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New Drug Update

Expanding horizons in the treatment of mantle cell lymphoma: Ibrutinib a novel BTK-targeting inhibitor

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ABSTRACT

Mantle cell lymphoma (MCL) is a non-Hodgkin lymphoma characterized by involvement of the lymph nodes, spleen, blood, and bone marrow with short remission duration to standard therapies and a median overall survival of 4–5 years. Small molecule inhibitors targeting dysregulated pathways (MAPK/ERK, PI3K/PKB/mTOR, JAK/STAT) have significantly improved clinical outcomes in cancer patients. Recently Bruton's tyrosine kinase (BTK), a crucial terminal kinase enzyme in the B-cell antigen receptor (BCR) signaling pathway, has emerged as an attractive target for therapeutic intervention in human malignancies and autoimmune disorders. Ibrutinib, a novel first-in-human BTK-inhibitor, has demonstrated clinical effectiveness and tolerability in clinical trials, recently been approved by FDA in the treatment of MCL.

Keywords: Mantle cell lymphoma, BTK-inhibitor, B-cell antigen receptor, Ibrutinib

INTRODUCTION

Identification of novel mediators that regulate the growth and death of cancer cells has enabled the evolution of more effective anti-cancer agents that have revolutionized therapeutic options and clinical outcomes in cancer patients.[1-5] For example, rituximab, a first-in-class chimeric monoclonal antibody targeting CD 20 molecule, has had clear impact on response rates and survival outcomes, and has become a standard component of treatment regimens for many patients with B-cell non-Hodgkin's lymphomas (NHLs).[6-8] Monoclonal antibodies targeting CD 19 molecule are also rapidly moving through clinical trials.[9] In recent times, Bruton's tyrosine kinase (BTK), a crucial terminal kinase enzyme in the B-cell antigen receptor (BCR) signaling pathway has emerged as a novel target.[10] This downstream signal transduction protein is a critical effector molecule that governs normal B-cell development, differentiation and functioning, and has also been implicated in initiation, survival and progression of mature B-cell lymphoproliferative disorders.[11,12]

Ibrutinib, a novel BTK-targeting inhibitor, has shown significant activities across a variety of B-cell neoplastic disorders and autoimmune diseases in preclinical models and clinical trials[13] and recently got FDA approval for the treatment of MCL. This article highlights the pharmacology, clinical evidences and regulatory status of Ibrutinib with current approved indications given by FDA.

PHARMACOLOGY: IBRUTINIB

Description and chemical structure[14]

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). It is a white to off-white solid with the empirical formula $C_{25}H_{24}N_6O_2$ and a molecular weight 440.50. Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol and practically insoluble in water.

The chemical name for ibrutinib is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has the following structure:

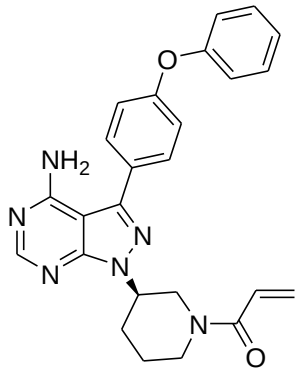

Figure 1: Chemical structure of Ibrutinib.

Mechanism of action

Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro*.[10,15]

Pharmacodynamics

In patients with recurrent B-cell lymphoma > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg).[16,17]

Pharmacokinetics[16,17]

Absorption

Ibrutinib is absorbed after oral administration with a median T_{max} of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC observed in patients at 560 mg is (mean ± standard deviation) 953 ± 705 ng·h/mL. Administration with food increases ibrutinib exposure approximately 2-fold compared with administration after overnight fasting.

Distribution

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. The apparent volume of distribution at steady state (Vd,ss/F) is approximately 10000 L.

Metabolism

Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. The range of the mean metabolite to parent ratio for PCI-45227 at steady-state is 1 to 2.8.

Elimination

Apparent clearance (CL/F) is approximately 1000 L/h. The half-life of ibrutinib is 4 to 6 hours. Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled [14C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites.

CLINICAL STUDIES

Mantle cell lymphoma

The safety and efficacy of ibrutinib in patients with MCL who have received at least one prior therapy were evaluated in an open-label, multi-center, single-arm trial of 111 previously treated patients. The median age was 68 years (range, 40 to 84 years), 77% were male, and 92% were Caucasian. At baseline, 89% of patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range, 1 to 5 treatments), including 11% with prior stem cell transplant. At baseline, 39% of subjects had at least one tumor ≥ 5 cm, 49% had bone marrow involvement, and 54% had extranodal involvement at screening.

Ibrutinib was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumor response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's

lymphoma (NHL) criteria. The primary endpoint in this study was investigator-assessed overall response rate (ORR). Responses to ibrutinib are shown in Table 1.

Table 1: Overall Response Rate (ORR) and Duration of Response (DOR) based on investigator assessment in patients with mantle cell lymphoma.

	Total (N=111)
ORR (%)	65.8
95% CI (%)	(56.2, 74.5)
CR (%)	17.1
PR (%)	48.6
Median DOR months 95% CI	17.5 (15.8, NR)

CI = confidence interval; CR = complete response; PR = partial response; NR = not reached

An Independent Review Committee (IRC) performed independent reading and interpretation of imaging scans. The IRC review demonstrated an ORR of 69%. The median time to response was 1.9 months.[13-17]

Lymphocytosis

Upon initiation of ibrutinib, a temporary increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) occurred in 33% of patients in the MCL study. The onset of isolated lymphocytosis occurs during the first few weeks (median time 1.1 weeks) of ibrutinib therapy and resolves by a median of 8 weeks.[18]

REGULATORY STATUS

On November 13, 2013, the U. S. Food and Drug Administration granted accelerated approval to ibrutinib for the treatment of patients with MCL who have received at least one prior therapy.[19]

INDICATIONS

Ibrutinib is indicated for the treatment of patients with MCL who have received at least one prior therapy. This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established.[19]

DOSAGE AND ADMINISTRATION

Dosage for mantle cell lymphoma

The recommended dose of ibrutinib for MCL is 560 mg (four 140 mg capsules) orally once daily.[20]

Dosing guidelines

Ibrutinib is administered orally once daily at approximately the same time each day. Capsules are swallowed whole with water.[20]

Missed dose

If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra doses of ibrutinib should not be taken to make up for the missed dose.[20]

Dose modifications for adverse reactions

Interrupt ibrutinib therapy for any Grade 3 or greater non-hematological, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), ibrutinib therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue ibrutinib.[20] Recommended dose modifications for these toxicities are given in Table 2.

Table 2: Recommended dose modifications for toxicities.

Toxicity Occurrence	MCL Dose Modification After Recovery Starting Dose = 560 mg
First	Restart at 560 mg daily
Second	Restart at 420 mg daily
Third	Restart at 280 mg daily
Fourth	Discontinue ibrutinib

ADVERSE EFFECTS

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 decreased appetite.[20,21]

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.[20,21]

WARNINGS AND PRECAUTIONS

Hemorrhage

Five percent of patients with MCL had Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, and hematuria). Overall, bleeding events including bruising of any grade occurred in 48% of patients with MCL treated with 560 mg daily.[20]
The mechanism for the bleeding events is not well understood.

Consider the benefit-risk of ibrutinib in patients requiring antiplatelet or anticoagulant therapies.

Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.[20]

Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of patients with MCL had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE). Monitor patients for fever and infections and evaluate promptly.[20]

Myelosuppression

Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of patients. These included neutropenia (29%), thrombocytopenia (17%) and anemia (9%). Monitor complete blood counts monthly.[20]

Renal toxicity

Fatal and serious cases of renal failure have occurred with ibrutinib therapy. Treatment-emergent increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients and from 1.5 to 3 times the upper limit of normal in 9% of patients. Periodically monitor creatinine levels. Maintain hydration.[20]

Second primary malignancies

Other malignancies (5%) have occurred in patients with MCL who have been treated with ibrutinib, including skin cancers (4%), and other carcinomas (1%).[20]

Embryo-fetal toxicity

Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL receiving the ibrutinib dose of 560 mg per day. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking ibrutinib. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.[20,21]

DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

CYP3A inhibitors

In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng · hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).[19-21]

Avoid concomitant administration of ibrutinib with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting ibrutinib therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the ibrutinib dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of ibrutinib.[19-21]

Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.[20]

CYP3A inducers

Administration of ibrutinib with strong inducers of CYP3A decrease ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction.[20]

SPECIAL POPULATION

Pregnancy and lactation

It has been assigned Category D in pregnancy, based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. If ibrutinib is used during pregnancy or if the patient becomes pregnant while taking ibrutinib, the patient should be apprised of the potential hazard to the fetus.[20]

It is not known whether ibrutinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ibrutinib, a decision should be

made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.[20]

Pediatric and geriatric use

The safety and effectiveness of ibrutinib in pediatric patients has not been established.[20]

During trials, no overall differences in effectiveness were observed between elderly patients and younger patients. However, cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis) and gastrointestinal events (diarrhea and dehydration) occurred more frequently among elderly patients.[20]

Renal impairment

Ibrutinib exposure is not altered in patients with Creatinine clearance (CLcr) > 25 mL/min as less than 1% of ibrutinib is excreted renally. However, there are no data available in patients with severe renal impairment (CLcr < 25 mL/min) or patients on dialysis.[20]

Hepatic impairment

Ibrutinib is metabolized in the liver and significant increases in exposure of ibrutinib are expected in patients with hepatic impairment. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3.0 x upper limit of normal (ULN) were excluded from clinical trials. There is insufficient data to recommend a dose in patients with baseline hepatic impairment.[20]

CONCLUSIONS

The current body of clinical evidences indicate that ibrutinib is effective for the treatment of patients with MCL who have received at least one prior therapy as it has shown significant activities across a variety of B-cell neoplastic disorders and autoimmune diseases in preclinical models and clinical trials.

Abbreviations

MAPK: Mitogen-activated protein kinases,
ERK: Extracellular signal-regulated kinases,
PI3K: Phosphatidylinositide 3-kinases,
PKB: Protein Kinase B,
mTOR: Mammalian target of rapamycin,
JAK: Janus kinase,
STAT: Signal transduction and transcription,
BTK: Bruton's tyrosine kinase

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