Ibrutinib: A New Targeted Therapy for Hematologic Cancers

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**Background:** Hematologic cancers can occur from the overactivity of Bruton’s tyrosine kinase, a proto-oncogene in blood cell maturation. Ibrutinib, a new oral targeted therapy drug, is the first agent that binds to the Bruton’s tyrosine kinases and inhibits overgrowth of B cells. In blocking this overgrowth, ibrutinib has been shown to achieve lengthy remissions for patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). Remissions are highly valued in these cancers; cure is rare in MCL, and CLL is incurable.

**Objectives:** This article reviews ibrutinib, its risks and benefits, and the role that oncology nurses play in educating patients and promoting drug adherence.

**Methods:** A comprehensive review of the literature was conducted using key words such as *ibrutinib, mantle cell lymphoma, chronic lymphocytic leukemia, tyrosine kinase inhibitor,* and *oral chemotherapy.*

**Findings:** Ibrutinib has been shown to be well tolerated, with manageable, low-grade toxicities compared to traditional cytotoxic agents. For all patients with a hematologic cancer, but particularly for the large proportion of older adults affected by hematologic malignancies, ibrutinib provides a new treatment option with a low toxicity profile.

Unlike traditional cytotoxic chemotherapy, which affects tumor cells and healthy cells, the targeted therapy agent ibrutinib focuses on tumor cells (Wujcik, 2011). Ibrutinib is intended for select hematologic cancers and is a small-molecule Bruton’s tyrosine kinase inhibitor (TKI) (Cameron & Sanford, 2014). Multiple TKIs are available, but ibrutinib is the first that is specific to Bruton’s tyrosine kinase (Cameron & Sanford, 2014). Overactive Bruton’s tyrosine kinases are proto-oncogenes that signal B cells to proliferate, differentiate, and survive, resulting in malignancy (Bhatt, Alejandro, Michael, & Ganetsky, 2014). B cells traditionally originate from stem cells in the bone marrow and mature into adaptive components in the humoral immune response (Manson & Porter, 2011). However, when the overactive Bruton’s tyrosine kinases signal B cells’ unregulated growth, the overabundant mutated B cells can lead to cancers such as mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), multiple myeloma (MM), and Waldenström’s macroglobulinemia (WM) (Bhatt et al., 2014; Treon et al., 2015).

Ibrutinib prevents the faulty Bruton’s tyrosine kinases from being able to signal this tumor cell growth and division.

**Indications**

Ibrutinib is indicated and approved by the U.S. Food and Drug Administration (FDA) for MCL, CLL, and WM. It received accelerated FDA approval in November 2013 for patients with MCL who have received at least one prior therapy (FDA, 2013b). Ibrutinib received accelerated approval in February 2014 for patients with CLL who have received at least one prior therapy (FDA, 2014a). In July 2014, the FDA granted full approval for patients with CLL who have received at least one prior therapy and for patients with CLL with a chromosome 17p deletion who may or may not have received prior therapy (FDA, 2014b). Chromosome 17p deletion is associated with a poor prognosis in CLL (University of Texas MD Anderson Cancer Center, 2013). In January 2015, the FDA approved ibrutinib for the treatment of patients with WM (FDA, 2015).
Pharmacology

Ibrutinib was developed by Pharmacyclics, Inc., and Janssen Biotech, Inc. (Cameron & Sanford, 2014). Ibrutinib binds to the Bruton’s tyrosine kinase and causes irreversible and selective inhibition of the tyrosine kinase (Bhatt et al., 2014). This inhibition blocks overstimulation of the B-cell receptor pathway that signals B cells to grow and divide unchecked (Bhatt et al., 2014). The half-life of ibrutinib is four to six hours, and it mainly is excreted through the feces with minimal urinary excretion (Pharmacyclics, Inc., 2015). Ibrutinib is metabolized in the liver primarily by the cytochrome P450 enzyme 3A (CYP3A) (Pharmacyclics, Inc., 2015). The capsules should be stored at room temperature (Pharmacyclics, Inc., 2015). The starting dose for MCL is 560 mg (four capsules) taken once daily (FDA, 2013b), whereas the starting dose for CLL and WM is 420 mg (three capsules) taken once daily (FDA, 2014a, 2015). The capsules are administered orally and should be swallowed whole at the same time each day (Pharmacyclics, Inc., 2015). The capsules should not be opened, broken, or chewed (Pharmacyclics, Inc., 2015). Ibrutinib should be taken with a glass of water and can be administered without regard to food (Bhatt et al., 2014; Pharmacyclics, Inc., 2015). If patients miss a dose, they can take it as soon as they remember on the same day, then take the next dose at the regular time on the following day (Pharmacyclics, Inc., 2015). Patients should not take two doses of ibrutinib on the same day to make up for a missed dose (Pharmacyclics, Inc., 2015).

Clinical Trial Results

Multiple studies have shown that ibrutinib is a groundbreaking approach for management of hematologic malignancies by inducing durable remissions (Chustecka, 2014), which is significant because multiple hematologic cancers (e.g., CLL, MM, follicular lymphoma) are incurable (Manson & Porter, 2011). Cure is rare in MCL (Manson & Porter, 2011). Optimizing remissions helps to give patients with hematologic malignancies longer overall survival and improved quality of life. See Figure 1 for definitions of responses in CLL and MCL.

A phase I study was conducted by Advani et al. (2013) with 56 patients with six different kinds of B-cell malignancies. The median participant age was 65 years, and the median number of prior therapies was three. Sixty percent (n = 30) of the 50 participants evaluated for tumor response had achieved complete or partial remission; most responses lasted 10 months or more, and the best responses were in patients with MCL, CLL, and WM (Advani et al., 2013).

A phase II study by Wang et al. (2013) involving 111 patients with relapsed MCL showed that 21% (n = 23) of the participants had achieved complete response, and 47% (n = 52) had achieved partial response. The median response duration of decreased or undetectable tumor load lasted 19.6 months (Wang et al., 2013). This pivotal trial helped to accelerate the FDA’s approval for ibrutinib’s use in patients with MCL (FDA, 2013a).

A phase Ib/II study by O’Brien et al. (2014) investigated ibrutinib as initial therapy in 31 older adults with CLL. Twenty-two of the participants achieved an objective response, four had a partial response with lymphocytosis, and three patients had stable disease. Ninety-six percent (n = 30) of the 31 participants had a progression-free survival at 24 months (O’Brien et al., 2014). The median time to initial response was 1.9 months,
and the median time to best response was 5.9 months (O’Brien et al., 2014).

Another phase II study, conducted by the University of Texas MD Anderson Cancer Center (2013), included 40 patients with CLL who were treated with ibrutinib and rituximab. This combination induced a response in 95% (n = 38) of the participants, with 78% (n = 31) showing no evidence of disease progression at 18 months (University of Texas MD Anderson Cancer Center, 2013). In addition, 20 of the 40 participants had mutations of the tumor-suppressing gene TP53 or chromosome 17p deletions, which are associated with poor prognosis; 90% (n = 18) of these patients had a response (University of Texas MD Anderson Cancer Center, 2013).

Full FDA approval was obtained for ibrutinib in patients with CLL in July 2014 based on results from the RESONATE (PCYC-1112) trial (FDA, 2014b). This phase III trial enrolled 391 patients with CLL who had received at least one prior therapy. The trial compared ibrutinib and ofatumumab, a standard therapy in CLL; ibrutinib was found to prolong the duration of progression-free survival and overall survival (Byrd et al., 2014). Patients receiving ibrutinib had progression-free survival at a median of 9.4 months, compared to a median of 8.1 months for those receiving ofatumumab (Byrd et al., 2014). At one year, 90% of the ibrutinib group were still living, compared to 81% of the ofatumumab group (Byrd et al., 2014). Similar results were found in 127 of the 391 participants who had chromosome 17p deletions (Byrd et al., 2014).

FDA approval was granted for ibrutinib in patients with WM following a phase II study by Treon et al. (2015) consisting of 63 previously treated patients with WM. Treon et al. (2015) found that 91% (n = 57) of the participants had an overall response to ibrutinib, with 16% (n = 10) of the participants having a very good partial response. The estimated two-year progression-free survival rate was 69%; among patients with progressive disease, the median time to progression was 9.6 months (Treon et al., 2015).

### Future Directions

Multiple clinical trials that examine the effects of ibrutinib alone and with additional therapies are underway, with the objective of gaining FDA approval for the drug’s use in patients with different hematologic malignancies (Wiestner, 2013). Phase III trials involving ibrutinib use in patients with CLL, WM, and DLBCL are also ongoing, as are phase II studies examining the drug’s use in patients with MM, follicular lymphoma, and central nervous system lymphoma (National Cancer Institute [NCI], 2015). Ibrutinib is also being studied as an initial therapy for patients with newly diagnosed MCL and CLL and is under investigation for treatment of acute myeloid and acute lymphocytic leukemias (NCI, 2015).

### Adverse Reactions

B-cell malignancies typically affect older adults with comorbidities and reduced bone marrow reserve (O’Brien et al., 2014). Older adults who receive traditional cytotoxic chemotherapy are at greater risk for myelosuppression and infections (O’Brien et al., 2014). Ibrutinib has been shown to be well tolerated and to have low toxicity with less myelosuppression and subsequent infections, making it a fitting therapeutic option for older adults (Chustecka, 2014). However, ibrutinib is also an option for all patients with MCL, CLL, and WM as indicated, regardless of age or health status. Ibrutinib received accelerated FDA approval for MCL and CLL in part because of its low toxicity profile. This early approval is given because a drug demonstrates “the potential to be a significant improvement in safety or effectiveness in the treatment of a serious condition” (FDA, 2013a, para. 6).

Although ibrutinib is well tolerated, adverse reactions have been reported (FDA, 2014a). Most are grade 1–2 in severity and are easily managed or reversible (Advani et al., 2013) (see Figure 2). The most common side effect is diarrhea, but it usually is self-limited (O’Brien et al., 2014). The next most common adverse reactions are nausea and fatigue (O’Brien et al., 2014). Grade 1–2 side effects of diarrhea, nausea, fatigue, upper respiratory infection, peripheral edema, dyspnea, decreased appetite, rash, and arthralgia occurred in 19%–44% of patients (Chavez, Sahakian, & Pinilla-Ibarz, 2013; Wang et al., 2013).

### CYP3A Drug Interactions

- **CYP3A Inducers**
  - Carbamezepine
  - Dexamethasone
  - Griseofulvin
  - Phenobarbital
  - Phenytoin
  - Rifabutin
  - Rifampin
  - St. John’s wort

- **CYP3A Inhibitors**
  - Aprepitant
  - Ciprofloxacin
  - Clarithromycin
  - Diltiazem
  - Erythromycin
  - Grapefruit juice
  - Indinavir
  - Itraconazole
  - Ketoconazole
  - Nefazodone
  - Posaconazole
  - Ritonavir
  - Telithromycin
  - Verapamil
  - Voriconazole

### FIGURE 3. Common Grade 3–4 AEs With Ibrutinib as Monotherapy in Patients With MCL (N = 111)

Note. Based on information from Wang et al., 2013.

![Figure 3](image-url)

### FIGURE 4. CYP3A Drug Interactions

Note. Based on information from Greener, 2009; RxList Inc., 2015.
Fever, dizziness, sinusitis, stomatitis, bruising, constipation, abdominal pain, and musculoskeletal pain are also common adverse effects (Pharmacyclics, Inc., 2015).

Grade 3–4 toxicities are infrequent with ibrutinib (Wang et al., 2013) (see Figure 3). Healthcare providers should note that the incidence of serious adverse reactions is two times more likely in patients who have had prior therapy (Berkrot, 2013). Neutropenia, thrombocytopenia, and anemia were the most common grade 3–4 toxicities, affecting 7%–13% of patients (Advani et al., 2015). Grade 3–5 pneumonia occurred in 6% of patients (Wang et al., 2013). Grade 3 bleeding occurred in about 5% of patients (Wang et al., 2013). Adverse events led to a discontinuation of therapy in 6% (Chavez et al., 2013), 7% (Wang et al., 2013), and 14% (Advani et al., 2013) of participants in three different studies. Ibrutinib is not known to cause significant liver or renal toxicities or cumulative toxicities with prolonged therapy (Advani et al., 2013).

If a patient experiences grade 3–4 toxicities, the drug should be stopped. The drug can be reinitiated at the starting dose if the patient returns to grade 1 toxicity or baseline (Pharmacyclics, Inc., 2015). However, if the toxicity reoccurs, the patient’s daily dose should be dose-reduced by one capsule (140 mg per day) (Pharmacyclics, Inc., 2015). The drug can be dose-reduced twice, but if toxicities continue after two dose reductions, the drug should be discontinued (Pharmacyclics, Inc., 2015). A dose reduction will be required in 6%–14% of patients with MCL, CLL, and WM (Pharmacyclics, Inc., 2015). In addition, ibrutinib can cause fetal harm when administered to a pregnant woman (Pharmacyclics, Inc., 2015). Therefore, women should avoid becoming pregnant and breastfeeding while taking ibrutinib (Pharmacyclics, Inc., 2015).

Patient Quality of Life

Ibrutinib has the potential to greatly improve patient quality of life. In the University of Texas MD Anderson Cancer Center (2013) study, patients reported improvement in their overall health and quality of life (QOL) six months after starting ibrutinib and rituximab. The study used the European Organisation for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire–Core 30. This questionnaire, used to assess the QOL of patients with cancer, includes questions pertaining to activities of daily living, symptoms, and psychosocial health (EORTC Quality of Life Group, 1995). After six months of ibrutinib combination treatment, the percentage of patients with a high QOL rating rose from 46% to 89% (University of Texas MD Anderson Cancer Center, 2013).

Implications for Nursing

As with all oral chemotherapeutic agents, nurses have an important role in assessing drug adherence and educating patients about the purpose, proper storage, safe handling, and self-administration of ibrutinib (Wilkes, 2011). In addition, the nurse educating the patient about possible side effects, instructing him or her about which symptoms to report to the healthcare provider, and managing toxicities all have been shown to increase adherence to the oral targeted therapy (Schneider, Adams, & Gosselin, 2014; Wujcik, 2011). An FDA-approved patient information web page about ibrutinib that is available on the Pharmacyclics, Inc., website (www.imbruvica.com/issi) can assist with teaching.

Oncology nurses play a distinct role in side-effect management and minimization of associated complications. For example, if a patient develops diarrhea with ibrutinib, the nurse can review laboratory studies for electrolyte depletion, assess for dehydration, educate the patient about the need for increased fluid intake, and advocate for an antidiarrheal agent to prevent complications secondary to diarrhea. Before starting ibrutinib, nurses should instruct women of childbearing age to obtain a pregnancy test and discuss the importance of contraception to prevent pregnancy.

Because of metabolism by CYP3A, patients should be instructed to avoid taking over-the-counter medications until they are reviewed by their healthcare provider; patients should also avoid drug interactions with CYP3A inhibitors and inducers (e.g., St. John’s wort, grapefruit juice) (Wilkes, 2011) (see Figure 4). Chronic use of ibrutinib with strong CYP3A inhibitors is discouraged (Pharmacyclics, Inc., 2015). If a patient requires short-term use (seven or fewer days) of a strong CYP3A inhibitor, ibrutinib can be interrupted during that time period (Pharmacyclics, Inc., 2015). If a patient requires a moderate CYP3A inhibitor, ibrutinib can be dose-reduced to 140 mg daily during the concomitant therapy (Pharmacyclics, Inc., 2015). If a patient requires surgery, the provider should consider holding ibrutinib for three to seven days before and after surgery to diminish the risk of bleeding (Pharmacyclics, Inc., 2015). The patient will also need to be followed on a regular basis for follow-up in clinic and scheduled laboratory testing, including monthly complete blood counts (Neuss et al., 2013; Pharmacyclics, Inc., 2015).

In addition, as ibrutinib exits the study realm and enters the market realm, medication cost will need to be taken into account. Ibrutinib is $91 per capsule, so nurses will need to be familiar with the medication assistance programs available to patients (Pollack, 2013).

Conclusion

Ibrutinib is the only FDA-approved inhibitor specific to Bruton’s tyrosine kinase. This drug blocks the overstimulation of the B cells found in certain hematologic cancers and has the potential to lead to durable remissions. Ibrutinib is FDA approved for patients with MCL and CLL who have received at least one prior therapy and as initial therapy for patients with WM and

Implications for Practice

- Collect and record positive clinical findings prior to initiating ibrutinib to help direct the clinic’s potential dose reductions.
- Collaborate with your clinic’s patient resource managers to ensure that patients have access to ibrutinib.
- Assess for oral agent adherence and barriers at every patient visit, and educate patients about hand washing, avoiding sick contacts, and reporting fevers and shaking chills.
CLL with 17p deletion, but it is being investigated as initial therapy in MCL and CLL and as a treatment option for other blood cancers. The drug has been shown to induce significant remissions, increase QOL, and is generally well tolerated, with most of the adverse reactions being grade 1–2. Nurses are vital in educating patients about ibrutinib, assessing for adherence and adverse reactions, and managing side effects with tailored nursing interventions.

References


