years (range 41–82 years). The median number of previous therapies was 2 (range 1–4). Twenty-three percent had deletion 17p, and 43% had deletion 11q. No added toxicity was observed with the addition of ibrutinib. With a median follow-up of 8.1 months, 23 of the 30 patients were still on study, with only 2 patients coming off protocol for disease progression. The ORR was 93% (13% CR, 80% PR), which is higher than the 59% seen with bendamustine-rituximab in historical controls. As with single-agent ibrutinib, responses were independent of high-risk genetic and molecular features.

Ibrutinib has also been evaluated in other lymphoid malignancies, including MCL, DLBCL, Waldenstrom macroglobulinemia, and multiple myeloma. In the preliminary results of a phase 2 study (PCYC-1104), Wang and colleagues[42] reported outcomes of 48 relapsed/refractory patients with MCL (29 bortezomib-naive; 19 bortezomib-exposed) who were treated with single-agent ibrutinib. Ibrutinib was administered orally at 560 mg daily until disease progression. The median age was 67 years (range, 62–72 years). Therapy was well tolerated, with most frequently reported AE being grade 1 or 2 diarrhea, fatigue, and nausea (similar to the CLL study). The ORR was 67% (16 of the 24 evaluable patients). Responses were seen in both bortezomib-naive and bortezomib-exposed cohorts.

Many ongoing/planned trials are exploring the role of ibrutinib in hematologic malignancies. Some examples include ibrutinib as a single agent in Waldenstrom macroglobulinemia and multiple myeloma, ibrutinib with rituximab in CLL, ibrutinib with bendamustine/rituximab in relapsed DLBCL/MCL, ibrutinib with R-CHOP chemotherapy in newly diagnosed DLBCL. A phase 3 randomized, open-label registration trial of ibrutinib versus ofatumumab in patients with relapsed or refractory CLL (RESONATE trial) has been initiated.[43] The primary end point of this trial is PFS, with key secondary end points being overall response rate, overall survival, and quality of life measures. Another planned phase 3 study includes a randomized study of bendamustine/rituximab plus ibrutinib versus bendamustine/rituximab plus placebo in relapsed or refractory patients with CLL/SLL.

SUMMARY

It is clear from the preclinical and preliminary clinical data (as stated earlier) that BTK inhibitors (along with other BCR signaling pathway inhibitors) are going to revolutionize the treatment of patients with CLL. Besides ibrutinib, there are other BTK inhibitors in clinical development, such as AVL-292 (Avila Therapeutics, now part of Celgene Corporation, Summit, NJ) and ONO-WG-307 (Ono Pharmaceutical, Osaka, Japan).

In the coming few years, there will be a barrage of preclinical and clinical data with these drugs. Thus far, the clinical responses with ibrutinib have been impressive, with manageable toxicities. It is likely that ibrutinib and other drugs targeting the BCR pathway will become an integral component of CLL and NHL therapy.

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