Review Article

Ibrutinib: A comprehensive review of a promising drug

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ABSTRACT

Ibrutinib is a recent Food and Drug Administration-approved drug for the treatment of lymphoid malignancies: mantle cell lymphoma and chronic lymphocytic leukemia (CLL). It is a Bruton's tyrosine kinase (BTK) inhibitor which increases the apoptotic susceptibility of malignant lymphocytes and also causes tissue redistribution of lymphocytes. Strong biological rationale makes BTK an ideal target for therapy of CLL and other B-cell malignancies. We are presenting a comprehensive review of this promising drug, highlighting its metabolism, safety profile, trials, and approved uses.

Key words: Chronic lymphocytic leukemia, ibrutinib, mantle cell lymphoma

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a neoplastic disease characterized by the accumulation of a monoclonal population of small, mature-appearing CD5+ B lymphocytes in the blood, marrow, and lymphoid tissues.[1] Although causes are unknown, genetic factors have been found to play a role. The median age at diagnosis is approximately 67 years and 90% are older than 50 years.[2] Men are affected twice as often as women. At the time of diagnosis, more than 3/4th of the patients have lymphadenopathy and almost half shows splenomegaly. CLL patients show clonal chromosomal abnormalities, in which decreasing frequencies are del 13q14-23.1, trisomy 12, del 11q22.3-q23.1, del 6q21-q23, del 17p13.1, and 14q abnormalities.[1] Strong biological rationale makes Bruton's tyrosine kinase (BTK) an ideal target for therapy of CLL and other B-cell malignancies.[3]

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Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.182059

Ibrutinib is a recently Food and Drug Administration (FDA) approved drug for the treatment of lymphoid malignancies: mantle cell lymphoma (MCL) and CLL. It is a BTK inhibitor which increases the apoptotic susceptibility of malignant lymphocytes and also causes tissue redistribution of lymphocytes.[4] We are presenting a comprehensive review of this promising drug, highlighting its metabolism, safety profile, trials, and approved uses.

PATHOGENESIS OF CHRONIC LYMPHOCYTIC LEUKEMIA

To understand the basic functioning of ibrutinib, an insight into the pathogenesis of CLL is desirable. The basic defect in CLL is one of the cellular accumulations rather than proliferation, i.e., reduced apoptosis because of an imbalance in the favor of anti-apoptotic proteins such as B-cell lymphoma 2 (Bcl-2), Bcl-xl, myeloid cell leukemia 1, Bcl-2 associated athanogene-1, and low levels of the pro-apoptotic proteins bax or Bcl-xs.[4] On the other hand, leukemic cells are also protected by the ability of marrow

Cite this article as: Kapoor A, Singh P, Beniwal S, Singhal MK, Nirban RK, Kumar HS. Ibrutinib: A comprehensive review of a promising drug. Clin Cancer Investig J 2016;5:203-7.

stromal cells, nurse-like cells, and follicular dendritic cells to inhibit spontaneous apoptosis of CLL cells, apparently through cell–cell contact and likely by the involvement of several chemokines such as stromal-derived factor 1 alpha (or CXCL13), CCL21, and/or CCL19.[5]

B-cell receptor (BCR) plays a central role in the pathogenesis and progression of CLL. The BTK is at the crossroad of the BCR pathway. Microenvironment led activated BCR directs BTK to transduce signals to prevent apoptosis and promote leukemic cell survival.[6]

The BCR is a CD79a/b membrane-bound immunoglobulin. Ligand binding to BCR recruits tyrosine kinases, including spleen tyrosine kinase and Src family kinases. This initial step translates into activation of a number of signal transduction molecules, including rat sarcoma viral oncogene homolog (RAF)-murine leukemia viral oncogene (RAF)-ERK/MAPK, PI3K, and BTK.[7]

The BTK promotes the signaling mediators DAG/IP3 and thus activates protein kinase C (PKCβ).[6] Increased PI3K causes a sustained calcium uptake and AKT/mTOR activation. Elevated calcium regulates the transcription factor, i.e., nuclear factor (NF) of activated T-cells, which activates prosurvival genes in B-cells. Ultimately, PKCβ leads to the recruitment of mucosa-associated lymphoid tissue lymphoma translocation gene 1 (MALT1) and B-cell CLL/lymphoma 10 protein (Bcl-10) into a multi-protein complex, and initiation of NF-kappa B signaling that ultimately causes increased survival, proliferation, and migration.[7]

DEVELOPMENT OF IBRUTINIB

Ibrutinib was originally developed by Celera Genomics for creating small molecules that irreversibly inhibit BTK. Later on, in April 2006, pharmacyclics acquired and continued Celera's small molecule BTK inhibitor discovery program, and chose PCI-32765 (ibrutinib) for further preclinical development based on the discovery of anti-lymphoma properties *in vivo*.[8]

Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol, and practically insoluble in water.[7] Its empirical formula is $C_{25}H_{24}N_6O_2$. Ibrutinib got US FDA approval for the treatment of MCL in November 13 and CLL in February 14.

MECHANISM OF ACTION

Strong biological rationale makes BTK an ideal target for therapy of CLL and other B-cell malignancies.[9] Ibrutinib is a selective tyrosine kinase inhibitor that covalently and irreversibly binds BTK and consequently blocks survival and proliferation of CLL cells by blocking survival signals from the microenvironment including soluble factors (CD40 L, B-cell-activating factor of the tumor necrosis factor [TNF] family, interleukin-6 [IL-6], IL-4, and TNF-α). Figure 1 shows the position of BTK in the BCR pathway. It also interrupts CXCL12- and CXCL13-mediated chemotaxis and stromal cell contact.[10]

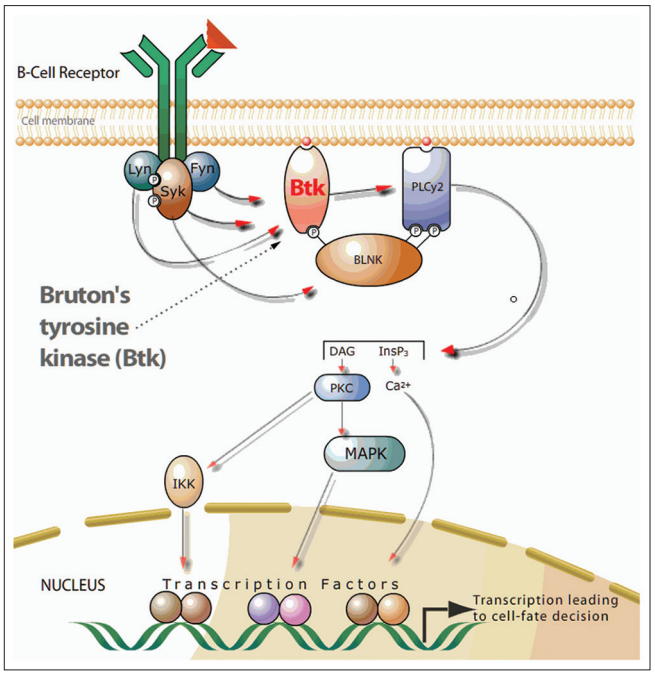

Figure 1: The position of Bruton's tyrosine kinase in the B-cell receptor pathway (available from: http://qoo.dromhhb.top/c/ibrutinib-mechanism-of-action/19019043. Last accessed: March 28, 2016)

Besides anti-proliferative activity, ibrutinib induces the redistribution of tissue-resident CLL cells into the blood with rapid shrinkage of the lymph nodes.[9] This interference with homing of leukemic cells causes prolonged accumulation of transcriptionally inert lymphocytes in peripheral blood. These lymphocytes have low mitotic index and simulate a state of anergy and quiescence.[10]

DRUG METABOLISM

Ibrutinib is given by oral route. Food increases its absorption by two fold. The apparent volume of distribution at steady state is approximately 10,000 L.[11] The prime route of elimination for ibrutinib is through metabolism. It is metabolized primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. PCI-45227 is the active metabolite which is 15 times less potent than ibrutinib.[12] The half-life of ibrutinib is 4–6 h. Ibrutinib is eliminated primarily via feces after metabolism. Unchanged ibrutinib accounts for approximately 1% of the radiolabelled excretion product in feces and none in urine, with the remainder of dose being metabolite.[11]

CLINICAL TRIALS OF IBRUTINIB

FDA approved ibrutinib for MCL in November, 2013. The approval was based on a study of 111 MCL patients whose disease had come back or was no longer responding to other treatments. In the phase II trial, labeled PCYC-1104, ibrutinib demonstrated an overall response rate (ORR) of 68%, including a complete response rate of 21%. Moreover, the median duration of response was 17.5 months.[13] Based on these data, the FDA granted ibrutinib a breakthrough therapy designation and the eventual approval. FDA expanded the approval of ibrutinib in February 2014 to include the treatment of patients with CLL who have received at least one previous therapy, based on a single-arm clinical trial demonstrating a durable improvement in ORRs.[14] The accelerated approval was supported specifically by 48 patients in the phase Ib/II PCYC-1102-CA study who received single-agent ibrutinib at 420 mg daily.[15] In these selected patients, at a median 15.6-month follow-up, the ORR was 58.3% (all partial responses) with duration of response of up to 24.2 months, according to the FDA. The analysis used for the approval neither include data from 34 patients enrolled in the trial who received daily ibrutinib at 840 mg nor three patients with small lymphocytic lymphoma (SLL) who received the 420 mg dose. In a head-to-head comparison of two drugs for the treatment of relapsed CLL or SLL, ibrutinib statistically significantly outperformed atumumab as a second-line therapy.[16] At a median follow-up of 9.4 months, ibrutinib significantly improved progression-free survival; the median duration was not reached in the ibrutinib group (with a rate of progression-free survival of 88% at 6 months), as compared with a median of 8.1 months in the atumumab group (hazard ratio for progression or death in the ibrutinib group, 0.22; $P < 0.001$).[16] Ibrutinib also significantly improved the overall survival (hazard ratio for death, 0.43; $P = 0.005$). At 12 months, the overall survival rate was 90% in the ibrutinib group and 81% in the atumumab group. The ORR was significantly higher in the ibrutinib group than in the atumumab group (42.6% vs. 4.1%, $P < 0.001$).[16]

SIDE EFFECTS OF IBRUTINIB

Most important and serious side effects are hemorrhage, infections, myelosuppression, renal toxicity, and second primary malignancies (especially skin malignancy).[17] The most commonly occurring adverse reactions (≥20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting, and anorexia.[18] The most common ≥3 Grade nonhematological adverse reactions are pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.[19]

In the treatment of CLL, the most commonly occurring adverse reactions (≥20%) in the clinical trial were thrombocytopenia (71%), diarrhea (63%), bruising (54%), neutropenia (54%), anemia (44%), upper respiratory tract infection (48%), fatigue (31%), musculoskeletal pain (27%), rash (27%), pyrexia (25%), constipation (23%), peripheral edema (23%), arthralgia (23%), nausea (21%), stomatitis (21%), sinusitis (21%), and dizziness (21%).[18] The most common Grade 3 or 4 nonhematological adverse reactions (≥5%) were pneumonia (8%), hypertension (8%), atrial fibrillation (6.0%), sinusitis (6%), skin infection (6%), dehydration (6.0%), and musculoskeletal pain (6%). Treatment-emergent Grade 3 or 4 cytopenias were reported in 35% of patients.[19]

In the treatment of MCL, the most commonly occurring adverse reactions (≥20%) in the clinical trial were thrombocytopenia (57%), diarrhea (51%), neutropenia (47%), anemia (41%), fatigue (41%), musculoskeletal pain (37%), peripheral edema (35%), upper respiratory tract infection (34%), nausea (31%), bruising (30%), dyspnea (27%), constipation (25%), rash (25%), abdominal pain (24%), vomiting (23%), and decreased appetite (21%).[20] The most common Grade 3 or 4 nonhematological adverse reactions (≥5%) were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5.4%), diarrhea (5%), fatigue (5%), and skin infections (5%). Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of the patients.

PRECAUTIONS

Ibrutinib should be taken by mouth with a glass of water. It should be swallowed as a whole. Opening, breaking, or chewing before swallowing are discouraged.[21] Food or drink containing grapefruit or Seville oranges should be avoided while taking ibrutinib. The patient is encouraged to drink extra fluids. As ibrutinib is chiefly metabolized by CYP 3A, drugs affecting CYP3A will affect its functionality. Its toxicity increases in hepatic dysfunction. Treating doctors should be more cautious in a sense, not to unnecessarily discontinue ibrutinib in the background of persistent lymphocytosis as these lymphocytes are transcriptionally inert.[22]

Ibrutinib should not be used if the patient is allergic to any ingredient in ibrutinib, pregnancy and breast feeding, liver problems, kidney problems, high blood pressure, blood problems, or bleeding problems, or if you have had recent surgery or plan to have surgery.[23]

FOOD AND DRUG ADMINISTRATION-APPROVED DOSAGE, INDICATIONS, AND MODIFICATIONS

- About 560 mg orally OD for MCL patients who have received at least one prior therapy[15]

Table 1: Dose modification recommended for restarting the treatment after Grade 3 or higher toxicity

Toxicity occurrence	MCL dose modification after recovery starting dose=560 mg	CLL dose modification after recovery starting dose=420 mg
1st	Restart at starting dose	
2nd	420	280
3rd	280	140
4th	Stop ibrutinib	

MCL: Mantle cell lymphoma, CLL: Chronic lymphocytic leukemia

- About 420 mg orally OD for CLL patients who have received at least one prior therapy.[16]

Dose modifications

If there is mild-to-moderate renal impairment (Cr clearance >25 mL/min), ibrutinib exposure is not altered.[21] In case of severe renal impairment (Cr clearance <25 mL/min), exact guidelines are not available due to lack of studies in this population.

Dose adjustment may be required in case of hepatic impairment; however, no specific guidelines have been suggested. Caution is recommended.[24]

Dose modifications for adverse reactions: If the patient suffers from Grade 3 or higher toxicities, ibrutinib should be interrupted. The recommended schedule for restarting ibrutinib is shown in Table 1.[25]

Dose modifications for use with CYP4503A inhibitors

Concomitant use of strong CYP450 3A inhibitors is not recommended. For short-term use (treatment for 7 days or less) of strong CYP450 3A inhibitors (e.g., anti-fungals and antibiotics), interruption of the therapy is considered until the CYP450 3A inhibitor is no longer needed. Reduce dose to 140 mg if a moderate CYP450 3A inhibitor must be used.

CONCLUSION

Ibrutinib is an effective drug for B-cell malignancies such as MCL and CLL. OD oral dosing is convenient for the patients and also more compliant. Given the promise for B-cells, ibrutinib in future may be effective for other lymphoid malignancies. Further studies are needed to evaluate long-term side effects and modifications in liver disease patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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