# Options for CLL Patients With Joint Pain

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**Beth:**
I'm on a clinical trial with ibrutinib (Imbruvica) plus rituximab (Rituxan) versus chemo. I'm in the ibrutinib wing. I've talked to a lot of other people here on ibrutinib who also have bone and joint pain. I wonder about inflammation and CLL, and why this is exacerbating my arthritis and joint pain. If you can, any of you clinicians can answer that.

**Andrew Schorr:**
Okay. Who wants to tackle that joint pain? Do you want to do it, Jeff?

**Dr. Sharman:**
I can probably get part of it, but I don't think we have all the answers to that question. Ibrutinib, when it was first being studied in animals, was being looked at as a potential therapy for rheumatoid arthritis. In certain inflammatory models of arthritis, the inflammation is decreased.

With all of these targeted drugs, the analogy I oftentimes think about is you take a balloon and you squeeze it in the middle, it comes out the sides. When we shut down a pathway, sometimes we don't know what those other areas are that are compensating for the inhibition of BTK. Now, BTK does have a role in osteoclasts, those cells that help form, work on bone remodeling.

There are, as Michael so carefully said, promiscuous effects as well. Things that perhaps we don't even know what it's doing. It is a common phenomena amongst patients on ibrutinib that joint pains are there. In my own practice, I can't say that I've found any silver bullet for overcoming that. I think that as CLL transitions from a chemotherapy towards a targeted therapy field, I think that sometimes the gravity of the disease might seem less to some patients. If I just take a pill, I'm fine. I worry that when people have these chronic, long-term side effects, doctors' knee jerk reactions to, "Hey this is bothering me," is take a break. Lower the dose. Why don't we just stop for now?

That's what I was speaking to earlier about the casual use of ibrutinib. If the alternative was chemotherapy and chemotherapy only, I think you would be more compelled to stay on ibrutinib despite the side effects. It is a significant advance, but it does have liabilities. I don't have a simple answer for joint pains. I'm curious if…

**Andrew Schorr:**
Anybody?

**Dr. Spurgeon:**
Other than stopping the drug or reducing the dose, no. I think this is one reason, though, when we talk about developing other BTK inhibitors, or this is one reason to do so. Because there are some emerging data to suggest, there are actually some trials that are designed for people that have intolerance or side effects from the ibrutinib to roll over to a different BTK inhibitor. The early signs of that show that maybe, again, all these side effects are not created equal. Just like someone may have a problem with one anti-inflammatory and tolerate another, that may be the case where we get into this with BTK inhibitors.

I don't understand the biology of it, quite frankly. I have patients with rheumatoid arthritis. You give them ibrutinib, and their rheumatoid arthritis goes away. Then, I have patients with osteoarthritis, like we all have, as you age and have use of your joints. It seems to be the patients that have an underlying history of osteoarthritis or arthritis that's not an issue that comes to the forefront. I suspect it's off-target effects. It may be some BTK, but, again, this is a promiscuous drug. Doesn't just inhibit BTK, it inhibits other things. The question is now, can we develop these inhibitors that are more targeted without those off-target effects and alleviate some of those side effects?

**Dr. Keating:**
I reduce the dose systematically. The symptoms get better. It raised the question in my mind, what are we doing wrong? I think when we start off on treatment, the patients have a lot of CLL, so they have a lot of BTK. If you take BTK, it goes into the plasma. It gets trapped by the BTK in the CLL cells. There's very little that's floating around free in the plasma. As time goes by, the amount of leukemia goes down. We've been able to demonstrate that there's free drug in the plasma. We did a study whether in the same patient if we gave three a day versus two a day versus one a day. How much blocking of the enzyme occurred? It was identical at all three doses. There was a free drug level that correlated with how many tablets, or how many capsules you were taking. There was a lot more free drug that could run around and become promiscuous by binding to these other things. So that I think the whole question of the dose has to be reevaluated. There was clearly activity in the early clinical trials of patients getting responses in their leukemia. The hundred-milligram range of treatment. Part of the reason that we wanted to do this is that we thought that if we could get down to one a day, it might actually be more accessible to people in socialized medicine who are not going to get access to ibrutinib, because socialized medical budget won't cover these drugs. We have to look at it as time goes by.