Imbruvica (Ibrutinib) for Mantle-Cell Lymphoma: First Bruton’s Tyrosine Kinase Inhibitor Approved for Use in a Hematologic Malignancy

By Lisa A. Raedler, PhD, RPh, Medical Writer

Mantle-cell lymphoma (MCL) is a rare malignancy, comprising approximately 5% of all cases of non-Hodgkin lymphoma.1 MCL can be an aggressive cancer and most often affects men aged >60 years.1,2 The median overall survival of patients with MCL is approximately 5 to 7 years, making MCL one of the poorest prognoses among B-cell lymphomas.3 Survival outcomes of MCL are poor in part because the disease is typically diagnosed in later stages, when the gastrointestinal tract and bone marrow become involved.2 Although the data suggest a possible increase in the incidence of MCL over the past 20 years, this may be the result of improved diagnostic methods.4

Treatment decisions for MCL are based on several factors, including the patient’s age, the patient’s overall health, and the disease stage.1 In clinical practice, combinations of chemotherapy agents with anti-CD20 monoclonal antibody therapy, high-dose chemotherapy followed by autologous stem-cell transplantation, and radioimmunotherapy are relevant options for treatment-naïve patients with MCL.2 Although MCL typically responds to initial treatment, it relapses within a few years or becomes refractory to treatment, such that second-line therapy is necessary.2 As of yet, there is no consensus regarding the management of patients with relapsed and/or refractory MCL.5

There are few assessments of the cost burden associated with MCL. One recent cost-effectiveness study, which used US payer data, showed that the average per-patient cost of bendamustine plus rituximab, and the average per-patient cost of the R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen both exceeded $100,000.6

Until recently, bortezomib (Velcade) and lenalidomide (Revlimid) were the only treatments approved by the US Food and Drug Administration (FDA) for use in patients with MCL. Bortezomib is indicated for patients with MCL who have received at least 1 previous therapy.7 Lenalidomide is approved for use in patients with MCL whose disease relapsed or progressed after 2 previous therapies, one of which included bortezomib.9 Novel options that are under investigation as single agents or in combination for MCL include phosphoinositide 3-kinase inhibitors (eg, idelalisib), histone deacetylase inhibitors (eg, vorinostat, panobinostat), monoclonal antibodies (eg, ofatumumab), and mammalian target of rapamycin (mTOR) inhibitors (eg, temsirolimus, everolimus).3,9

Ibrutinib for Relapsed and/or Refractory MCL

On November 13, 2013, ibrutinib (Imbruvica; Pharmacyclics) was granted accelerated approval by the FDA to treat patients with MCL who have received at least 1 previous therapy.10 Ibrutinib is the first drug designed to target Bruton’s tyrosine kinase (BTK), a protein necessary for the growth and survival of B-cells.11

The approval of ibrutinib for MCL was based on the results of a phase 2 multicenter, international, single-arm trial involving 111 patients with previously treated MCL. The primary end point of this trial was the overall response rate.10,12

Michael Wang, MD, Director, Myeloma Tissue Bank, at M.D. Anderson Cancer Center, Houston, and lead investigator of the phase 2 study of ibrutinib, commented on the trial results to date, saying, “These are unprecedented response rates for monotherapy in the relapsed setting. Based on these results it is apparent that ibrutinib therapy provides a well-tolerated, effective, and convenient (orally administered) therapy for relapsed patients with MCL.”13

Mechanism of Action

Ibrutinib is a small molecule that inhibits BTK, a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways.14 As an irreversible covalent inhibitor, ibrutinib continues to inhibit BTK even after it is metabolized.14,15 Preclinical studies have demonstrated that ibrutinib prevents the activation of downstream pathways affected by BTK, promotes cancer cell apoptosis, and inhibits cell proliferation.14,15
Dosing and Administration

In patients with MCL who have received 1 previous therapy, the recommended dose and schedule for ibrutinib is 560 mg orally once daily. Ibrutinib should be administered at the same time each day, swallowed whole with water. Capsules should not be opened, broken, or chewed.14

Table 1 summarizes ibrutinib dose modification guidelines for patients with any grade ≥3 nonhematologic toxicity, grade ≥3 neutropenia with infection or fever, or grade 4 hematologic toxicities. Ibrutinib may be reinitiated at the starting dose after symptoms of toxicity have resolved to grade 1 or to baseline.14

Because ibrutinib is primarily metabolized by the cytochrome (CY) P3A enzyme, it should not be coadministered with strong or moderate CYP3A inhibitors. The concomitant use of strong CYP3A inhibitors that would be taken on an ongoing basis (eg, long-term ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) with ibrutinib is not recommended.14

Increased drug exposure is also expected in patients with hepatic impairment. However, there are insufficient data to recommend a dose of ibrutinib in patients with baseline hepatic impairment.14

Pivotal Phase 2 Clinical Trial

In the phase 2 single-arm, open-label, multicenter, international trial that led to the FDA approval of ibrutinib for MCL, Wang and colleagues enrolled 111 patients with MCL who had received multiple therapies, as well as patients who were bortezomib-naïve and patients who had received at least 2 cycles of bortezomib (ie, bortezomib-exposed).12

Ibrutinib was given orally at 560 mg daily in continuous 28-day cycles until disease progression. The primary end point of this phase 2 study was the overall response rate, defined as partial response and complete response.12 Duration of response, progression-free survival, overall survival, and safety served as secondary end points. Tumor response was evaluated every 2 cycles per the revised International Working Group for non-Hodgkin lymphoma criteria.12 Efficacy parameters were assessed by the investigators, as well as by an independent central review committee.12 The bortezomib-naïve and bortezomib-exposed patient subgroups were evaluated separately.12

Table 2  Best Response to Ibrutinib Therapy

<table>
<thead>
<tr>
<th>Investigator-assessed response</th>
<th>All patients (N = 111), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>65.8 (95% CI, 56.2, 74.5)</td>
</tr>
<tr>
<td>Complete response</td>
<td>17.1</td>
</tr>
<tr>
<td>Partial response</td>
<td>48.6</td>
</tr>
<tr>
<td>Median duration of response in months</td>
<td>17.5 (95% CI, 15.8, NR)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; NR, not reached.
Source: Imbruvica (ibrutinib) capsules prescribing information; 2013.

Patient Population

The median age of the patients with MCL enrolled in the phase 2 trial of ibrutinib was 68 years.12,14 Most patients (77%) were male with an Eastern Cooperative Oncology Group performance status of 0 or 1 (89%).12,14 Almost half (45%) of the enrolled patients with MCL had refractory disease, and 72% had advanced disease.12 Patients had received a median of 3 previous therapies, including (1) rituximab-containing regimens (89%); (2) hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (30%); (3) lenalidomide (24%); and (4) and stem-cell transplantation (11%).12,14

Efficacy

With a median treatment duration of 8.3 months, the overall response rate was 65.8% among patients with MCL who received ibrutinib; 17.1% of patients achieved complete response and 48.6% of patients achieved partial response.14 The ibrutinib response rates did not differ between the bortezomib-naïve and bortezomib-exposed patient subgroups, or according to other baseline characteristics or risk factors associated with treatment failure.12

The overall response rate and complete response rate improved over time with continued use of ibrutinib therapy.12 Table 2 includes the efficacy parameters reported in the phase 2 clinical trial of ibrutinib.14

Safety

The adverse events that were most frequently observed with continuous ibrutinib treatment were of grade 1 or 2 severity.14 The most common nonhematologic adverse events were diarrhea (51%, all grades), 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%).14 Grade ≥3 hema-
tologic adverse events were neutropenia (29%), thrombocytopenia (17%), and anemia (9%).

Ten patients (9%) discontinued ibrutinib treatment because of adverse reactions in the MCL trial, with subdural hematoma (1.8%) representing the most frequent adverse reaction leading to discontinuation. Adverse reactions led to ibrutinib dose reductions in 14% of the patients in the MCL trial.

During the study, a temporary increase in lymphocyte counts was reported in 33% of patients. The lymphocyte count returns to baseline by a median of 8 weeks.

**Warnings and Precautions**

**Hemorrhage.** Bleeding events, including bruising of any grade, were observed in 48% of patients with MCL who were administered ibrutinib at the recommended dose of 560 mg daily. Overall, 5% of patients with MCL had grade ≥3 bleeding events, including subdural hematoma, gastrointestinal bleeding, and hematuria. Clinicians should consider the benefits and risks of administering ibrutinib to patients who require antiplatelet or anticoagulant therapies, and the benefits and risks of withholding ibrutinib for at least 3 to 7 days pre- and postsurgery, depending on the procedure and bleeding risk.

**Infections.** Fatal and nonfatal infections occurred in patients with MCL who were administered ibrutinib during the clinical trial. At least 25% of patients with MCL had grade ≥3 infections. Clinicians should regularly monitor patients receiving ibrutinib therapy for signs of fever and infections and evaluate promptly.

**Myelosuppression.** Grade 3 or 4 cytopenias, including neutropenia (29%), thrombocytopenia (17%), and anemia (9%), were reported in 41% of patients receiving ibrutinib. Patients should undergo monthly complete blood cell counts while receiving ibrutinib therapy.

**Renal toxicity.** Serious to fatal cases of renal failure have occurred with ibrutinib therapy. Increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients receiving ibrutinib and from 1.5 to 3 times the upper limit of normal in 9% of patients. Patients receiving ibrutinib should undergo periodic creatinine level monitoring and maintain hydration.

**Second primary malignancies.** Other malignancies, including skin cancers (4%) and other carcinomas (1%), have been observed in patients with MCL who were treated with ibrutinib.

**Embryo-fetal toxicity.** Based on animal studies, ibrutinib can cause fetal harm when administered during pregnancy. Women should be advised to avoid becoming pregnant while taking ibrutinib.

**Use in Specific Populations**

**Pregnancy.** Because animal studies have shown that ibrutinib can cause harm to the fetus, patients should be counseled about the potential risks to the fetus if they take ibrutinib during pregnancy or become pregnant while taking ibrutinib.

**Nursing mothers.** Although it is not known whether ibrutinib is present in human milk, nursing or use of ibrutinib should be stopped, because of the potential for serious adverse reactions from ibrutinib in nursing infants.

**Pediatric use.** The safety and efficacy of ibrutinib has not been established in pediatric patients.

**Geriatric use.** Overall, there was no difference in the efficacy of ibrutinib between patients aged ≥65 years and younger patients. However, cardiac adverse events, infections, and gastrointestinal events occurred more frequently among older patients.

As the first BTK inhibitor approved by the FDA, ibrutinib offers clinicians a unique treatment option for patients with MCL who have received 1 previous therapy. Orally administered ibrutinib has demonstrated uniquely high response rates, as well as a favorable toxicity profile.

**Renal impairment.** Ibrutinib exposure is not affected in patients with creatinine clearance ≥25 mL/min. There are no data in patients with severe renal impairment or on dialysis.

**Hepatic impairment.** Significant increases in exposure of ibrutinib are anticipated in patients with hepatic impairment. There are insufficient data to recommend a dose of ibrutinib in patients with baseline hepatic impairment.

**Females and males of reproductive potential.** Women should be advised to not get pregnant while taking ibrutinib because of the potential harm to the fetus.

**Conclusion**

As the first BTK inhibitor approved by the FDA, ibrutinib offers clinicians a unique treatment option for patients with MCL who have received 1 previous therapy. Orally administered ibrutinib has demonstrated uniquely high response rates, as well as a favorable toxicity profile. Clinical studies are currently under way to evaluate the use of ibrutinib as part of combination regimens in MCL and other hematologic malignancies.

**References**


2. Lymphoma Research Foundation. Getting the facts: mantle cell lymphoma. 2013. Updated January 2013. www.lymphoma.org/article%7Bc=bf64-3-24-3-40c-ate5-6903-