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IBRUTINIB IN WM

by Jeffrey Matous, MD

Dr. Jeffrey V. Matous

The story of ibrutinib (Imbruvica) is perhaps one of the most exciting in the annals of Waldenstrom's macroglobulinemia (WM) and serves as a spectacular example of how scientific perseverance coupled with the skill of talented physician scientists can change the lives of patients in a very real way.

In order to understand the importance of ibrutinib in WM, it is helpful to review some basic biology of the disease.

WM is a type of B-cell non–Hodgkin lymphoma (NHL), one of dozens. One feature of lymphomas, and indeed cancer in general, is that the abnormal or cancerous cells do not follow the rules that normally govern the behavior of healthy cells. We know various ways in which B-cell lymphomas and therefore WM misbehave. The production and lifespan of healthy cells is carefully and beautifully orchestrated. The body maintains a perfect inventory of these B-cells, because they are produced and turned over in a tightly regulated fashion. In WM the cell that produces healthy B-cells and plasma cells (a very mature type of B-cell) undergoes one or several mutations (changes in the DNA inside the B-cell that were not present at birth but which were acquired by chance), and those mutated cells no longer follow the normal rules. They grow more than they ought to and fail to turnover or die when their time is due. The end result is that WM patients accumulate far too many cancerous cells (lymphoplasmacytic or LPL cells), which produce the typical signs and symptoms characteristic of WM.

We will focus on the over-production side of things since that is primarily how ibrutinib helps WM patients.

This abnormal behavior is largely influenced by a series of molecular steps, the end result of which is to grow and divide uncontrollably. Think of a row of dominoes. The first domino is outside the WM cell (a "receptor") but most of them are inside the cell ("intracellular signaling pathways") and connect all the way to the core or nucleus of the cell, where the chain of falling dominoes results in changes in the DNA – which make the cell cancerous. In WM and other B-cell lymphomas, there are a few critical paths of dominoes, and the problem is that the dominoes tip over *on their own, and just keep doing so*. The scientific term for this is "constitutively activated," that is "always turned on."

The reader may be asking what any of this has to do with ibrutinib. There is a critical protein, specifically an enzyme, inside B-cells called BTK (Bruton's tyrosine kinase) that is involved in the growth and development of normal B-cells. In several B-cell cancers, including WM, there is too much of it, and this is a big part of what fuels those dominoes to keep tipping over, causing the cancer cells to be overproduced. There is also an important molecule called the B-cell receptor (BCR) sitting on the outside or surface of the cell, and in these cancers it is always turned on when it shouldn't be. *BTK helps translate that message* (domino effect) to the DNA inside the nucleus. In other B-cell cancers such as chronic lymphocytic leukemia (CLL), it has long been recognized that inhibiting BTK can kill the cancer cell (apoptosis). Ibrutinib inhibits BTK, was tested in CLL and in another B-cell blood cancer called mantle cell lymphoma, shown to be effective, and subsequently approved by the US Food and Drug Administration for those cancers.

None of this went unnoticed by Dr. Steve Treon at Dana-Farber Cancer Institute in Boston. Dr. Treon and his group made the most important discovery to date in WM when they found a mutation in a gene called MYD88, which was present in virtually every individual with WM. It turns out that MYD88 is one of those critical proteins inside certain cells that helps those cells over-produce when mutated. MYD88 does this by associating with a lot of other proteins inside the cell, including BTK! Dr. Treon then postulated that perhaps inhibiting BTK (ibrutinib was out there being studied in other blood cancers) might help WM patients, and he designed a clinical trial to address that question.

Dr. Treon, along with collaborators at Stanford University and Memorial Sloan Kettering, treated WM patients who had experienced a relapse after having had at least one previous chemotherapy treatment with 420 mg daily of ibrutinib.

Beginning in May 2012, 63 patients were enrolled in this clinical trial. It is important to understand what kind of WM patient was treated in this study. All patients had previously been treated for WM. They could not be too ill or too frail and had to have reasonably healthy blood counts. They could not have been taking a blood thinner called warfarin. They could not have lymphoma in the central nervous system.

The results were impressive and published in the *New England Journal of Medicine* in 2015. By one month most patients were showing a benefit. Nine of out 10 patients

responded favorably to ibrutinib, and 7 out of 10 had a dramatic improvement. IgM levels plummeted in most patients, and those who were anemic generally had a noticeable improvement in their anemia and energy levels. Side effects were generally mild and the drug was well tolerated. The drug was continued so long as it was working and side effects were acceptable.

Dr. Treon and colleagues further showed that by determining the status of two critical mutations in their patients – MYD88 and CXCR4 – they could define those patients more likely to benefit from ibrutinib treatment. The patients who had a mutation in MYD88 but not CXCR4 did the best, followed by those who had mutations in both MYD88 and CXCR4. The latter group had a lower chance of a really good remission and it took longer to see the maximal benefit. This work led to FDA, Canadian, and European Commission approval of ibrutinib not only for those patients who had been previously treated and experienced a relapse, but also for patients who had never had treatments.

WM PATIENTS HAVE MANY QUESTIONS ABOUT IBRUTINIB

Because of the increasing clinical use of ibrutinib in WM and the fact that we are now gaining more experience with it, patients who are already on the drug or who are considering starting it have many questions. I have attempted to provide answers to some of the most common ones asked by patients in my practice, on IWMF-Talk, and at the recent IWMF Educational Forum.

General Questions about Taking Ibrutinib

What is the dose of ibrutinib?
The recommended dose is 3 capsules (140 mg each) daily taken all at once (total 420 mg). Ibrutinib can be taken with or without food with a glass of water at roughly the same time each day. Some patients prefer it earlier or later the day depending on side effects such as nausea or dizziness, and it is OK to switch – just try to be consistent.

Is 420 mg really important? Don't lesser doses of ibrutinib work just as well and have fewer side effects?
We really believe that in order for the drug to most efficiently work against BTK, 420 mg is strongly recommended. The scientific reason for this relates to a concept called "BTK occupancy," which basically means that you want to use enough of the drug to effectively block the BTK sites in the B-cells. Some patients require reductions of the dose due to side effects but we try and give the full 420 mg whenever possible. In a recent study called iNNOVATE, few patients required modification of the dose, and the most common reasons for doing so related to gastrointestinal side effects.

Is ibrutinib the best initial treatment or mostly used for relapsed WM?
Almost all of the data supporting the use of ibrutinib come from studying it in patients with relapsed WM. That is, they have had prior chemotherapy for WM. That is generally how I use it. Outside of a clinical trial, I will consider it as initial

treatment for older, frailer WM patients who, following my assessment, appear to be able to tolerate the drug.

Once I start ibrutinib do I have to take it forever?
Right now we believe that as long as the drug is working and tolerated it ought to be continued indefinitely. Ibrutinib works a little bit like a light switch – when the drug is stopped all the lights are turned back on, and we have seen patients who stop the drug experience fairly rapid rises in their IgM levels.

Is ibrutinib ever combined with other chemotherapy treatments?
It was approved by the regulatory agencies to be used as a single agent, all by itself. Clinical trials are addressing combination usage. One large study is testing ibrutinib in combination with rituximab. We will see more combinations being studied in the future.

Do I need to inform my doctor if I am taking herbal or alternative treatments when I am also on ibrutinib?
Absolutely! Many supplements (such as ginkgo biloba) can lessen the benefits of ibrutinib, and some (such as fish oil) can increase the risk of side effects.

I have heard that I have to know my MYD88 and CXCR4 mutational status before I can start ibrutinib? Is that really true?
This is a point of debate among WM specialists. We know that WM patients who have mutated MYD88 and unmutated CXCR4 respond best to the drug, but to be honest, I try the drug to see if it works. Other WM docs like to test for those mutations first.

Important Information to Know When You Are Taking Ibrutinib

Do I need to temporarily stop ibrutinib when I undergo surgery or other procedures?
Yes. For minor procedures withhold the drug for 3 days before and 3 days after the procedure. For major surgery we make it 7 days before and 7 days after. These are general recommendations, and other physicians make have slightly different ones.

Are there any foods which should be avoided when I am on ibrutinib?
We recommend avoiding grapefruit, star fruit, and Seville oranges at all times while you are on ibrutinib. They make the ibrutinib too strong and could significantly increase side effects. St. John's wort theoretically could lessen the effectiveness of ibrutinib.

I have arthritic pain and take NSAIDs (such as ibuprofen). Is it safe to take NSAIDs with ibrutinib?
This is a tough one. These drugs can act as blood thinners and must be used with caution and only with the approval of your physician.

Side Effects of Ibrutinib

What are the most common side effects of ibrutinib?

1. Rash or cracked brittle nails
2. Diarrhea (~40%, rarely severe), decreased appetite, heartburn
3. Bleeding or bruising
4. Atrial fibrillation (not so common, ~5%)
5. Lowering of normal blood counts
6. Aches and pains
7. Dizziness (~10%)
8. Tiredness

Tell me more about bruising and bleeding caused by ibrutinib. If my doctor wants me to take blood thinners (for a blood clot history) are there any I can take when I am also on ibrutinib?

Ibrutinib has blood-thinning properties resembling aspirin. Some patients experience a lot of bruising on ibrutinib whereas others have absolutely none. In the most important clinical trials with ibrutinib, patients taking warfarin were not allowed to participate in the study. I tend to avoid warfarin and if need be use other types of blood thinners for patients who require them. I do not start ibrutinib in patients with a history of blood clots until I know that they are stable and can tolerate their blood thinner.

Can ibrutinib cause or worsen high blood pressure?

I think it does and can even cause it in patients who have been on the drug a long time. It can be managed in many ways, including the normally used blood pressure medications.

Can ibrutinib cause atrial fibrillation? If I had atrial fibrillation in the past, is it safe for me to take ibrutinib?

It can cause atrial fibrillation but the risk is low, about 5%. Patients with a history of previous atrial fibrillation of course carry a higher risk of recurrence. Certain medications to combat atrial fibrillation can interact with ibrutinib, and vice-versa, and this must be kept in mind when selecting a treatment for the arrhythmia.

I have been taking ibrutinib for over a year and now have cracked and brittle nails and flaky skin. Could that be due to ibrutinib? Is there anything I can do about it?

Yes, it is the ibrutinib. Biotin may help the nails. Use alcohol-free moisturizers. Sometimes we will recommend a light steroid cream for particularly bothersome skin rashes. Keep the nails short.

Other Commonly Asked Questions

Does ibrutinib cause IgM flare?

No, at least not when used by itself.

Can ibrutinib be used in hemodialysis patients?
We do not know and I have not done so.

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Please keep in mind that everyone's WM is different and that the effectiveness of ibrutinib or any other treatment varies greatly among WM patients. There is no substitute for staying really well informed and communicating with your health care team.

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Dr. Jeffrey Matous is the Medical Director at the Colorado Blood Cancer Institute and Clinical Professor of Medicine at the University of Colorado. After graduating from Medical School in 1985 from the University of Washington, he completed an Internal Medicine residency and chief residency at the University of Colorado. Fellowship training in Hematology and Bone Marrow Transplantation followed at the University of Washington and the Fred Hutchinson Cancer Research Center. Since 1994 he has worked in private practice in Denver, focusing on the care of patients with blood cancers. He is an enthusiastic educator and a member of committees of both the American Society of Hematology and the American Society of Clinical Oncology. He co-chairs the Sarah Cannon Myeloma Committee and is a Board member of the Rocky Mountain Chapter of the Leukemia & Lymphoma Society (LLS), having been honored with the Chairman's citation for LLS volunteerism in 2012. Dr. Matous has been a past contributor to the Torch *and a presenter at two IWMF Educational Forums, including the most recent one in Providence where he spoke about treatments for relapsed/refractory WM and co-moderated a breakout session on ibrutinib.*

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