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This knowledge-based activity is targeted for all pharmacists and is acceptable for .5 hour (.05 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

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Objectives

After completion of this program, the reader should be able to:

1. Identify current first-line treatments for mantle cell lymphoma (MCL) when considering functional status of the patient and stage of the cancer.
2. Explain the importance of MCL cell migration, as seen in ex vivo study of ibrutinib.
3. Describe the pharmacology of ibrutinib.
4. Discuss the benefits of ibrutinib treatment in relapsed/refractory MCL observed in phase II development.
5. State key patient counseling points, including side effects and dosing of ibrutinib for MCL.

Abstract

Mantle cell lymphoma (MCL) is a rare and moderately aggressive form of non-Hodgkin's lymphoma (NHL) that predominantly presents at an advanced stage in older males. Patients often present with multiple involvement in the lymph nodes, blood, spleen, bone marrow and gastrointestinal tract (GIT). Some patients may be asymptomatic in early stages or present with an incurable, indolent (slow progressing) form, while other patients display rapid growth of more aggressive lymphomas. Overall survival for patients diagnosed with MCL is four to five years and treatment should be initiated in those who are symptomatic. Mantle cell lymphoma responds well to first-line treatment, but recurrent relapses are common, and no regimen has been proven superior for relapsed or refractory MCL. The U.S. Food and Drug Administration (FDA) has recently approved ibrutinib (Imbruvica™) as breakthrough MCL therapy. Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor that interferes with malignant B-cell proliferation and survival. In a recent clinical study, ibrutinib proved to be a highly active monotherapy with a favorable toxicity profile in 111 patients with relapsed or refractory MCL. As an oral chemotherapy drug, ibrutinib has the potential to improve patient compliance. Additionally, specialty pharmacies dispensing ibrutinib will be able to play an important role in patient counseling and monitoring.

Introduction to Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a rare form of NHL with about 4,000 new cases each year in the United States.[1,2] Most patients with MCL present at the advanced stages, stage III and IV, with lymphadenopathy that is generalized and not bulky.[1] The lymphoma will likely affect multiple tissues and organs including lymph nodes, blood, spleen, and bone marrow, and lymphomatoid polyposis, which are lymphoid polyps in the gastrointestinal tract (GIT), may be present.[3] Clinically, a patient with MCL may present with enlarged lymph nodes, swollen abdomen, chest pain or pressure, or satiety after a small amount of food due to enlarged tonsils, liver or spleen. Presentation may also include dyspnea, fever, unexplained weight loss, nausea and vomiting, fatigue due to anemia or drenching night sweats.[2,4] MCL presents most commonly at a moderately aggressive stage in men in their fifth and sixth decades of life.[1]

If a patient presents with suspected MCL, a tumor biopsy is performed to confirm diagnosis.[1] An MCL biopsy lacks blastic cell involvement, but otherwise resembles other lymphomas. Cyclin D1 overexpression, elevated lactate dehydrogenase, and beta-2 microglobulin may assist in diagnosis of MCL.[5] Overexpression of cyclin D1, a promoter of cell cycle progression, is present in up to 90 percent of MCL cases, due to a (11;14) chromosomal translocation involving IgH and cyclin D1 loci.[3] Elevated levels of lactate dehydrogenase and beta-2 microglobulin are present in 25 to 50 percent of patients with MCL.[5,6] About 20 percent of MCL patients will progress to an incurable, indolent lymphoma, accompanied by the rapid growth of aggressive lymphomas.[1] This unique presentation of MCL contributes to a general life expectancy of four to five years past the diagnosis. Patients in this stage will often present similarly to chronic lymphocytic leukemia (CLL), having a lymphadenopathy that is slow to progress and a low tumor count.[7] If asymptomatic, the patient should be observed; however, in symptomatic patients who present with bulky lymphadenopathy or splenomegaly, constitutional symptoms, or present with cytopenia requiring transfusion, treatment is required.

Current Treatments

First-line treatments for MCL vary according to the physical status of the patient. Stem cell transplants are the first-line treatment for patients who are younger than 65 years and have good performance status, as they are more likely to tolerate this intensive treatment.[7] These patients receive high-dose chemotherapy (HDT), including Ara-C and rituximab, followed by an autologous stem cell transplantation (ASCT).[1] In eligible patients, this treatment is recommended once, and provides a longer time to treatment failure (TTF) and im-

proved overall survival (OS) as compared to protocols that do not utilize rituximab.

Many patients, however, present at late stages of MCL and/or may not be eligible for a transplant.[1] Radiation therapy is usually ineffective at late stages and, therefore, chemotherapy is the mainstay of treatment.[7] Generally, patients receive the R-CHOP regimen, which consists of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.[1] This therapy increases overall response rate (ORR), the percentage of patients whose cancer responds favorably to the treatment, and complete response (CR) in which all signs of cancer are eliminated due to treatment, but there is no improvement in OS.[1,8] While other treatment regimens are available, R-CHOP therapy has the best evidence.[1]

First-line treatments for MCL are often successful, but nearly all patients will relapse within two years.[1] The high relapse rate has directed research to identify novel therapies. While no regimen has yet been shown superior, many agents are currently undergoing clinical trials. Bortezomib is a proteosome inhibitor with an ORR of 33 percent.[21,7] Temsirolimus and other mammalian target of rapamycin (mTOR) inhibitors are also being studied and have an ORR of 22 percent. Lenalidomide is an immunomodulator with an ORR of 53 percent. Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor with an ORR of 68 percent, CR of 22 percent, and partial response (PR), a decrease in tumor size or cancer extent due to treatment, of 46 percent. Ibrutinib was recently FDA approved for the treatment of relapsed MCL and is the focus of this article.[9]

Ibrutinib Pharmacology and Pharmacokinetics

Ibrutinib was approved in November 2013, for treatment of MCL in patients who have been treated at least once previously.[9] Ibrutinib was also approved in February 2014, for chronic lymphocytic leukemia in patients who have received one prior therapy.[10] This paper will focus on the indication for MCL, which was approved via the accelerated approval program, as ibrutinib received breakthrough therapy designation.[9,11] Ibrutinib inhibits BTK, a terminal non-receptor tyrosine kinase, which promotes downstream activity of growth factors, B-cell antigens, chemokines and innate immune receptors.[12] Normally, BTK signaling promotes development, differentiation, and functioning of B-cells. By inhibiting BTK, ibrutinib inhibits proliferation of the lymphoma in MCL.

Ibrutinib inhibits kinase activity of BTK through covalent binding to the non-catalytic cys-481 residue of BTK, which is present in only 10 other kinases at this exact position.[13] Therefore, ibrutinib is a fairly selective inhibitor of BTK, being 1,000 times more selective for BTK of B-cells than CD69 of T-cells. Ibrutinib irreversibly inhibits BTK-driven gene expression. When compared with a known reversible inhibitor of BTK, ibrutinib inhibited gene up-regulation following a washout period while the reversible inhibitor did not. In vitro, one-hour exposure compared to continuous exposure to ibrutinib has the same inhibitory activity, demonstrating that one-time exposure is sufficient to inhibit BTK. Ibrutinib is relatively potent with an IC_{50} of 0.5 nM.

In vitro, ibrutinib appears to induce apoptosis of B-cells by two main mechanisms: inhibiting anti-apoptotic mechanisms and stimulating pro-apoptotic mechanisms. First, ibrutinib blocks anti-apoptotic pathways by decreasing ERK phosphorylation, decreasing NF-kB signaling, and decreasing expression of Akt, a serine threonine kinase that promotes cell cycle progression.[14-18] Secondly, ibrutinib stimulates pro-apoptotic mechanisms in B-cells by activating caspases.[14]

Additionally, ibrutinib decreases anti-IgM-induced signaling that stimulates B-cells by decreasing adhesion to VCAM, an adhesion molecule, and fibronectin, a glycoprotein involved in adhesion and migration.[17,19,20] Ibrutinib also decreases signaling induced by chemokines such as CXCL-12 and CXCL-13, that are secreted by stromal cells, and decreases production of cytokines such as interleukin-10.[15,17,21] By interfering with this signaling, ibrutinib inhibits the migration, adhesion, and proliferation of malignant B-cells.

The cellular mechanisms of ibrutinib that were delineated in vitro were substantiated in a study published by Chang and colleagues.[22] This study provided ex vivo insight to the mechanism of action of the anti-tumor effect of ibrutinib by examining the migration of MCL cells from the tumor into the peripheral blood and the characteristics of these malignant cells once in the periphery. Phenotyping, adhesion molecule assessments and migration assays were performed on blood samples collected from 22 patients participating in ibrutinib clinical trials. Following ibrutinib treatment, there was a statistically significant increase in the absolute lymphocyte count (ALC) in the peripheral blood, demonstrating the migration of malignant cells to the periphery, which contributes to the death of these cells. The lymphocytes tested, CD19 and CD5, had a decreased expression of CXCR4, CD38, and Ki57, all of which are surface molecules necessary for successful cell cycle progression. Ibrutinib suppressed the B-cell receptor (BCR)-stimulated cytokine and chemokine production from MCL cells and inhibited BCR-stimulated adhesion of MCL cells.

By inhibiting adhesion molecule expression, chemokine production and the downstream signaling of BTK, ibrutinib therapy forces malignant cells to migrate from their host tissue and enter the peripheral blood.[22] These micro events were further documented at the macro level as the lymph tissue mass clinically decreased. Ibrutinib decreased expression of CXCR4, a protein necessary for chemotaxis of malignant cells back to preferred tissues. The entrance and maintenance of malignant cells in the periphery is important because the MCL cells meet their demise in the peripheral blood. In the periphery, these cells do not have soluble factor exposure and other necessary components for proliferation and survival, and consequently, the malignant cells die and are cleared from the body. This study is important as it shows the mechanisms of anti-tumor action of ibrutinib and provides micro level insight of the positive macro level clinical results.

Pharmacokinetic studies on ibrutinib have also been conducted. Without food, the T_{max} of ibrutinib is approximately one to two hours, with an area under the curve (AUC) of 953 ng*h/mL at steady state.[23] In the body, the drug is highly protein bound, evidenced by a volume of distribution of 10,000 L at steady state. Ibrutinib is primarily metabolized by CYP3A4, with some metabolism via CYP2D6. The half-life of ibrutinib is four to six hours, and the majority of metabolites are excreted in feces.

Clinical Study

A phase II open-label, non-randomized, multicenter, monotherapy study by Wang and colleagues investigated the use of oral ibrutinib in 111 patients with relapsed or refractory MCL.[24] Other clinical trials are currently in progress, but the accelerated approval of ibrutinib was based on this trial.[9,25] The study enrolled subjects into two cohort groups based on their treatment history.[24] The first group included subjects who had previously received at least two, but not more than five, cycles of bortezomib therapy, while the second group included those who had received less than two complete cycles or no prior bortezomib therapy. Eligible patients were required to have a confirmed diagnosis of MCL. Diagnosis was based on either cyclin D1 overexpression or chromosomal translocation break points and an increase in lymph node diameter as a measure of staging the disease.

The primary end point was ORR, defined as the proportion of study subjects who achieved either complete or partial remission as their best overall response as defined by the modified Revised Response Criteria for Malignant Lymphoma.[24,26] According to the Response Criteria, complete remission was the disappearance of all evidence of disease, and partial remission was regression of measurable disease with no new sites.[27] Efficacy, safety, pharmacokinetics, and patient-reported outcomes regarding quality of life were all considered as secondary end points.[26] Subjects received 560 mg of oral ibrutinib daily in 28-day cycles until progression of the disease or an unacceptable level of adverse events was observed.[24] The timing of patient visits and assessments were based on the treatment cycles.[26]

The response rate for all patients was 68 percent, which included a partial response in 47 percent of subjects and a complete response in 21 percent.[24] The response rate did not vary with baseline characteristics or risk factors among the 111 subjects. Based on near equivalence of response between the two cohorts, the ORRs were reported together as a single percentage. The median time to a response was 1.9 months, the estimated median response duration was 17.5 months, and the estimated median progression-free survival was 13.9 months among all treated. The National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 were used to evaluate adverse events.[26] The criteria include a scale of grades corresponding with the severity of adverse events: grade 1 (mild), grade 2 (moderate), grade 3 (severe or medically significant but not immediately life threatening), grade 4 (life threatening), and grade 5 (death related to adverse events).[28] The majority of the adverse events observed with ibrutinib treatment were classified as grade 1 or grade 2, while grades 3, 4 and 5 were uncommon.[24] Over 20 percent of patients experienced mild side effects such as diarrhea, fatigue, nausea, peripheral edema, dyspnea, constipation, upper respiratory tract infection, vomiting and decreased appetite.

Peripheral blood lymphocytes were characterized post-ibrutinib treatment, and it was found that 34 percent of subjects had an increase in ALC that decreased and then tapered off by cycle 4 or cycle 5.[24] The increase included mostly CD19+CD5+CD3- lymphocytes with a pattern of light chain restriction that is consistent with MCL cells in peripheral blood. Investigators also found that ibrutinib caused a decrease in the secretion of macrophage inflammatory proteins 1-alpha (CCL3) and 1-beta (CCL4), macrophage-derived chemokine (CCL22) and TNF-alpha in most patients.

In a separate study, Chang and colleagues effectively demonstrated the ability of ibrutinib to inhibit the adhesion of MCL cells ex vivo, resulting in their mobilization to the peripheral blood.[22] Similar inhibitory effects were observed with in vitro ibrutinib treatment for CLL.[29] Wang and colleagues cited these findings as part of their reasoning for investigating the presence of MCL cells in the peripheral blood of study subjects. The ex vivo analysis, conducted by investigators within the in vivo study, also indicated that ibrutinib caused a transient increase in blood lymphocytes as well as a decrease in the secretion of certain inflammatory molecules.[24] Therefore, the phase II trial by Wang and colleagues demonstrates the benefit of ibrutinib treatment on a micro level in study subjects who also exhibited favorable macro level effects such as high response rate accompanied with a favorable level of toxicity. These effects indicate that ibrutinib has the potential to be a less intensive but more effective regimen than other treatments available for relapsed and refractory MCL.

Investigators in this phase II trial concluded that ibrutinib is a highly active, single agent with considerable duration of activity in relapsed and refractory MCL along with a favorable toxicity profile.[24] A major strength in the study design was the combination of two cohorts that allowed representation of a broad population of subjects with relapsed or refractory MCL within a moderately small sample size. Patients receiving ibrutinib demonstrated statistically and clinically significant data indicating the potential for ibrutinib as a new treatment for relapsed and refractory MCL.

Pharmacist Focus

Dosing for ibrutinib is 560 mg daily, which equates to four 140 mg capsules once daily. Dosing is based on evidence from the previously discussed clinical trial.[24] Ibrutinib may cause fetal harm in pregnant women and secretion into breast milk is unknown, as therapy should be carefully considered in the affected population.[23] Concurrent CYP3A inducers should be avoided, as they can decrease the plasma concentration of ibrutinib. Concurrent CYP3A4 inhibitors increase the risk of toxicity by increasing the AUC and C_{max} of ibrutinib, and ibrutinib should be discontinued if short-term therapy with a CYP3A4 inhibitor is utilized.

An advantage of ibrutinib is a more favorable adverse effect profile for certain patient populations in comparison to other agents for relapsed MCL including bortezomib, temsirolimus and lenalidomide. The more severe adverse effects of these drugs include profound myelosuppression, anemia, cardiac effects, metabolic acidosis and hepatotoxicity.[30-32] Serious adverse effects of ibrutinib include hemorrhage, infections, myelosuppression, renal toxicity and risk of secondary primary malignancies.[23] While ibrutinib still exhibits serious adverse effects, it is a preferred choice for patients who have cardiac or hepatic complications.

Being an oral chemotherapy agent, ibrutinib has many benefits acknowledged by health care providers. These benefits include patient convenience and comfort, more favorable risk-benefit profiles and the availability of specialty pharmacies to help with reimbursement challenges and financial assistance and are among the top reasons oncologists would be more likely to prescribe an oral chemotherapy agent over an intravenous (IV) agent.[33,34]

Another benefit of oral ibrutinib is the ability of patients to utilize outpatient services to obtain the medication. In regard to outpatient pharmacy services, specialty pharmacies, as previously mentioned, are expected to be often utilized. While their place in care is evolving, specialty pharmacies are essentially "niche" pharmacies.[35] As defined by Scott Kober, "[Specialty pharmacy] serve[s] a limited number of patients with a small number of high-cost, low-volume and high-maintenance conditions...."[35] These pharmacies offer special services such as high-quality counseling and assistance in navigating payment options for treatment.[34,36] As an oral chemotherapy agent, ibrutinib will likely be frequently dispensed at specialty pharmacies.

Conclusion

There is a need for effective chemotherapy agents that can be used to treat relapsed or refractory cases of MCL. Molecularly targeted drugs such as bortezomib, temsirolimus and lenalidomide have shown anti-lymphoma activity useful in treating difficult cases of MCL.[6] As a BTK inhibitor, ibrutinib also works on a molecular level to interfere in the malignant B-cell signaling cascade.[6,22] Clinical trials have shown impressive response rates for this newly introduced therapy.[24] Treatment with ibrutinib offers advantages including oral route of administration and a favorable toxicity profile compared to other more intensive treatments. Furthermore, some oncologists have indicated that they prefer oral chemotherapies over IV regimens, with one reason being the role that specialty pharmacies may then take in optimizing patient care through counseling and monitoring.[7,33,34] Although MCL is a moderately aggressive form of NHL, high response rates with ibrutinib therapy offers patients a chance for progression-free survival when first-line therapies have failed.

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Assessment Questions

1. KL is a 68 year old male with poor functional status who has recently been diagnosed with late stage MCL. He is about to start his first treatment. Which of the following is the most appropriate treatment regimen for him?
   A. External beam radiation therapy
   B. Ibrutinib x 28 day trial
   C. Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP)
   D. Stem cell transplantation
   E. More than one of the above

2. Which of the following CORRECTLY describes the importance of MCL cell migration?
   A. By inhibiting adhesion molecule expression, MCL cells are forced to enter peripheral blood.
   B. Ibrutinib decreases expression of CXCR4, which prevents malignant cells' return to their tissues.
   C. Once in the periphery, MCL cells do not have the necessary components for survival and die.
   D. Two of the above
   E. Three of the above

3. TR is a 57 year old female coming to your specialty pharmacy. She has arrived to pick up her new prescription for ibrutinib to treat her relapsed MCL. While excited that there are no needles involved with this drug, she is nervous about starting the new treatment and any adverse effects it might bring. What counseling points about the adverse effects do you offer her?
   A. "You may bleed more easily. Take care to avoid injury."
   B. "If you feel very tired or weak, have an upset stomach, have a fast heartbeat or are breathing fast, call your doctor. These may be signs of too much acid in your blood."
   C. "This drug makes you more likely to catch illnesses, such as the flu or a cold. Stay away from people who are sick."
   D. Two of the above
   E. Three of the above

4. Ibrutinib works by inhibiting which protein?
   A. Proteasome
   B. CD20
   C. Bruton's tyrosine kinase
   D. Epidermal growth factor receptor
   E. Cyclin D1

5. What is the dosing of ibrutinib for MCL?
   A. 560 mg daily
   B. 140 mg TID
   C. 560 mg BID
   D. 280 mg daily
   E. 280 mg BID

6. Which enzyme is primarily responsible for ibrutinib's metabolism?
   A. CYP2C19
   B. VKOR
   C. CYP2A9
   D. CYP3A4
   E. Ibrutinib is excreted unchanged in urine

7. Which of the following statements accurately describes the toxicity profile associated with ibrutinib:
   A. Ibrutinib is not associated with a high occurrence of severe side effects such as grade 4 hemorrhagic events.
   B. Patients taking ibrutinib most commonly experience grade 1 or 2 adverse events.
   C. Possible side effects of ibrutinib include diarrhea, fatigue, dyspnea, and decrease in appetite.
   D. Two of the above
   E. Three of the above

8. What were the major advantages associated with ibrutinib treatment in the main phase II clinical trial utilized for accelerated FDA approval?
   A. All participants achieved a complete response.
   B. Ibrutinib was found to be a highly active, single agent.
   C. Ibrutinib therapy had a considerable duration of action.
   D. Two of the above
   E. Three of the above

9. During clinical development, both ex vivo and in vivo research indicated that ibrutinib had the potential to be a less intensive but more effective regimen than other treatments currently available.
   A. True
   B. False

10. The protein target of ibrutinib normally has what function in a healthy body?
   A. Induces apoptosis of B-cells
   B. Stimulates chemokine release
   C. Promotes B-cell development
   D. Two of the above
   E. Three of the above

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Program Title: **Ibrutinib (Imbruvica™) for Treatment of Mantle Cell Lymphoma**
UAN: 0048-0000-14-173-H01-P CEUs: .05

All information must be printed CLEARLY to ensure accurate record keeping for attendance and the awarding of continuing education credit. Certificates will be distributed as a PDF document to a valid email address.

Name:

Address:

City: **State:** **Zip:**

Phone: **Email:**

Pharmacy License #: **State:** **ONU Alumni?** **Y** **N**

Program Content:	Strongly Disagree				Strongly Agree
The program objectives were clear.	1	2	3	4	5
The program met the stated goals and objectives:					
Identify current first-line treatments for mantle cell lymphoma (MCL) when considering functional status of the patient and stage of the cancer.	1	2	3	4	5
Explain the importance of MCL cell migration, as seen in ex vivo study of ibrutinib.	1	2	3	4	5
Describe the pharmacology of ibrutinib.	1	2	3	4	5
Discuss the benefits of ibrutinib treatment in relapsed/refractory MCL observed in phase II development.	1	2	3	4	5
State key patient counseling points, including side effects and dosing of ibrutinib for MCL.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. A B C D E
2. A B C D E
3. A B C D E
4. A B C D E
5. A B C D E
6. A B C D E
7. A B C D E
8. A B C D E
9. A B
10. A B C D E

Any questions/comments regarding this continuing education program can be directed to Lauren Hamman, Advanced Administrative Assistant for the Office of Continuing Education (email: l-hamman@onu.edu, phone 419-772-2280).

Ohio Northern University is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is eligible for credit until 05/07/2017.