Imbruvica (Ibrutinib) plus Rituxan (Rituximab) New Combination Approved for the Treatment of Waldenström’s Macroglobulinemia

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

In 1944, Jan G. Waldenström, MD, published his observations about a series of patients who presented with anemia, hepatosplenomegaly, hyperviscosity, bleeding, lymphoplasmacytic infiltrate in the bone marrow, and a large serum protein or “macroglobulin.”1 Today, Waldenström’s macroglobulinemia, also known as lymphoplasmacytic lymphoma, a type of non-Hodgkin lymphoma, is classified as a rare, indolent, and heterogeneous type of lymphoma of the lymphatic system.2-4

B-lymphocytes or B-cells (a type of white blood cell) typically mature into plasma cells that produce immunoglobulin (Ig) to fight infections.2 In patients with Waldenström’s macroglobulinemia, malignant B-cells multiply and overproduce the IgM antibody in the bone marrow or blood, overwhelming healthy cells.2

Approximately 1500 Americans are diagnosed with Waldenström’s macroglobulinemia annually.2 The definitive cause of this cancer is not known, but white, older men (aged ≥65 years) are at an increased risk for the disease.5

According to the International Prognostic Scoring System for Waldenström’s macroglobulinemia, the 5 factors that influence disease prognosis include increasing age (>65 years), hemoglobin level <11.5 g/dL, a platelet count of <100×10^9/L, β2 microglobulin of >3 mg/L, and a serum monoclonal protein concentration of >70 g/L.2 The 5-year overall survival rate is approximately 78% for patients with this rare cancer.2

The treatment of Waldenström’s macroglobulinemia is not standardized; therapy decisions are personalized based on the patient’s age, symptoms, comorbidities, and preferences.4 Currently, there is no known cure for this disease.2

In January 2015, the targeted drug ibrutinib (Imbruvica) became the first medication to receive approval by the US Food and Drug Administration (FDA) for the treatment, as monotherapy, of patients with relapsed Waldenström’s macroglobulinemia, based on a prospective study that demonstrated high rates of durable responses to ibrutinib monotherapy in patients with relapsed disease.3,8

FDA Approves Imbruvica plus Rituxan for Waldenström’s Macroglobulinemia

On August 27, 2018, the FDA expanded the indication of ibrutinib (Imbruvica; Pharmacyclics/Janssen Biotech), an oral inhibitor of Bruton’s tyrosine kinase (BTK), in combination with rituximab (Rituxan), a monoclonal antibody immunotherapy that targets the CD20 antigen expressed on the surface of pre-B cells and mature B-lymphocytes, for the treatment of adults with Waldenström’s macroglobulinemia.9 This is the first nonchemotherapy treatment approved by the FDA for Waldenström’s macroglobulinemia.9

This approval was based on the iNNOVATE study, which demonstrated improved outcomes when combining the targeted therapy ibrutinib plus immunotherapy with rituximab versus ibrutinib alone in patients with Waldenström’s macroglobulinemia.10

“The combination of Imbruvica and rituximab provides health care professionals with a new treatment option for patients living with this serious blood cancer.”9

“…the first nonchemotherapy treatment approved by the FDA for Waldenström’s macroglobulinemia.”9

Ibrutinib was previously approved by the FDA as monotherapy for mantle-cell lymphoma in adults who
have received ≥1 previous therapies; for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) in patients with or without 17p deletion; for marginal zone lymphoma in patients who have received at least 1 previous anti-CD20-based therapy; as monotherapy for relapsed Waldenström’s macroglobulinemia; and after ≥2 lines of systemic therapy for chronic graft-versus-host.

And most recently, on January 28, 2019, the FDA approved the combination of ibrutinib and obinutuzumab (Gazyva) for first-line treatment of adults with CLL/SLL.12 This is the first FDA approval of a nonchemotherapy combination regimen for patients with CLL/SLL who have not received previous treatment.12

Mechanism of Action
Ibrutinib, an oral small molecule that targets BTK, leads to the inhibition of BTK-specific enzymatic activity. BTK signaling occurs through B-cell antigen receptor and cytokine receptor pathways and affects B-cell trafficking, chemotaxis, and adhesion.11

Dosing and Administration
The recommended dose of ibrutinib for Waldenström’s macroglobulinemia, as a single agent or in combination with rituximab, is 420 mg orally (as tablets or capsules) once daily until disease progression or unacceptable toxicity. When ibrutinib is used in combination with rituximab, the oral dose of ibrutinib should be administered before the rituximab infusion.11

Ibrutinib should be taken at approximately the same time each day, with a glass of water. Ibrutinib tablets should not be cut, crushed, or chewed, and ibrutinib capsules should not be opened, broken, or chewed.11

The iNNOVATE Clinical Trial
The efficacy of ibrutinib plus rituximab in treatment-naïve or in patients with previously treated Waldenström’s macroglobulinemia was evaluated in the phase 3 iNNOVATE clinical trial.10,11 In this study, 150 patients were randomized to ibrutinib 420 mg daily plus rituximab or to placebo plus rituximab until disease progression or unacceptable toxicity. Rituximab was administered weekly at a dose of 375 mg/m² for 4 consecutive weeks (weeks 1-4) followed by a second course of weekly rituximab for 4 weeks (weeks 17-20). The primary efficacy end point was progression-free survival (PFS), as assessed by an Independent Review Committee.10,11

Most patients who enrolled in the iNNOVATE study were male (66%) and Caucasian (79%), with a baseline Eastern Cooperative Oncology Group performance status of 0 or 1 (93%).8 The patients’ median age was 69 years (range, 36-89 years).10,11 Overall, 45% of the patients with Waldenström’s macroglobulinemia were treatment naïve.10,11 Among treated patients, the median number of previous treatments was 2 (range, 1-6).11

After a median 26.5-month follow-up, a significant improvement in PFS was demonstrated in patients who received ibrutinib plus rituximab compared with placebo plus rituximab.10,11 At 30 months, the PFS rate was 82% with ibrutinib plus rituximab versus 28% in the placebo plus rituximab arm.10 The efficacy data are summarized in the Table.11

**Table** Efficacy of Ibrutinib in the iNNOVATE Study

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Ibrutinib plus rituximab (N = 75)</th>
<th>Placebo plus rituximab (N = 75)</th>
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</thead>
<tbody>
<tr>
<td><strong>PFS</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hazard ratio 0.20 (95% CI, 0.11-0.38)</td>
<td>Not evaluable (95% CI, &lt;.0001)</td>
</tr>
<tr>
<td>Median PFS after median follow-up of 26.5 months, mo</td>
<td>Not evaluable (95% CI, 13.7-27.6)</td>
<td>20.3 (95% CI, 13.7-27.6)</td>
</tr>
<tr>
<td><strong>Responses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete/partial/very good partial response,&lt;sup&gt;b&lt;/sup&gt; %</td>
<td>72</td>
<td>32</td>
</tr>
<tr>
<td>Complete response/very good partial response,&lt;sup&gt;b&lt;/sup&gt; %</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>Duration of response, mo</td>
<td>Not evaluable (95% CI, 1.9+ to 36.4+&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>21.2 (95% CI, 4.6-25.8)</td>
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</table>

<sup>a</sup>Assessed by Independent Review Committee.

<sup>b</sup>P value associated with response rate was <.0001.

CI indicates confidence interval; PFS, progression-free survival.

Source: Imbruvica (ibrutinib) capsules/tablets prescribing information; January 2019.

**Adverse Events**
The safety of ibrutinib plus rituximab combination is based on data from 75 patients with Waldenström’s macroglobulinemia who participated in the iNNOVATE study. The median duration of treatment with ibrutinib plus rituximab in this study was 25.8 months.11

The most common (≥20%) adverse reactions of any grade in the patients receiving ibrutinib plus rituximab, in order of decreasing frequency, were bruising, musculoskeletal pain, hemorrhage, anemia, diarrhea, rash, arthralgia, nausea, and hypertension.11

Grade 3 or 4 adverse events that occurred more frequently with ibrutinib plus rituximab than with placebo plus rituximab were atrial fibrillation (12% vs 1%, respectively) and hypertension (13% vs 4%), respectively.10 Severe events that occurred less frequently with ibrutinib plus rituximab included infusion reactions (1% vs 16%, respectively) and any grade of IgM flare (8% vs 47%, respectively).10 In both study arms, 4% of patients had major hemorrhage.11

Imbruvica has no contraindications.11

**Drug Interactions**

The coadministration of ibrutinib with a strong or
Use in Specific Populations

Ibrutinib can cause fetal harm. Women of reproductive potential should use effective contraception during treatment and for at least 1 month after the last dose of ibrutinib. Male patients should avoid fathering a child for at least 1 month after the last dose of ibrutinib.11

Women should not breastfeed during treatment with ibrutinib and for 1 month after the final dose of ibrutinib.11

The safety and effectiveness of ibrutinib treatment have not been established in children.11

No differences were seen in the effectiveness of ibrutinib between older patients (aged ≥65 years) and younger patients in clinical trials. Older patients who received ibrutinib had more adverse events, including pneumonia, anemia, thrombocytopenia, hypertension, and atrial fibrillation.11

In patients with Waldenström’s macroglobulinemia, plasmapheresis may be necessary for the management of hyperviscosity before and during ibrutinib treatment, but ibrutinib dosing does not need to be modified.11

In patients with mild or moderate hepatic impairment, modification of ibrutinib dose is recommended. Ibrutinib should be avoided in patients with severe hepatic impairment. The safety of ibrutinib has not been evaluated in patients with mild-to-severe hepatic impairment.11

Warnings and Precautions

Serious and fatal cardiac arhythmias have occurred with ibrutinib therapy, and increased rates have been observed in patients with cardiac risk factors, hypertension, acute infections, or a history of cardiac arhythmias.11

Patients who are receiving ibrutinib should be monitored for hypertension, including new-onset hypertension.11

Bleeding events have occurred with ibrutinib, with fatalities occurring in 0.3% of >1000 patients who have received ibrutinib in clinical trials.11

Patients who are receiving ibrutinib should be monitored for cytopenias. Because fatal and nonfatal infections (bacterial, viral, or fungal) can occur with ibrutinib therapy, patients at increased risk for opportunistic infections should be considered for standard-of-care prophylaxis.11

Tumor lysis syndrome has been reported with ibrutinib therapy. High tumor burden at baseline increased the risk for this syndrome.11

Second primary malignancies, most often being non-melanoma skin cancer, have also been documented with ibrutinib therapy.11

Conclusion

The FDA approval of ibrutinib in combination with rituximab, the first chemotherapy-free treatment regimen for patients with Waldenström’s macroglobulinemia, provides a new and improved treatment option for patients with this rare disease, for which there is no cure. This new combination regimen demonstrated superior outcomes compared with either agent alone in patients with untreated or with relapsed or refractory Waldenström’s macroglobulinemia. This was the ninth FDA indication for ibrutinib since its initial approval in 2013. And in 2019, the FDA approved the tenth indication for ibrutinib, in combination with obinutuzumab, for first-line treatment of patients with CLL or SLL.

References