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Pharmacokinetic and pharmacodynamic evaluation of ibrutinib for the treatment of chronic lymphocytic leukemia: rationale for lower doses

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Abstract

Introduction—Ibrutinib, a first-in-class covalent inhibitor of Bruton's tyrosine kinase (BTK), is approved in many countries for the treatment of relapsed/refractory chronic lymphocytic leukemia (CLL) and for previously untreated disease with a 17p deletion and, most recently, as a frontline therapy for CLL. In controlled trials in CLL, ibrutinib produced high response rates and improved survival in both the frontline and relapsed settings. While ibrutinib controls CLL with impressive efficacy, it only infrequently induces complete remissions, particularly of relapsed CLL, and does not eradicate minimal residual disease. Finally, ibrutinib is extremely expensive, has off-target toxicities, and requires indefinite therapy.

Areas covered—In this article, we provide an overview of the CLL therapeutic landscape and discuss the pharmacokinetic and pharmacodynamic aspects of ibrutinib. Major clinical trials of ibrutinib in CLL are summarized, and its safety profile explored.

Expert Opinion—Ibrutinib represents a transformative advance in CLL management and has validated BTK as a therapeutic target in this disease, but has some limitations, leading to the emergence of other BTK inhibitors and mechanism-based combination strategies. Given complete BTK occupancy at lower doses of ibrutinib and declining levels of BTK on ibrutinib therapy, lower doses of ibrutinib in CLL are being explored.

Keywords

Bruton tyrosine kinase; B-cell receptor; chronic lymphocytic leukemia; dosing; ibrutinib; pharmacokinetic; pharmacodynamics

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1. Introduction

The last several years have seen an unprecedented increase in the availability of targeted therapeutics for chronic lymphocytic leukemia (CLL), the most common leukemia in the Western hemisphere, with 18,960 new cases estimated in the United States this year, with 4,660 deaths.[1] Indeed, gains in the treatment of CLL were hailed as the “advance of the year” in 2015 by the American Society of Clinical Oncology. This reflects the translation of key concepts underlying the biology of the disease, chiefly the critical importance of signaling via the B-cell receptor (BCR) pathway (reviewed in ref. [2]) and the exquisite dependence of CLL cells on the B-cell lymphoma 2 (BCL2) anti-apoptotic protein for survival.[3] Ibrutinib, an irreversible inhibitor of Bruton tyrosine kinase (BTK), a key signaling molecule in the BCR pathway, has undoubtedly revolutionized the landscape of CLL therapy and heralded a paradigm shift in the management of relapsed CLL.[4] Chemoimmunotherapy (CIT), using a number of different combinations based on age and overall fitness, remains the standard of care for initial therapy of most patients with CLL, except the minority of treatment-naïve patients with deletion 17p, who should receive ibrutinib.[5] The recent Food and Drug Administration (FDA) approval of ibrutinib in the frontline setting for all patients with CLL based on findings from the RESONATE-2 trial[6] is poised to greatly expand the use of this expensive drug, at least in the United States, which calls for a critical appraisal of this agent in CLL. In this review, we evaluate the currently available data with ibrutinib in CLL, emphasizing the pharmacokinetic and pharmacodynamic aspects.

2. Overview of the market

The therapeutic armamentarium for CLL has expanded considerably in recent years, and the landscape continues to evolve. Ibrutinib was initially granted accelerated approval by the US FDA in February 2014 for patients with CLL after at least one prior therapy.[7] High response rates (91% overall response rate (ORR), including 20% partial response with lymphocytosis (PR_L)) were seen at the FDA-approved 420 mg once daily dose in a phase I/II study in 85 patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL).[8] This was subsequently converted to full approval upon the demonstration of statistically significant improvements in progression-free survival (PFS) and overall survival (OS) in a head-to-head trial versus ofatumumab (RESONATE) in patients with relapsed CLL.[9] Ibrutinib achieves high ORRs in patients with CLL and deletion 17p/*TP53* aberrations,[10] and was separately approved for this highly refractory group of patients in any line of therapy. In the phase II RESONATE-17 trial, among 144 patients with previously treated CLL/SLL and deletion 17p, the ORR was 82.6%, including 17.4% PR_L, and 79.3% of patients were alive and progression-free at 12 months.[11] Most recently, the findings of the RESONATE-2 trial,[6] which compared ibrutinib to chlorambucil in previously untreated patients with CLL led to the approval of ibrutinib in the frontline setting. “Real-world” data on 95 patients receiving ibrutinib through a compassionate use program in Sweden were recently published.[12] Nearly two-thirds of patients had del17p/*TP53* mutation and Rai stage III/IV disease, and 28% had bulky lymphadenopathy. At median follow-up of 10.2 months, the ORR was 84% and PFS 77%, mirroring the clinical trial results in general. PFS and OS were significantly shorter among patients with del17p/*TP53*

mutation, and ibrutinib was overall well-tolerated.[12] Acalabrutinib is a second-generation, more selective, irreversible inhibitor of BTK currently in phase III trials in CLL. In a phase I/II study in 61 patients with relapsed CLL, an ORR of 95% was reported, including 85% with partial remission (PR) and 10% with PR_L; the remaining 5% of patients had stable disease.[13] Other selective inhibitors of BTK include ONO/GS-4059 and BGB-3111. In a phase I trial of the former in patients with relapsed/refractory B-cell malignancies, 24 of 25 (96%) CLL patients responded, and no maximal tolerated dose (MTD) was reached.[14] No dose-limiting toxicities (DLTs) or MTD were identified in a phase I trial of BGB-3111 either, and 6 of 8 (75%) CLL patients had an objective response.[15]

The first-in-class phosphatidylinositol-3-kinase (PI3K) delta isoform inhibitor idelalisib was approved by the FDA in combination with rituximab in 2014 for patients with relapsed CLL and co-morbidities for whom rituximab alone would be considered appropriate therapy.[16] Obinutuzumab, a type II, glycoengineered monoclonal antibody against CD20, was FDA-approved in 2013 in combination with chlorambucil for upfront therapy in patients with CLL and co-morbidities based on the superiority of this combination over that of rituximab and chlorambucil (in terms of PFS) and chlorambucil alone (in terms of PFS and OS) in a phase III trial (CLL 11) in previously untreated patients with CLL and a Cumulative Illness Rating Scale score higher than 6 or compromised renal function.[17] Finally, venetoclax, a selective, small-molecule “BH3-mimetic” inhibitor of BCL2,[18] received accelerated approval from the FDA in 2016 for CLL patients with deletion 17p after at least one prior therapy. In a phase I study in relapsed or refractory CLL/SLL, the drug produced an ORR of 79% and notably, a CR rate of 20%, including 5% who had no minimal residual disease (MRD) on flow cytometry.[19] A nearly identical ORR (79.4%) was reported in a phase II study confined to relapsed or refractory CLL patients with deletion 17p.[20]

2.1 Limitations of current CLL therapeutics

Despite the remarkable pace of drug development and approval for CLL in recent years, there remain several areas of unmet need. Durable remissions and functional “cures” have been reported with fludarabine, cyclophosphamide and rituximab (FCR) CIT in patients with somatic hypermutation of the variable region of the immunoglobulin heavy chain gene (*IGHV*) and favorable cytogenetic characteristics (e.g., deletion 13q, normal, trisomy 12), [21] and it appears that abbreviated courses of FCR (e.g., 3 cycles) may be sufficient for those patients who achieve MRD-negative status.[22] However, long-term outcomes with CIT are far less gratifying in the setting of unmutated *IGHV*, deletion 11q and in particular, deletion 17p, and therapy-related myeloid neoplasms remain a problem after FCR.[23] *IGHV*-unmutated CLL may be particularly sensitive to ibrutinib due to high levels of phosphorylated BTK, correlating with higher proliferative capacity.[24]

2.2 Limitations of ibrutinib

While ibrutinib certainly provides benefits in previously difficult to treat CLL cases, such as disease with unmutated *IGHV* and patients with deletion 17p [10, 20], cures remain elusive with ibrutinib monotherapy, the drug induces very few CRs, particularly in previously treated patients,[25] and resistance-conferring mutations (e.g., in BTK or in the downstream molecule phospholipase C gamma 2 (PLCγ2)) emerge in some patients on ibrutinib therapy,

[26] as do other resistant subclones, e.g., those bearing deletion 8p with additional driver mutations.[27] Finally, complex karyotype has been shown to be a powerful predictor of inferior outcomes among patients with relapsed or refractory CLL treated with ibrutinib-based regimens.[28] Combination strategies are therefore needed, and combinations that appear promising preclinically, e.g., that of ibrutinib with venetoclax,[29] are being pursued in clinical trials, with or without the addition of obinutuzumab (NCT02756897 NCT02758665 NCT02427451).

Another limitation of ibrutinib is its significant off-target toxicity, e.g., atrial fibrillation (6–9%) and bleeding (grade 3/4 in up to 6%). Several studies have implicated inhibition of other kinases in ibrutinib-induced bleeding and atrial fibrillation. First, ibrutinib's effect on cardiac signaling through the phosphatidylinositol-3-kinase (PI3K)/Akt cassette has been suggested as the mechanism underlying atrial fibrillation.[30] Second, several studies have implicated ibrutinib in causing platelet dysfunction.[31] Ibrutinib impairs both collagen and von Willebrand factor-dependent platelet functions,[32] as well as collagen-mediated platelet aggregation.[33] Other targets of ibrutinib include the epidermal growth factor receptor (EGFR),[34] interleukin-2-inducible kinase (ITK),[35] T-cell receptor axis signaling and TEC kinases.[13] While the Cys481 residue of BTK is the primary target of ibrutinib, several other kinases that contain cysteine residues homologous to Cys481 of BTK are also inhibited at low nanomolar concentrations.[36] These off-target actions of ibrutinib and their effects on the immune system and hematopoietic cells are not yet well-defined. Table 1 lists kinases inhibited by ibrutinib, along with the corresponding IC₅₀ values. Some off-target effects of ibrutinib have been recognized for their potential therapeutic benefit in other diseases, e.g., inhibition of ITK and resultant Th1 “skewing” in Th2-mediated diseases like asthma, inhibition of BTK and TEC in overactive osteoclasts in osteoporosis and rheumatoid arthritis, and inhibition of BTK, ITK and TEC in mast cells in allergic conditions and pancreatic tumors.[37]

Yet another limitation of ibrutinib is its prohibitive cost. In a recent analysis, the average lifetime cost of treatment of CLL per patient in the US was estimated to be over \$700,000 for patients beginning therapy in the 2017–2025 period.[38] In this analysis, the incremental cost per life-year gained was \$204,000 and that per quality-adjusted life-year gained was \$262,000.[38] Another recent analysis published before the approval of the drug for frontline use in the US compared the costs of CLL treatment before the approval of ibrutinib to the “current” cost using ibrutinib as salvage therapy and to the potential “future” cost, assuming approval of ibrutinib for first-line use.[39] Estimated 10-year pharmaceutical costs per newly diagnosed patient and per treated patient, respectively, were: \$45,659 and \$157,446 for the historical scenario, \$77,948 and \$268,788 for the “current” scenario for ibrutinib, and \$164,141 and \$566,002 for the potential “future” scenario.[39] Total out-of-pocket cost per treated patient with newly diagnosed CLL under Medicare Part D increased from \$325 under the historical scenario to \$8,800 under the “current” scenario and to \$35,564 under the “future” scenario.[39] In the United Kingdom, the upper limit for approval of a drug for National Health Service (NHS) use is £30,000 per year of good-quality life or £50,000 for a drug given towards the end of life. Ibrutinib was initially included in the UK Cancer Drugs Fund (CDF) for patients with CLL who have received at least one prior therapy and for whom treatment or re-treatment with purine analog-based

therapy would not be appropriate.[40] Earlier this year, the National Institute for Health and Care Excellence (NICE) provisionally recommended against making ibrutinib, priced at £5151 for a 4-week course, available for the treatment of CLL patients in the UK through the National Health Service.[41] More recently, however, NICE has asked the manufacturer of ibrutinib to put forward a case for its inclusion in the CDF, particularly for treatment-naïve patients with deletion 17p or a *TP53* mutation.[42]

3. Introduction to the compound

Ibrutinib (formerly PCI-32765) is an orally administered, potent (IC_{50} , 0.5 nM), irreversible inhibitor of BTK, forming a covalent bond with the cysteine 481 residue in the adenosine triphosphate (ATP)-binding domain of the kinase.[36] Besides its current FDA approval status for all patients with CLL as discussed above, the drug is also indicated for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy[43] and those with Waldenstrom's macroglobulinemia.[44]

4. Chemistry

The chemical name for ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one (**Box 1**). Its molecular formula is $C_{25}H_{24}N_6O_2$, and its molecular weight is 440.5 g/mol.[45]

5. Therapeutic target and mechanism of action

BCR signaling plays a key role in CLL pathogenesis, and BTK has a pivotal role in BCR signaling in both normal and malignant B-cells.[2, 46] BTK is important for antigen-induced BCR activation in both normal, mature B-cells and in CLL lymphocytes and mediates survival and proliferation via amplification of downstream effector pathways, e.g., PI3K/Akt, mitogen activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and nuclear factor kappa B (NF- κ B).[2, 46] Additionally, autonomous BCR signaling has also been described in CLL, which is not, however, associated with activating mutations in any of the BCR components.[46]

Ibrutinib inactivates BTK through irreversible, covalent binding to the Cys481 residue in the ATP-binding domain of BTK.[36] BTK has been shown to be critical for the development and expansion of CLL and an important target of ibrutinib.[47] Indeed, BTK point mutations (C481S) that convert ibrutinib to a reversible inhibitor, as well as activating mutations in PLC γ 2, located immediately downstream of BTK, have been implicated in the pathogenesis of acquired resistance to ibrutinib in CLL.[26] The success of the more selective BTK inhibitors, acalabrutinib and ONO/GS-4059, in heavily pretreated patients with CLL, further testifies to the relevance of BTK as a major therapeutic target in this disease.[13, 14]

6. Pharmacodynamics

Because ibrutinib binds irreversibly and covalently to BTK, the enzyme is permanently inhibited. Furthermore, because there is only one site (Cys481) for drug binding, a one to one stoichiometric concentration of ibrutinib is needed. Hence, a concentration of the drug

that occupies >95% of the BTK molecules in CLL lymphocytes is considered ideal. Such measurements are achieved using BTK occupancy assays and were performed in the context of early phase I and II studies.[8, 48] BTK occupancy is measured using a highly specific fluorescent affinity probe, whose binding to the BTK active site had previously been shown to tightly correlate with blockade of BCR signaling and *in vivo* efficacy.[36] 95% BTK occupancy was achieved 4 hours post-dose at a dose of 2.5 mg/kg/day of ibrutinib in the phase I study in relapsed/refractory B-cell malignancies.[48] Dose escalation proceeded up to three dose levels above the level at which full BTK occupancy was observed (the 5 dose levels were 1.25, 2.5, 5, 8.3 and 12.5 mg/kg/day), and all dosing cohorts from 2.5 through 12.5 mg/kg/day had 95% BTK occupancy and similar clinical response rates.[48]

At a signaling level, ibrutinib binding inhibits activity of BTK, autophosphorylation of the enzyme, and abrogates activation of downstream survival pathways (PI3K, ERK, NF- κ B), inducing modest apoptosis and inhibiting activation-induced proliferation of CLL cells *in vitro*. It effectively blocks survival signals provided externally to CLL cells from the microenvironment.[49] These actions were observed in primary, patient-derived CLL cells (from blood, lymph nodes and bone marrow) as well as in mouse models.[50–52] Additionally, the drug blocks the interaction of CLL cells with tissue homing chemokines (CXCL12, CXCL13, CCL19), possibly through blockade of BCR-induced activation of lymphocyte cytosolic protein 1 (LCP1)[53] and restoration of the balance between expression levels of the homing receptors CCR7 and CXCR4 and the S1P receptor 1 (S1P1). [54] Figure 1 depicts the major pathways and consequences of BTK activation in CLL cells. Additionally, ibrutinib down-regulates secretion of BCR-dependent chemokines (CCL3, CCL4) by CLL cells, both *in vitro* and *in vivo*, and causes a transient early lymphocytosis in mouse models.[52, 55] This characteristic “redistribution lymphocytosis” is routinely and uniquely observed in patients receiving ibrutinib or other BCR pathway inhibitors and is believed to be a result of mobilization of CLL cells from their protective tissue microenvironmental niches into the peripheral blood, where they eventually undergo apoptosis from the lack of prosurvival signals.[56] The observations that ibrutinib abolishes the adhesion of CLL cells to fibronectin and VCAM-1 and reduces CLL cell surface expression of key adhesion molecules such as CD49d, CD29 and CD44, mechanistically explain this treatment-induced lymphocytosis.[55, 57] In a mouse model of aggressive TCL1 CLL-like disease, BTK inhibition by ibrutinib reduced surface membrane levels of CXCR4, CD49d and other adhesion/homing receptors, resulting in rapid redistribution of CLL cells from spleens and lymph nodes into the circulation, and failure of these cells to home to spleens.[58]

The redistribution lymphocytosis characteristic of treatment with ibrutinib has been extensively investigated. While an efflux of tumor cells from the tissue compartments into the blood has been conclusively shown,[59] mathematical models have estimated the fraction of the tissue CLL cells redistributed into the blood during ibrutinib therapy to be $23.3\% \pm 17\%$ of the total tissue disease burden, arguing that the reduction of tissue disease burden is due more to CLL cell death and less to egress from nodal compartments.[60] While the lymphocytosis resolves within 8 months in the majority of patients, it may last for over a year in some patients.[61] Importantly, this persistent lymphocytosis does not

represent disease progression or clonal evolution, and these patients do not have inferior PFS.[61]

BTK belongs to the TEC family kinases (TFKs), and other members of this family (TEC, ITK, BMX, RLK/TXK) are also targeted by ibrutinib, albeit at higher concentrations (e.g., 78 nM for TEC).[37] Other kinases targeted by ibrutinib include the HER family kinases EGFR, HER2/ErbB2 and HER4/ErbB4, and JAK3 (Table 1).[37, 46] Ibrutinib inhibits yet other kinases at low nanomolar concentrations, e.g., BRK, CSK, FRG, HCK, BLK; indeed, the IC₅₀ for BLK is the same as for BTK, i.e., 0.5 nM.[36, 37] Much attention has been directed towards ibrutinib's irreversible inhibition of ITK in T-cells, resulting in subversion of Th2 immunity and potentiation of Th1-based immune responses.[35] This action of ibrutinib may underlie the synergism between the drug and immune checkpoint inhibitors (anti-PD1/PDL1 monoclonal antibodies) in mouse models of a number of tumor types.[62] Conversely, ibrutinib has been reported to antagonize rituximab-dependent NK-cell mediated cytotoxicity[63, 64] and impair the phagocytosis of rituximab-coated patient-derived CLL cells,[65] but these effects have not been demonstrated in murine xenograft models[64] or observed in clinical trials,[66, 67] possibly due to the promotion by ibrutinib of both positive and negative interactions with anti-CD20 monoclonal antibodies.[68]

Recently, correlative studies from a clinical trial examining the effects of ibrutinib on the CLL microenvironment were published.[69] Serum levels of key chemokines and inflammatory cytokines decreased significantly in patients on ibrutinib. Ibrutinib decreased overall T-cell numbers and particularly the Th17 subset of CD4+ T-cells, along with reduced expression of activation markers and PD1 on T-cells, inhibited secretion of CXCL13, decreased the chemo-attraction of CLL cells, and interfered with the interactions of macrophages and CLL cells in the bone marrow microenvironment.[69]

7. Pharmacokinetics and metabolism

Ibrutinib is absorbed after oral administration with a median time to maximal plasma concentration (T_{max}) of 1 to 2 hours.[48] Ibrutinib exposure increases with dosage up to 840 mg daily. The steady-state area under the curve (AUC, mean $\pm$ standard deviation) observed in patients on 420 mg daily is 680 ± 517 ng·h/mL.[70] No food restrictions are warranted.[71]

Like other kinase inhibitors, ibrutinib binds to plasma proteins. Reversible binding of ibrutinib to human plasma protein *in vitro* was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL (Table 2). The apparent volume of distribution at steady state ($V_{d,ss}/F$, the sum of the volumes of the central and peripheral compartments) was approximately 10,000 L.[72]

Ibrutinib is metabolized to several metabolites in the liver, primarily by cytochrome P450 CYP3A,[73] and to a minor extent by CYP2D6; this is considered the main route of elimination (Table 2). The active metabolite, PCI-45227, is a dihydrodiol derivative with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib.[70] The range of the mean metabolite to parent ratio for PCI-45227 at steady-state is 1 to 2.8.[70]

In line with a high first-pass effect, the apparent oral clearance of ibrutinib is approximately 2000 and 1000 L/h in fasted and fed conditions, respectively.[72] The half-life of ibrutinib is 4 to 6 hours and the drug does not accumulate after repeated oral dosing.[48]

Ibrutinib is not significantly cleared renally; urinary excretion of metabolites is <10% of the dose.[74] In concert, creatinine clearance (Cr_{CL}) >25 mL/min has no influence on the exposure to ibrutinib. There are no data in patients with severe renal impairment (Cr_{CL} < 25 mL/min) or in patients on dialysis.[70] Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces.[74] As mentioned above, these metabolites are generated in the liver. As a result, ibrutinib AUC and maximal plasma concentration (C_{max}) do increase progressively in the presence of mild, moderate and severe liver impairment.[70] For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 140 mg daily (one capsule).[70] Ibrutinib is not recommended in the setting of moderate or severe liver impairment (Child-Pugh classes B and C).[70] The systemic clearance of ibrutinib is not altered by gender, and dose adjustment by age is not warranted.[70]

8. Pharmacogenetics

It is too early to comment on pharmacogenetic variability as there are limited data. In a phase I study conducted in 15 Japanese patients with relapsed/refractory B-cell malignancies (6 with CLL/SLL), the ORR was 73.3% and the most common (occurring in 20% of patients) adverse events (AEs) were neutropenia, anemia, nasopharyngitis, increased bilirubin, and rash.[75] One patient in the CLL/SLL cohort experienced grade 3 pneumonia and sepsis.[75] Overall, these data are similar to observations in Caucasian populations.

9. Clinical efficacy

In a phase I study in 56 patients with relapsed or refractory B-cell lymphoma or CLL, dose escalation of ibrutinib continued through 12.5 mg/kg/day without reaching a MTD.[48] Notably, full occupancy of the BTK active site occurred at 2.5 mg/kg/day.[48] The ORR in 50 evaluable patients was 60%, including a CR rate of 16%. Median PFS in all patients was 13.6 months. Table 3 summarizes the major trials of ibrutinib in CLL, either as single agent, in combination with a CD20 monoclonal antibody, or with CIT. The results of 3-year (median) follow-up of 132 patients receiving ibrutinib as a single agent[25] demonstrated that longer treatment was associated with improvement in response quality and durability of remissions.[25] Progression was uncommon, occurring primarily in some patients with relapsed deletion 17p and/or deletion 11q disease.[25] Outcomes after ibrutinib discontinuation on clinical trials have been reported to be poor, but this likely reflects the unavailability of other effective therapies at the time.[76, 77] In the MD Anderson Cancer Center experience, 33 of 127 patients discontinued ibrutinib, 14 due to disease progression and 14 due to AEs or sudden death.[76] In the Ohio State University experience, 76 of 308 patients discontinued ibrutinib, 31 because of disease progression and 37 because of AEs or sudden cardiac death.[77] In general, Richter's transformations tended to occur early, while most CLL progressions were late events.[77] Seven Richter's transformations occurred in the Swedish "real-world" cohort of 95 poor-prognosis CLL patients who received ibrutinib through a compassionate use program.[12]

10. Safety, tolerability, toxicity, and potential off-target effects related to safety liabilities

In the phase I study of ibrutinib mentioned above, most AEs were grade 1 or 2 in severity and self-limited, and DLTs did not occur.[48] Ibrutinib was well-tolerated in the two trials that led to accelerated and full approval, respectively, for relapsed CLL, with predominantly grade 1/2 adverse events, e.g., nausea, diarrhea, fatigue, pyrexia and upper respiratory infection.[8, 9] In the registration trial in the frontline setting, AEs occurring in 20% of patients on ibrutinib included diarrhea, fatigue, cough and nausea; additionally, peripheral edema, dry eye, arthralgia, neutropenia (including grade 3) and vomiting occurred in 10% of patients.[6] Infections in CLL patients have been shown to decline over time during ibrutinib therapy.[78]

Atrial fibrillation (AF) and flutter have occurred in 6–9% of patients treated with ibrutinib.[70] This effect has been attributed to the binding of ibrutinib to BTK and TEC in the heart and subsequent inhibition of cardioprotective PI3K/Akt signaling.[30] Other targets of ibrutinib, viz., HER2/ErbB2, HER4/ErbB4 and BMX play important roles in cardiac physiology, and their inhibition could represent additional mechanisms through which ibrutinib could cause AF and cardiac dysfunction.[37]

Bleeding is a relatively common AE of ibrutinib and grade 3 bleeding events have occurred in up to 6% of patients.[70] Bleeding events of any grade, including bruising and petechiae, have occurred in approximately half of patients.[70] In the Swedish “real-world” experience, 46 of 95 patients developed hematomas, without any major bleeding.[12] The low frequency of subarachnoid hemorrhages in several patients receiving concomitant warfarin in the phase 1b-2 trial of ibrutinib prompted the exclusion of concurrent therapy with oral vitamin K antagonists in all subsequent studies of ibrutinib.[4] Additionally, ibrutinib is typically held for 3 to 7 days before and after surgical procedures.[4] Both BTK and TEC play important roles in collagen-induced platelet adhesion mediated through glycoprotein (GP) VI, and TEC is able to compensate for loss of function of BTK in this setting.[79, 80] However, BTK is essential for von Willebrand factor (vWF)-induced (GPIIb-dependent) platelet aggregation and thrombus formation.[81] The risk of bleeding in CLL patients treated with ibrutinib does appear to decrease with continued therapy.[82]

Mice lacking BTK and TEC show severe osteopetrosis caused by a defect in bone resorption.[83] Receptor activator of NF- κ B (RANK) and ITAM-harboring adaptors signal through BTK, TEC, B-cell linker (BLNK) and PLC γ to activate an essential calcium signal in osteoclasts, and inhibition of TEC reduces osteoclastic bone resorption in models of osteoporosis and inflammation-induced bone destruction.[83] While this could argue for a therapeutic role of ibrutinib in diseases of enhanced osteoclastic bone resorption such as osteoporosis or rheumatoid arthritis, these findings raise concern over the long-term effects of ibrutinib treatment on bone homeostasis, particularly since systematic studies of bone density have not been performed in patients receiving ibrutinib.[37]

Inhibition of ITK and resultant modulation of cellular immunity have been invoked as potentially contributing to the development of panniculitis, an unusual, recently recognized

AE in ibrutinib-treated patients.[84] Even more recently, the development of painful, purpuric skin nodules with a Th1-rich lymphocytic infiltrate (as opposed to the expected Th2 milieu) on ibrutinib therapy in a patient with CLL that resolved with cessation of the drug has been reported,[85] consistent with ITK inhibition by ibrutinib.[35] Brittle nails and textural hair changes have been reported during long-term therapy of CLL with ibrutinib, but the underlying mechanisms remain unknown.[86]

11. Drug-drug interactions

As mentioned in the Pharmacokinetics section, ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.[73] Consistent with this observation, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively, in healthy volunteers,[73] indicating that concomitant administration of ibrutinib with strong or moderate inhibitors of CYP3A should be avoided.[70] For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin), interruption of ibrutinib therapy should be considered[70] and chronic use of strong CYP3A inhibitors should be avoided. If a moderate CYP3A inhibitor must be used, the dose of ibrutinib should be reduced to 140 mg daily (from the approved dose of 420 mg daily).[70] Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of toxicity. Grapefruit and Seville oranges should be avoided during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.[70] Not only strong CYP3A inhibitors, but strong CYP3A activators (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort) also should be avoided; indeed, administration of ibrutinib with rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.[73]

12. Dosing routes

Ibrutinib is dispensed as 140 mg capsules. It is dosed orally. Since the recommended daily dose in CLL is 420 mg, patients take 3 capsules orally per day.

13. Regulatory affairs

The remarkable activity of ibrutinib is reflected in the fact that this drug was selected for all four expedited programs of the FDA, i.e., fast-track and breakthrough therapy designation, priority review, and accelerated approval.[7] As discussed above, ibrutinib was initially approved in the United States for patients with CLL/SLL who had received at least one prior therapy. It was subsequently approved for patients with CLL/SLL with deletion 17p, and most recently for previously untreated patients with CLL/SLL. In the European Union, it is also now approved for CLL patients across all lines of therapy, i.e., in the frontline or relapsed settings, irrespective of the presence or absence of del17p/*TP53* mutation. The same is true of ibrutinib's Health Canada approval status. In Australia, ibrutinib is indicated for the treatment of patients with CLL/SLL who have received at least one prior therapy or as first line in patients with CLL with 17p deletion, while in the United Kingdom, the

availability of ibrutinib through the NHS is currently restricted to patients with relapsed CLL for whom purine analog-based therapy is considered inappropriate.

14. Conclusion

Ibrutinib is a highly effective and generally well-tolerated oral drug that has ushered in a new era in CLL treatment. Important limitations include the rarity of CRs in the relapsed setting and achievement of MRD-negative status with ibrutinib monotherapy.[87] The need for indefinite therapy poses unique challenges given the high cost of ibrutinib. Finally, the significant potential for off-target toxicities as well as the development of resistance are additional short-comings.

15. Expert Opinion

Ibrutinib undoubtedly represents a great advance in the treatment of CLL and is a one of few examples in oncology of successful therapeutic targeting of a kinase that is not mutated.[88] However, while highly effective at controlling disease, best monotherapy responses with ibrutinib are typically PRs, necessitating indefinite use of the drug.[87] Achieving MRD-negative CR in the bone marrow is associated with superior PFS and OS, and MRD status is the single best post-treatment predictor of long-term outcomes after CIT.[87] The inability to achieve MRD eradication, or even CR in the majority of patients, is an important shortcoming of ibrutinib, invoking the need for laboratory-based rational combination strategies, such as with venetoclax,[29] proteasome inhibitors,[89] heat shock protein 90 inhibitors[90], selective inhibitors of nuclear export[91] and caspase activators.[92]

As discussed above, the high cost of ibrutinib, like that of other targeted, oral anti-cancer agents, especially given the need for indefinite therapy and its recent approval in the frontline setting in the US, creates a considerable societal economic burden.[38, 39] The cost of lifelong tyrosine kinase inhibitor therapy has already been noted to be unsustainable by experts in chronic myeloid leukemia,[93] and one could easily draw a parallel with the situation with the oral kinase inhibitors such as ibrutinib and idelalisib in CLL.[38] Finally, while generally well-tolerated, ibrutinib does have some significant off-target toxicities, notably atrial fibrillation[30] and bleeding,[32, 33, 79–81] and it is conceivable that the more selective and specific irreversible BTK inhibitor, acalabrutinib, which does not inhibit other kinases such as EGFR, TEC and ITK at pharmacologically active concentrations, will possess an advantage over ibrutinib in this regard.[13] Similar considerations apply to other selective BTK inhibitors in earlier stages of clinical development.[14, 15]

Drug cost, toxicities, and off-target effects of ibrutinib may be mitigated by lowering the total daily dose. The optimal dose of ibrutinib should inhibit or bind to >95% of cellular BTK protein. Prior investigations in murine models demonstrated that total BTK protein levels increased after B-cell receptor stimulation in normal B-cells[94] or malignant CLL B-cells, tested in an adoptive transfer CLL murine model.[58] As a corollary, inhibition of BTK by ibrutinib in this murine model resulted in a decline in total BTK along with internalization of CXCR4 receptors.[58] Consistent with these data, total BTK protein was decreased in primary circulating CLL cells obtained from patients undergoing ibrutinib

therapy (Figure 2).[95] Furthermore, in CLL patient-derived lymphocytes, the decline was also observed for BTK transcript levels. Ibrutinib attenuates BTK-dependent NF- κ B activation, resulting from both BCR[96, 97] and toll-like receptor (TLR)[98] activation. NF- κ B regulates the level of BTK protein through transcriptional control,[99] providing another mechanism by which ibrutinib therapy may lead to reduced levels of BTK protein. Collectively, these observations suggest that for stoichiometric inhibition of the enzyme, a lower level of BTK protein would mean a lower concentration of ibrutinib required to effectively inhibit it. In fact, the 420 mg dose of ibrutinib may result in higher levels of circulating ibrutinib than are required to establish full BTK occupancy, thus increasing the likelihood of off-target binding of the drug, potentially leading to AEs.

In light of the above considerations, we have designed a pilot clinical protocol (NCT02801578, full protocol available as supplemental file) to identify the optimal dose of ibrutinib that can inhibit BTK protein after a cycle at the full dose (420 mg/d). In this study design, each patient will receive the full dose (three capsules daily) during the first cycle and then progressively lower doses, i.e., 280 mg/d (two capsules daily) during the second cycle and 140 mg/d (one capsule daily) during the third cycle. Extensive sampling for correlative studies will be performed to cover plasma pharmacokinetics and a number of pharmacodynamic endpoints, including but not limited to BTK occupancy, levels of total and phospho-BTK, BTK mRNA and protein levels, and NF- κ B activity, at several different time points. The findings from this pilot study could justify a larger and more definitive trial of lower doses of ibrutinib in CLL with clinical endpoints in the future.

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Drug summary box

Drug name: Ibrutinib (formerly PCI-32765)

Phase: IV (approved worldwide)

Indication: Chronic lymphocytic leukemia (all patients in the United States, relapsed/refractory or with deletion 17p in other countries)

Pharmacology description/mechanism of action: Irreversible (covalent) inhibitor of Bruton's tyrosine kinase, an important mediator of B-cell receptor signaling

Route of administration: Oral; 3 capsules (140 mg each) per day

Chemical structure:

Pivotal trials: RESONATE [9]
RESONATE-17 [11]
RESONATE-2 [6]

Figure 1. BTK signaling pathways

BTK is involved in the signaling of multiple receptors that together control cell migration, adhesion, survival and proliferation. Activation of BTK is triggered upon BCR stimulation, for example, after antigen (Ag) binding, as shown on the left hand side. The BCR signaling pathway is thought to play a major role in mediating B-cell survival and proliferation in normal and neoplastic B-cells. In addition, BTK mediates signals derived from chemokine receptors, such as the CXCR4 receptor, which binds to the chemokine CXCL12 (SDF-1) to mediate homing and migration. Both CXCR4 and the BCR also regulate adhesion molecules such as integrins, which are essential for tissue homing and retention. Consequently, inhibition of BTK results in redistribution of tissue-resident CLL cells into the blood and inhibition of re-homing. Reproduced, with permission, from [102].

Figure 2. Ibrutinib therapy decreases total protein and mRNA transcript levels of BTK

Primary CLL cells from patients were isolated fresh from peripheral blood samples prior to treatment (baseline), and at 2, 4, and 12 weeks of 420 mg daily oral dosing of ibrutinib.

Blood samples were collected from six patients in green-top tubes and CLL cells were isolated by Ficoll-Hypaque gradient. Cell pellets were used for total BTK protein levels (A) and BTK mRNA levels (B) from six patients with CLL. For the former, cell lysates were prepared and after protein quantitation, immunoblots were run to analyze total BTK protein levels. Immunoblots were quantitated and plotted as a percentage of the control level (baseline sample). For mRNA transcript levels, RT-PCR assay was performed in triplicate from each sample as described previously.[29] Student's t-tests (two-tailed) were performed using the GraphPad Prism6 software (GraphPad Software, Inc. San Diego, CA) to compare values in untreated samples compared to all treated samples and the p values for the comparisons in figure A and figure B are 0.0001 and 0.0003, respectively. Reproduced, with permission, from [95].

Table 1

IC₅₀ values and fold selectivity for inhibition of enzymatic activity by ibrutinib.

Kinase	IC ₅₀ , nM	BTK selectivity, fold
BTK	0.5	--
BLK *	0.5	1
BMX *	0.8	1.6
CSK	2.3	4.6
FGR	2.3	4.6
BRK	3.3	6.6
HCK	3.7	7.4
EGFR *	5.6	11.2
YES	6.5	13
ErbB2 *	9.4	18.8
ITK *	10.7	21.4
JAK3 *	16.1	32.2
FRK	29.2	58.4
LCK	33.2	66.4
RET	36.5	73
FLT3	73	146
TEC *	78	156
ABL	86	172
FYN	96	192
RIPK2	152	304
c-SRC	171	342
LYN	200	400
PDGFR α	718	1436
FMS	5545	>10,000
FER	8070	>10,000
JAK1	>10,000	>10,000
JAK2	>10,000	>10,000
NEK2	>10,000	>10,000
p38	>10,000	>10,000
PI3K	>10,000	>10,000
PLK1	>10,000	>10,000
RSK1	>10,000	>10,000
SYK	>10,000	>10,000

* Kinases that contain a cysteine residue aligning with Cys-481 in BTK. Reproduced, with permission, from reference [36]: Honigberg LA et al. Proc Natl Acad Sci U S A 2010;107:13075–80.

Table 2

Summary of pharmacokinetic parameters of ibrutinib.

Route of administration	Oral, without regard to food intake.
Absorption	Median $T_{\max}$ 1–2 hrs. Steady state AUC at 420 mg/d dose = 680 ± 517 ng.h/ml.
Distribution	97.3% plasma protein bound <i>in vitro</i> (reversible). V_d at steady state 683 L.
Metabolism	Primarily through CYP3A. Active dihydrodiol metabolite. DDIs with moderate to strong CYP3A inducers and inhibitors.
Elimination	Mainly as metabolites via feces; high first-pass effect. Half-life 4 to 6 hours.

Abbreviations: $T_{\max}$, time to maximal plasma concentration; AUC, area under the curve; V_d , volume of distribution; CYP, cytochrome P450; DDIs, drug-drug interactions.

Table 3

Major clinical trials of ibrutinib in CLL/SLL.

Trial (reference)	Population studied (n)	Phase and design	Response rates	Survival
[8]	Relapsed or refractory (n=85) with a median of 4 prior therapies	Ib/II, two doses: 420 mg (n=51) and 840 mg (n=34)	ORR 71% with both doses; another 20% and 15% had PR _L , respectively; 2 CRs at 420 mg/d	At 26 months, estimated PFS 75% and OS 83%, median PFS not reached
[100]	Frontline, elderly (65, n=31)	Ib/II, initially two doses, later 840 mg dose discontinued	ORR 71% after median f/u of 22.1 months (13% CRs, 3% nPRs, 55% PRs)	At 24 months, estimated PFS 96.3% and OS 96.6%, median PFS not reached
RESONATE [9]	Relapsed or refractory (n=391); median 3 prior therapies in ibrutinib group and 2 in ofatumumab group; crossover allowed	III, RCT (1:1) of ibrutinib 420 mg/d vs. ofatumumab (300 mg in week 1, followed by 2000 mg weekly x 7, then every 4 weeks x 16)	ORR 42.6% vs. 4.1% favoring ibrutinib; another 20% in ibrutinib group had PR _L	At median f/u of 9.4 months, median PFS not reached vs. 8.1 months; PFS at 6 months 88% vs. 65%; OS 90% vs. 81% at 12 months
RESONATE-17 [11]	Relapsed or refractory with deletion 17p (n=144); median 2 prior therapies	II; single arm (420 mg/d)	ORR 82.6% (including 17.4% PR _L , 3 patients with CR/CRi)	At median f/u of 13 months, median PFS not reached; 79.3% PFS at 12 months
[10]	Treatment-naïve (n=35) or relapsed or refractory (n=16) with <i>TP53</i> aberrations (47 had deletion 17p)	II, single arm (420 mg/d)	ORR 97% (55% PR + 42% PR _L) among previously untreated; 80% (40% PR + 40% PR _L) among R/R	At 24 months, estimated PFS for all patients 82% and OS 80% (ITT); 24-month OS 84% in previously untreated and 74% in R/R pts
RESONATE-2 [6]	Previously untreated, elderly (65, n=269); crossover allowed	III, RCT (1:1) of ibrutinib 420 mg/d vs. chlorambucil (up to 12 28-day cycles; 0.5 mg/kg (could be ↑ to 0.8 mg/kg) on days 1 and 15)	ORR 86% with ibrutinib vs. 35% with chlorambucil (CRs 4% vs. 2%); 4% in ibrutinib group had PR _L	At median f/u of 18.4 months, estimated PFS not reached vs. 18.9 months; estimated OS at 24 months 98% vs. 85%; 84% reduction in risk of progression or death with ibrutinib
[66]	High risk (del17p, <i>TP53</i> mutation, del11q, PFS < 36 months after CIT, n=40); median 2 prior therapies	II, single arm, ibrutinib 420 mg/d plus rituximab (375 mg/m ² , weekly in cycle 1, then once per cycle till cycle 6)	ORR 95% (87% PR + 8% CR); 1 patient achieved MRD-negative CR; 2 CRs occurred in patients with deletion 17p	At 18 months, PFS in all patients 78%; 72.4% in patients with deletion 17p or <i>TP53</i> mutation (n=20)
[67]	Patients who had failed 2 prior therapies; PLL (n=2) and RT also included (n=3); median 3 prior therapies	Ib/II, ibrutinib 420 mg/d plus ofatumumab x 12 (ibrutinib lead-in, n=27; concurrent start, n=20; ofatumumab lead-in, n=24)	ORRs in CLL/SLL pts (n=66) 100%, 79% and 71% in the 3 groups, respectively (overall 83.3%); 1 CR and 54 PRs	Estimated 12-month PFSs for all patients 89%, 85% and 75% in the 3 groups, respectively
HELIOS [101]	Relapsed or refractory (n=578) without deletion 17p; crossover allowed	III, RCT (1:1) of bendamustine (70 mg/m ² /dose x 2) plus rituximab x 6 cycles plus ibrutinib 420 mg/d or placebo	ORR 83% in IBR group vs. 68% in BR group; CR/CRi rate 10% vs. 3%; MRD-negativity rates 13% vs. 5%	At median f/u of 17 months, estimated PFS not reached in IBR group vs. 13.3 months in BR group; at 18 months, PFS 79% vs. 24%

Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; ORR, overall response rate; CR, complete remission; CRi, complete response with incomplete count recovery; PR, partial response; PR_L, partial response with lymphocytosis; nPR, nodular partial response; MRD, minimal residual disease; RCT, randomized controlled trial; PFS, progression-free survival; OS, overall survival; R/R, relapsed/refractory; IBR, ibrutinib, bendamustine and rituximab; BR, bendamustine and rituximab; f/u, follow-up.