

## CHRONIC LYMPHOCYTIC LEUKEMIA

SANDRA E. KURTIN, RN, MS AOCN, ANP-C      Our first talk is a lecture entitled “Defining the New Treatment Paradigm for Patients with Chronic Lymphocytic Leukemia.” I think you’re in for a real treat. Mollie Moran, a friend and a colleague, and Dr. Jeffrey Jones were here a couple years ago, rock stars from Ohio State University Comprehensive Cancer Center. Welcome.

MOLLIE      We are going to talk, as Sandy said, about defining the treatment paradigm for patients with chronic lymphocytic leukemia. These are the learning objectives. We’ll talk about diagnosis, treatment, and follow-up in both the previously untreated and treated. These are our financial disclosures. Let’s jump in. Before we talk about new, we’ve got to talk about old, and since I’m old, I get to do the old stuff.

This is the first slide in almost every single CLL talk, paper, anything that’s ever written about CLL -- it’s the most common leukemia in the western hemisphere, about 15,000 cases per year. It’s a disease of older folks; median age is about 72. Men more than women for whatever reason; whites more than blacks more than Asians. About 4,400 deaths, so a lot of people live with the diagnosis of chronic lymphocytic leukemia. And you’ll see that a lot of people live longer than they used to with the diagnosis of chronic lymphocytic leukemia, and long survival makes CLL the most prevalent of the leukemias.

This from the American Cancer Society -- 60% of patients are living after 5 years with the diagnosis of CLL, and the 10-year survival rate has gone up over the last 2 years as well.

We talk about staging; this happens in all diseases, whether they're hematologic events, these are solid tumors. The more disease the higher the stage, the more disease the worse the prognosis, the shorter the expectancy of the life span. The higher the disease, the more the disease, the shorter the survival, both Binet and in Rai staging.

Prognosis is influenced by other factors, not just age and stage, as would with so many of the leukemias and lymphomas that we work with as well. Things like the serum markers, beta-2 microglobulin, the doubling time, how rapidly is the disease progressing? There are chromosomal abnormalities that predict who's going to do better, who's going to do worse. We said some people from diagnosis live beyond 10 years, never have to have treatment; others are diagnosed within a year and require some kind of treatment almost immediately. And so things like a deletion of 17p, deletion of 11q, these are chromosomal deletions, things like mutational status and immunoglobulin heavy chains.

The immunoglobulin heavy chain mutation happens when the B cells are maturing and they pass through the thymus, they get their instructions, their stamp. When they're mutated, that's a good thing. Mutated means you've been given your instructions to go on. Unmutated is a bad thing. It sounds counterintuitive because we think of a mutation as a bad thing, but when it comes to having mutational status, being mutated is a good status.

TP53 mutation -- it does not mean that there's a mutation in their toilet paper status, TP is a region. Things like CD38, ZAP70 -- age; the older you are counts against you in your prognosis. Again, gender -- men more than women.

And then health status -- general fitness and comorbidities affect the outcome and how folks are going to do with their disease.

When I said earlier, a slide ago, about mutational status, you don't have to be a statistician to look at my Kaplan-Meier curves. The steeper the curve, the more poorly the people are doing. Anybody can figure that out. The red line, these people are doing worse; the blue line, these people are doing better. Mutated versus unmutated in Binet staging -- it didn't matter, it's this mutational status, that affects how well folks are going to do.

Interface-sided genetics -- deletion 17p, 13q, 11q, all those things matter in prognosis as well. 17p is the deletion that has the most steep falloff curve, so those folks tend to do the worst; they don't respond well to single-agent therapies. They usually have to be treated with combination therapies. They usually progress at an earlier onset than folks who have either normal chromosomes or something like a 13q, which is considered a good prognosis indicator. If you have normal-sided genetics -- no problems when they do a FISH analysis of your chromosomes -- it just puts you in the middle of the road; it's not good or bad, which I always found interesting. Is that normal? No problems doesn't equate to anything better.

Before we run, we have to walk. We have to talk about what's old before we can talk about what's new. And so the current standards for treating -- we'll talk about a case study here. A 55-year-old gentleman presents for sinus infection, improves with oral antibiotics, but quickly recurs. We treat so much sinusitis in Columbus, Ohio, I don't know what the heck is going on. But I noticed

it when I came there 16 years ago; I had never seen so much sinusitis. And I think it's because everything just -- there's no mountains, right? Everything just blows off the prairie right into our noses and stops. We're carrying it all.

Infection recurs, the PCP checks the CBC, he's got a white count that's elevated, 22,000, with an ALC that's also elevated, 17,000, but he has normal platelets, normal hemoglobin. He gets sent off to hematology because of this lymphocytosis, and they do peripheral blood that shows, again, lymphocytosis. His ECOG performance is 0, he works full time, and that's important too. ECOG performance status -- the lower the ECOG performance status, the better folks do across the board with all cancers, all treatments, all therapies. The better off you are as a specimen, the better off you're going to do with treatment. We keep that in mind when we talk about prognosis.

Peripheral blood, phenotyping, monoclonal proteins, meaning they all came from the same one, so it's cancer. Positive for CD19, CD5, dim for CD20, which means there's not a lot of it on the surface, but it is present. And then also positive for CD23. He's got normal karyotype, and his FISH is positive for deletion 11q, and he's IGHV mutated. Good mutational status, 11q bad, higher-risk side of genetics. He has some small lymph nodes, a couple of centimeters, that you can find on physical exam, but otherwise he's doing well.

He is diagnosed with asymptomatic CLL, we watch him for 2 years. We call it "watch and wait," patients call it watch and -- exactly. I don't know how I would do if someone said, "You have cancer, come back in 6 months."

After 2 years he starts to develop progressive fatigue, he gets more tired, he starts to develop night sweats. We're talking soak the jammies, soak the sheets, soak the pillow. Not like I do; stick my leg out, stick my leg in, turn the pillow, stick my leg out. I call it "thermo regulation."

He's got some more lymph nodes, but no big spleen, no big liver. And we start to talk about, "What are we going to do with this guy for treatment, front line, previously untreated?" Why do we treat physicians with CLL? We don't treat them until they need it, until they're symptomatic from it and they require treatment. And what makes someone require treatment? Well, CLL symptoms; night sweats, fevers, infections, tumor burden. Are things getting bigger? Are lymph nodes getting bigger? Do you have a big spleen that's pushing your stomach out of the way and you can't get a full meal in? Bone marrow failure, thrombocytopenia, anemia, things like that that are progressing, and then immune dysfunction. Do you develop things like autoimmune hemolytic anemia or autoimmune thrombocytopenia? Things of that nature would push you toward the treatment as well.

Lymphocytosis alone is not a reason to treat a patient. You can have lymphocytosis in the couple of hundred thousands with a lot of lymphocytes. As long as the other numbers are good, you don't have end organ dysfunction, and you're feeling well, lymphocytosis can hang around for a long time. Dr. Jones and I follow a few patients who hang out in the hundred thousands, and we've been following them for 10 years, so it is not a predictor of how poorly or how well a patient is going to do with treatment.

We'll look at the CLL8 trial, which answered the question of FC or FCR. Everybody was kicking it around every meeting and intuitively knew that adding rituximab to fludarabine and cyclophosphamide was a good idea, but we finally got the information to support that, so they randomized patients to receive fludarabine and cyclophosphamide, or fludarabine and cyclophosphamide and rituximab, and then long-term follow-up. Overall response rates were better when you added the R. Adding the rituximab made a difference in how long people survived. CRs were better, PRs were a little bit less, and then stable disease. Stable disease is stable disease and sometimes that's all you're going to get out of a treatment.

But median progression-free survival, meaning the time that you go on to require another therapy -- you're kind of just cruising along, not requiring any therapy; you may have lymph nodes, you may have counts that are a little off, but you don't actually require therapy -- median survival was definitely improved in the folks who got rituximab added to the regimen.

The other thing that they looked at where they went back and pulled the data out was creatinine clearance that was better, if you have a good creatinine clearance, and that affected the outcome of how folks did. Progression-free survival was the primary endpoint, overall survival, response, and safety. Divided and found out that this was meaningful if you had a better creatinine clearance.

The other thing that came out of this information was the comorbidity factors. If you have more than two comorbidities in addition to the CLL, that affects your prognosis poorly. Those folks tend to do a little bit worse than folks

who have less than two comorbidities. And they looked at the normal -- just remember, we said these folks are in their 70s and these are normal older people problems -- hypertension, hyperlipidemia, a prior malignancy, diabetes, respiratory, COPD. It's the typical patient that we see with CLL. So comorbidities make a difference in how you're doing to do.

Let's look at the next drug combination that we came across treating folks for CLL was bendamustine plus rituximab, or fludarabine and cyclophosphamide; so, FCR versus BR. And everybody kind of jumped on the BR bandwagon quite early because it was 2 days a week, there seemed to be less side effects, and so what did that translate into overall survival and response rates? Let's talk about that.

The complete remission rates were better in the FCR arm, ever so slightly. But overall response -- all the folks that responded to the therapy, identical, either group, whether it was FCR or BR, 2 days of therapy, no possibility of hair loss, folks seemed to tolerate it well. The median survival, median for progression-free survival, was not reached in the FCR arm for younger patients, but in older patients not reached for the BR arm. A little swap there. Older patients may have a little bit less toxicity.

And then when you did break down the toxicity it was much less in the BR arm, significantly, hematologic toxicities and neutropenia, things like that. Treatment-related mortality slightly improved well. FCR more efficient than BR in front-line therapy of CLL patients with more CRs, but the progression-free survival was lost on the older patients. The progression-free survival was better

in the BR arm, but there's more toxicity with FCR compared to BR. So looking at the age of the patient, the condition of the patient, is it easier for them to get to you for 2 days? Is it okay for them to get to you for how many ever -- 3 or 5 days, whatever the FCR is going to be? And taking these into consideration, front-line FCR or BR?

We'll talk about some of the newer CD20 antibodies here. This is a graphic representation of squiggly lines, circled lines, and dotted lines. And that means it shows you where the receptors are for the B cell, for the CD20. We have two new antibodies, monoclonal antibodies, that were approved in the past maybe 3 or 4 years for the treatment of CLL and they're rituximab, which is one that's been a long time, but obinutuzumab and ofatumumab target a little bit different areas on the CD 20, and then that's what makes them a little different. They may have a better affinity, they may be a little better binding, there's some class II upregulation in the recognition and that changes the way the cells are attacked. There's a little more technical to it, but they actually all cling on a little bit differently.

This is a randomized study, CLL trial 11, which was obinutuzumab, one of the new antibodies, with chlorambucil versus chlorambucil and rituximab. Chlorambucil is still a reasonable front-line therapy for patients with CLL. Older patients certainly tolerate it. It's got some toxicities, it's got some hematologic toxicities, but still a very well-tolerated therapy. A lot of these studies were done in Europe, these very large phase III head-to-head front-line therapies, where they still use a lot of chlorambucil and they accrue patients very quickly so that

we get some data quickly. It looked at chlorambucil by itself, chlorambucil with obinutuzumab, and chlorambucil with rituximab, and it showed that if you add an antibody, those folks do better. If you add the obinutuzumab versus the rituximab, the overall survivors were a little bit better. That brought that into the front line.

And this is survival -- again, Kaplan-Meier curves, don't have to be a genius. The upper curve is progression-free survival; the lower curve is overall survival. They even out in the long run, but with a little bit better on the obinutuzumab. But the progression-free survival was better certainly when you added the obinutuzumab.

This is the part that you need to memorize and it will be tested in your quiz. If you're a smarty, it'll have this picture and you have to put all those letters in. I'll give you a second to write it down.

So what this crazy mélange of pictures does, it says that it's not just one thing that makes CLL happen, it's a whole bunch of different pathways. Switches get flipped, proteins get incorporated, and trying to figure out which of these pathways is most important to knock off a cell, induce apoptosis, stop proliferation, depending on where you hit in the chain how much of that's going to happen. And that's where a lot of these new therapies work, these B-cell pathway inhibitors, or these small molecules.

The first one we'll talk about is the RESONATE trial, which is one of the more common drugs that we see now used in the treatment of CLL. A lot of patients, 269 patients. CLL over 65, comorbidity, they weren't going to tolerate

chemotherapy or they weren't going to tolerate FCR. They got randomized ibrutinib once a day or chlorambucil for whatever, up to 12 cycles. And then they could stay on ibrutinib if they continued to respond. If they stopped responding to chlorambucil, they could cross over at the end. Progression-free survival, clearly better with the ibrutinib. The downward stepping of the upper curve, certainly less as opposed to the chlorambucil by itself. An 84% reduction in the risk of progression or death with ibrutinib. Folks are living longer on the ibrutinib.

This is a subgroup analysis that you cannot read. I can't either and it's big up here. It talks about how the patients were divided -- the demographics -- and it was pretty even on either side, so the lines don't stick out huge on either side is what that says. They were evenly distributed.

Again, this looks at overall survival. This is the same recap. There were only three deaths on ibrutinib as opposed to 17 on chlorambucil and deaths occurring from overwhelming infections, other things that go along with having CLL and a bit of aging. The most common adverse events of any kind; diarrhea. But it's usually not debilitating diarrhea, it's usually just bubble guts where you got blub, blub, blub, blub, blub, and you can control it with some Imodium. If it goes beyond that, then it certainly needs to be evaluated, but it's usually early on in the onset. And it has to do with a lot of these oral inhibitors as the mucosal membranes are being affected by the oral inhibitors and especially the kinase inhibitors.

There's some fatigue; don't forget, these folks still have cancer. That's the hardest thing for our patients to get over. "I thought I would feel better

immediately.” Most of them do, but you’re still treating CLL and you’re still treating them with therapy, so sometimes it may take a little while to catch up. Sometimes a cough nonproductive, peripheral edema, neutropenia, some GI distress, like with nausea and vomiting. If you change when they take it, change how they take it, maybe with some food, a little bit later in the day before they go to bed, you can usually skirt around all these. There’s also an issue of rash with ibrutinib and that can be anything from just a red rash that doesn’t bother to big, purple nodules, like erythema nodosum, that need to be treated with either a dose reduction, a break from the drug, or steroids. We often treat through with steroids. Neutropenia happened a bit more in the chlorambucil arm. Like I said, the diarrhea was a bit more in the ibrutinib arm, but overall a very well-tolerated drug.

These are the NCCN therapy recommendations for front-line therapy. We’re kind of jumping a little ahead here. If you don’t have a deletion 17p and you’re under 70 years old, they recommend chemotherapy immunotherapy, FCR, FR, bendamustine, rituximab, PCR, pentostatin and rituximab, obinutuzumab, chlorambucil. If you’re over 70, the list isn’t too terribly different; obinutuzumab ibrutinib falls in there, the oral therapies. Still bendamustine, chlorambucil, rituximab as a single agent. It doesn’t have much great play. But if you’re a deletion 17p, they do recommend ibrutinib as front-line therapy. FCR, FR, bendamustine, rituximab, alemtuzumab. Do people give alemtuzumab anymore? Not so much in CLL, in some of the other T-cell strange things.

He gets started on FCR, you plan for six cycles. He doesn't really have any treatment, he has a bone marrow biopsy after six, he has a complete response, and 3 years after therapy, he has no evidence of recurrence. What I will say about this is that if he has 6 months of therapy, he's done with front-line FCR, front-line BR. If you go on to therapy with ibrutinib or an oral inhibitor, you're in it for the long haul. You're on that therapy full time until it stops working. We don't know what the endpoint, what the stopping point is with that. Whereas, BR, FCR, they're finite therapies. And that may fit better into some folks' lifestyle. Six and done.

What if instead he goes on ibrutinib for front-line therapy and continues on it after a month, he's approved for nondeletion, he goes on a clinical trial, then he gets approved for non-17p, which is now approved for a front-line therapy, his nodes go down, lymphocytosis increase in the first few weeks, common side effect. With ibrutinib, he normalizes his peripheral counts and then continues on the oral ibrutinib for 3 years. That's the difference. Oral therapy, he has not much of a chance to get CR from ibrutinib, BR, FCR. FCR, certainly we see CRs. And 6 months of therapy versus now 3 years later he's still on oral therapy. That may make a difference.

Then if you've got 5 to 7 years of CR out of a 6-month therapy, who knows what's going to be available in 5 years down the road. Or we're hoping. That's the old stuff, and now Dr. Jones.

DR. JONES We're going to talk about relapse CLL, and that's really where a lot of the changes come over the last 5 years, in particular in the

management of CLL, and it's really led the way across lymphoid malignancies. You'll hear other people speaking about lymphoma and a lot of the advances with some of the small molecules targeting important pathways that Mollie highlighted and which you have all taken mental notes, are really started in CLL and we'll talk about some of those.

This was a pretty typical case, not a clinical trial patient, but the kind of patient that you normally see in clinic. An 82-year-old man, he's an avid golfer, takes care of his wife, who has progressing dementia, and he's had CLL for a long time that has finally become a problem for him. He's got other medical problems though. He's got atrial fibrillation and he requires anticoagulation for that. He's got type 2 diabetes, he uses insulin. And probably the thing he's most troubled by is restless leg syndrome since it disrupts his sleep. But now he's developing progressive dyspnea because he's having trouble on the golf course. And when he is assessed, he's got progressive mediastinal lymphadenopathy and bilateral pleural effusions, leading his physician to begin treatment with very standard front-line chemotherapy like Mollie described -- bendamustine and rituximab, which would be a common choice in community practice for older patients before obinutuzumab and chlorambucil was approved, or mostly recently ibrutinib.

He runs into problems with slowly recovering counts, his doc switches to low intensity chemotherapy with rituximab CVP, but his effusions persist and he comes to see us. We were worried that perhaps 15 years into his diagnosis he had progressed his Richter's transformation, so always if there's a question, if the

behavior of the disease is unclear, always appropriate to biopsy again. And then the most important thing here, he underwent a repeat of cytogenetic studies that showed that his disease had evolved to include a deletion of chromosome 17p.

If you take nothing away from today's lecture, always before making an important treatment decision with a patient with CLL, repeat cytogenetics. If the patient's disease is not behaving as expected, reassess, re-biopsy, repeat cytogenetics. Those are the things that are very important in making the best decision for your patient.

If we looked historically, why are these advances in CLL so tremendous? That's because when I started in practice 10 years ago, I was borrowing letters from Mollie Moran to appeal clinical trial participation, and these are the kinds of statistics that we included. We said that patients that had fludarabine-refractory disease with CLL had a median life expectancy of only about a year. Their response rates were markedly attenuated over patients who received chemo or chemoimmunotherapy in the front line, and many of them had problems with persistent cytopenias and a significant risk for infection, many times fatal -- disaster. And all of these patients, just like Mollie highlighted, older, comorbid medical illnesses, that made this situation even more challenging. Many of them, if they got into this position didn't really have many options for treatment.

The initial phase II study of ibrutinib that we won't talk too much about really showed something different. Mollie showed you a lot of survival curves, these are survival lines. If you look at patients with standard-risk CLL, intermediate-risk CLL, without the presence of high-risk cytogenetic features --

that's that green curve there on the left -- those patients tended not to relapse on ibrutinib, even going out to 2 years of treatment -- remarkable.

And then if you looked even at the patients with deletion 17p CLL, their progress on ibrutinib was twice as good as anything that had been reported for deletion 17p patients under treatment even in the front line. And for that reason, ibrutinib was not only approved for relapse CLL on the basis of this study, but also for deletion 17p CLL in the front line -- very remarkable outcome.

But in oncology we're always interested for randomized phase III data to demonstrate whether or not those initial findings in phase I and II studies are truly important. And right around the time I started practice, ofatumumab, an anti-CD20 monoclonal antibody, fully humanized, was approved for a double refractory. That is, patients who had failed alemtuzumab and fludarabine, relapsed and refractory CLL on the basis of a 50% overall response rate and a median progression-free survival of 6 months. That was an advance. People were excited.

But here, ibrutinib was achieving response rates of around 90%, and if you compare the experience, ibrutinib there on the top line to single-agent ofatumumab, marked improvements not only in progression-free survival, but also overall survival. And on this basis, the drug received unrestricted approval for relapse and refractory disease.

How well do patients do? Mollie's already talked about the diarrhea issue that's usually self-limited in mild, early on in treatment, but a lot of the problems that plague CLL patients who are on treatment, problems like neutropenia,

thrombocytopenia, infections, are far less common among patients taking ibrutinib, but still problems. And they also tend to decrease as patients become more mature on therapy and recover a lot of their bone marrow function.

But there are a couple of important side effects to remember. The first is that atrial fibrillation of any grade has been reported in up to about 10% of patients in clinical trials, and reports from the community are suggesting -- and you'll start seeing these in journals, since I've reviewed a couple of these papers in recent months -- the rates may be even higher: 15, 16, even 17%. Bleeding-related adverse events -- there are antiplatelet effects of ibrutinib. These are off-target kinase effects in part, and they do lead to an aspirin type or a Plavix type bleeding phenotype, and that can increase the risk for bleeding in patients who are otherwise at high risk because of inherited problems with their bleeding or because they're taking therapeutic anticoagulation, warfarin in particular. We'll talk a little bit more about that at the end.

What about other targets of B-cell receptor signaling? They didn't talk about idelalisib and benralizumab since it's only approved in relapsed disease. On the results of this, a randomized comparison of rituximab, which would often be given to older patients for relapse disease, compared to the comparison of the oral agent idelalisib, a target of the PI3-kinase delta isoform. What this study showed, like the comparison of ibrutinib to ofatumumab, it showed that by giving idelalisib along with rituximab, you substantially improved not only progression-free but also overall survival.

Now, like ibrutinib, that benefit does not come without toxicity and there are important toxicities of idelalisib, like there are with ibrutinib. And they're not the typical toxicities that we experience with chemotherapy, it's things like diarrhea, it's things like transaminitis, and in some cases, problems with blood cell counts. We'll come back to some of the more specific toxicities and how we'll manage those to close with some very practical information. But to highlight here that idelalisib and rituximab was subject to an important safety alert earlier this year in some front-line studies of patients largely receiving idelalisib in combination with bendamustine and rituximab, there was an unexpectedly high risk of infection, including opportunistic infections.

Now we manage those kinds of problems when taking care of hematologic malignancy all the time, so not a deal breaker with this drug, but it does require additional monitoring. So patients should receive prophylaxis for opportunistic infections with Bactrim and antiviral agents, just like you would say fludarabine and in some cases bendamustine. It's also important to monitor patients for neutropenia during the initial phases of treatment and remind them that fevers require attention, just as they would with chemotherapy, until the patient's neutrophil count recovers. Neutropenic sepsis was an important cause of death in some of those patients.

The most recently approved targeted therapy in CLL is venetoclax. Venetoclax, unlike the B-cell receptor signaling drugs that disconnect the accelerator from the engine of the CLL cell, venetoclax restores the brakes. Because that's what cancer cells do, right? They careen down the hill, the gas is

pressed, and the brakes have failed. Venetoclax helps restore the brakes, so it helps restore apoptosis.

The phase I study, which includes a substantial number of high-risk patients, was published quite recently in the *New England Journal of Medicine*. And in that study, just like with the targeted therapies for B-cell receptor signaling, the overall response rate, even in high risk, heavily pretreated patients, was about 80%. In addition, there were a substantial number of patients who achieved a complete remission, which is decidedly uncommon with single-agent kinase inhibitor agents.

That led to this study, also recently published, this one in *Lancet Oncology*, the final publication, very recently. This study was targeting the most high-risk patients. That is, patients who have chromosomal deletions of 17p relapsed after previous therapy. There were a smattering of patients in this study who had even received prior therapy with both ibrutinib and idelalisib.

What did this study show? Before we talk about the results, let's remind you that there is a risk with venetoclax of hyperacute tumor lysis. Many of you who've taken care of leukemia patients know about tumor lysis. You know that that can lead to rapid changes in electrolytes, particularly phosphorus and potassium, as well as uric acid, leading to renal failure and all of the attendant consequences of electrolyte disturbance.

This can happen very fast with venetoclax, and as a result, the dose must be carefully titrated in an inpatient manner starting with 20 mg a day during the first week, and then escalated over the subsequent 5 weeks to the final dose of

400 mg daily. At each dose escalation, this must require laboratory monitoring. And whether that monitoring can be safely performed on an outpatient basis or requires hospitalization is based on disease bulk. The prescribing information, as well as information from the manufacturer, very clearly delineates the kind of assessment that should be performed and the basis for making that judgment, and you should review that carefully before prescribing venetoclax.

How well did it work in this high-risk group of patients? Very reassuring that the results, like the advanced trials in ibrutinib, confirmed the initial response rates of 80%+ -- fantastic, although the complete response rate was a bit attenuated. These were very high-risk patients, and that's not completely unexpected. We're always interested to know how long the good news lasts, and so far it seems pretty good.

For a group of patients, very high risk, added 18 months. The majority of patients are still stable and in remission, and those estimates of the 12 months for progression-free and overall survival compare favorably with the kinase inhibitors, taking it from a different side altogether of the molecular equation.

Adverse events that are important for you to consider with venetoclax in addition to tumor lysis, as the drug is introduced, are neutropenia, and this is neutropenia that is very responsive to growth factor administration. Unlike chemo where sometimes you might have to give a week's worth of G-CSF or a shot of pegfilgrastim to get the neutrophil count to come back up, sometimes patients with venetoclax-associated neutropenia can get a single shot of G-CSF or maybe twice a week and see their neutrophil counts go from 300 to 2,000 -- quite

remarkable, suggesting that it's not so much a myelosuppression problem as it is a peripheral destruction decreased longevity of mature neutrophil problem. Other things -- some diarrhea sometimes occurs, although that is typically early in treatment and somewhat self-limited.

With this dose escalation, with careful monitoring of risk and prophylaxis, tumor lysis can be managed, but it is probably the single most important risk other than the neutropenia and monitoring for infection to consider when giving venetoclax.

The last of the new drugs we'll talk about before really talking about some practical management issues in managing patients taking these drugs is acalabrutinib. Acalabrutinib, as the name would suggest, is a second-generation Bruton's tyrosine kinase inhibitor very much like ibrutinib, but far more specifically targeting the BTK enzyme. As we've come to understand with the development of ibrutinib, many of the side effects that patients experience, the diarrhea, some of the rashes, may be related to off-target effects on EGFR. If you've given erlotinib, you know the drug -- an EGFR inhibitor, causes rashes and diarrhea. The thought was if we developed a more specific BTK inhibitor, you would have all of the good parts and less of the bad.

This study was a phase I/II study, a very complicated trial that started as a phase I study and then expanded to include a much larger group of patients with relapsed CLL, as well as some patients who had not tolerated ibrutinib and were previously BTK exposed. Before talking about the efficacy, let's look at the

difference in the toxicity profile. Some of the things that occur with ibrutinib continue to occur, things like diarrhea, but at a far lower rate.

The most important thing for you to consider is that significant bleeding events, problems with atrial fibrillation, and rashes -- some of the more niggling problems that patients taking ibrutinib experience, as well as some of the more clinically significant -- are really not reported among patients taking acalabrutinib, although headache is a far more common symptom.

It's very reassuring to know that even without those off-target kinase effects, which could have some benefits since those pathways are important in a lot of cells, the drug works very similarly to ibrutinib, hard to compare head-to-head. There's an ongoing trial comparing the two drugs that will be important for us all to follow, both in terms of efficacy and toxicity profile. But for now, it looks to be similarly efficacious but perhaps better tolerated. There are ongoing trials in the U.S. comparing head-to-head acalabrutinib and ibrutinib, as well as trials of acalabrutinib enrolling patients who were unable to tolerate ibrutinib because of side effects that they experienced that forced them to discontinue.

Totally different world in the NCCN recommendations in 2016, these continue to evolve. This is from earlier this year; it's in the process of being updated again. But the first thing to know is that for relapse CLL, the top-line recommendations across the board are for kinase inhibitors before other drugs. And now for patients with deletion of chromosome 17p, ibrutinib, idelalisib, and rituximab, and then venetoclax are all favored treatment options, and patients in that group should not receive chemotherapy. There are not too many places in

oncology where there's a wrong answer; that's a wrong answer. No chemo for relapse deletion 17p patients -- fuels the fire, doesn't do the patient any good, suppresses their immune system further, and they'll land in clinic with Mollie and me, which is not so bad.

So, what happened to our patient? He started idelalisib and rituximab. We were reluctant because he had a catheter in his side to drain the pleural effusions and was also on therapeutic anticoagulation long term to give him ibrutinib for concern about bleeding risk. So he started on idelalisib and rituximab and has remained on the drug. He's very memorable because he's one of the first patients to be treated in our new hospital that opened in December of 2014. He had diarrhea, one episode that started pretty soon after he began treatment, but it resolved. He had been put on metformin in addition to his insulin, and it was probably related to that.

But we did have this other patient, and this was a patient who was treated on a clinical study with idelalisib and rituximab; he was also 82. And he did beautifully until he developed a sinus infection -- as Mollie tells you it's pretty common -- and he was started on Augmentin by his primary care physician, developed diarrhea, which could have been related to Augmentin, and then when it didn't resolve off the Augmentin, he was treated with two serial courses of metronidazole for *Clostridium difficile* diarrhea. The only problem was both tests that he had for *C. diff* were negative. The problem that he had when he came to see us was a pretty severe kind of diarrhea that can occur in patients taking idelalisib and it's an inflammatory colitis, late occurring. Unlike many of the kinds

of diarrhea, you start a new pill, a patient gets diarrhea, you expect maybe diarrhea then, but this is a kind of diarrhea that can occur 6, 7, 8 months into treatment and is very different. In fact, histologically and biologically, it appears far more like inflammatory bowel disease, ulcerative colitis, or Crohn's disease.

That leads us to talk a little bit more about adverse events. Ibrutinib-related toxicities -- we've spoken about the two most important ones. First, diarrhea with ibrutinib is usually early and self-limited. Severe diarrhea should really lead you to think about other causes and in most patients, even if their bowel movements stay loose over time, it's not usually dysentery-style diarrhea and can occur in other clinical contexts. That should be evaluated for something else.

Bleeding risk is usually mild in patients with ibrutinib; it's bruising, it's maybe some mucosal bleeding. But in patients who require therapeutic anticoagulation for another issue, you must revisit the issue and the risk balance benefit of continuing ibrutinib versus considering another drug. It's possible to continue patients on ibrutinib -- we do all the time -- but those are lower-risk patients, and we do our best to avoid therapeutic anticoagulation, always avoid warfarin, and we consider other drugs like the novel oral anticoagulants.

Atrial fibrillation can be managed but requires a risk benefit discussion. It's always a question of what's the risk associated with the patient's disease or their next best therapeutic alternative.

We talked about that. We talked about diarrhea. Let's talk a little more specifically about the side effects of idelalisib. As I mentioned, there are two

types of diarrhea with idelalisib; there's one that's early and usually self-limited, and there's the second that's late emerging and usually requires a very different kind of management. For grade 1 diarrhea, particularly when it's occurring early in treatment, symptomatic measures after exclusion of infection is appropriate. For patients who have more severe diarrhea, grade 3 or 4 diarrhea, it's late occurring, and in the absence of specific signs of infection idelalisib should be withheld, the patients should be evaluated, consider colonoscopy. And in instances where an inflammatory, noninfectious colitis is identified, the patient should be treated with an ulcerative colitis algorithm with budesonide and even in some cases of severe diarrhea of a systemic steroids, either IV or oral.

Some patients have been restarted at lower doses, although I think with the availability of other therapeutic alternatives, diarrhea of that severity is usually treatment limiting.

Transaminitis with idelalisib occurs early and can often be managed by briefly withholding the drug. When the transaminases are in the 5 to 20 times the upper limits of normal range, with careful reintroduction of the drug, usually at a lower dose, 100 versus 150 twice a day, when the transaminases have resolved. If a patient develops severe hepatitis from the drug, that is, elevations in excess of 20, think of something else.

Pneumonitis -- again, high clinical suspicion. This occurs less frequently, far less frequently, with ibrutinib, but has been reported. But inflammatory reactions in the lungs that cannot be explained as infection really require

interruption of the drug, consideration for steroids, and then probably a different choice of therapy.

Mollie mentioned obinutuzumab; it is different in terms of its biological behavior. It appears to be more potent than the other anti-CD20 antibodies, and it also has a very different profile for infusion reactions. Infusion reactions are most common with the first infusion, and they're usually a one and done. Many patients never experience another infusion reaction, but all patients should receive prophylaxis with antihistamines, Tylenol, as well as steroids, before the first reaction.

The first dose of obinutuzumab is broken up, it's given 100 and 900 mg to comprise the total 1 gm dose over 2 days and that has also limited the risk for infusion reactions. Neutropenia, thrombocytopenia, more common than with some of the other anti-CD20 antibodies, but haven't been associated with increased risk for infection, but does require some monitoring and should be considered when you're following these patients. If you haven't, usually check blood cell counts in patients who are coming in for subsequent weeks of rituximab, it's reasonable to do so with obinutuzumab.

Venetoclax -- we spoke about the toxicities here, an increased risk for neutropenia that requires monitoring, careful administration of G-CSF in cases where their neutrophil count is severely suppressed, but does not usually require interruption of therapy. Tumor lysis is the most significant, most life-threatening risk, and really requires careful adherence to the prescribing information after CT

evaluation for lymph node bulk and careful assessment of their tumor lysis risk, per the U.S. prescribing information.

Where are we now in CLL? I met Mollie Moran 10 years ago, and we've been in practice together since that time and our world has completely changed.

MOLLIE On many levels.

DR. JONES On many levels. Chemotherapy is a small part of our business now. We still see a lot of lymphoma patients, but our CLL patients are very rarely treated with chemotherapy and in fact, our whole program continues to grow as a place where patients come to avoid chemotherapy treatment for CLL. B-cell receptor signaling agents are the core of that. They are still probably the single most effective drugs in terms of the rates of response, the durability of response, and the favorable risk benefit balance, but they do require long-term therapy. And I tell patients all the time, "The absence of severe side effects is not the absence of chronic, low-level side effects." And so managing these patients over the longer term really does require attention to low-grade, nagging side effects that can adversely affect quality of life over time.

There's a lot still to come. There's a better ibrutinib maybe in the form of acalabrutinib. Venetoclax is now a part of the armamentarium, and we're trying to understand how to sequence these drugs. And we're also trying to understand whether giving them in combinations will improve the outcomes and allow patients to discontinue treatment just as they do with chemotherapy, and that's our business on a daily basis right now on the clinical trial front.

And with that, I will conclude.

**[END]**