

**Applying Genomics to Rare Lymphomas and Leukemias (Hodgkin Lymphoma and Chronic Lymphocytic Leukemia)**

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MEGAN Welcome back, everyone. And please remember to silence your cell phones please for this next lecture. We are delighted to have our next speakers join us. Please welcome Ms. Ann McNeill of the John Theurer Cancer Center and Ms. Sandy Kurtin of The University of Arizona Cancer Center as they discuss “Applying Genomics to Rare Lymphomas and Leukemias.”

DR. KURTIN Well, you guys are holding up, huh? This is lots and lots of learning, that’s a good thing. So we have our focus tonight is, or this afternoon, is on rare lymphomas. We are going to specifically focus on Hodgkin lymphoma and chronic lymphocytic leukemias. So I’m going to get started. We have a lot of material to cover. Objectives are there for you to review; these are our disclosures. We’ll start with Hodgkin lymphomas. This is something we don’t really talk a lot about because it’s been around a long time. You always say, what if you had to have cancer, this is a good one to have. We don’t see that many patients as you can see there; roughly 8,000 new cases a year. Not that many deaths, which is always a good thin. And you look at this bimodal distribution, so we have a younger population, and these are often in my practice anyway. I see a lot of university students who have just registered for classes and boom, they go to student health and have various symptoms and they end up with Hodgkin disease.

But we also have this older group of patients that presents a different challenge. In 2013, roughly 200,000 survivors with Hodgkin lymphoma. So we know there are a lot of survivors. We have learned about survivorship primarily from this group even before we learned about it in breast cancer, which is the other big group. We often seen these vague symptoms, and again, this is a perfect scenario: you have a young person having asymptomatic lymphadenopathy, they get treated for various sinus infections and whatnot, they may develop a cough, again they are thinking that it's an upper respiratory infection, but then they begin to have this very intensive pruritus, alcohol-induced pain at the sites of disease, that's always an interesting conversation when you have a university student to say "Are you having pain after drinking alcohol?" and they're not of age and so that brings up a conversation. Usually if their parents aren't with them, they will divulge that.

But then if they do have B symptoms, and I want you to keep this in mind that basically adds an element of risk that's substantial in these patients. The other thing is that Hodgkin lymphoma morphologically and pathologically is a very inflammatory disease, and these lymphocytes attract all these extra cells, dendritic cells, natural killer cells, eosinophils, inflammatory cells, and this is often why when you biopsy these patients, you just get fibrosis, and often that biopsy is nondiagnostic. We do a history and physical, and I'm not going to go through a lot of that, but I want to call out a couple of things. The sed rate is critical. This is part of the risk stratification for this disease, so you have to get a sed rate. In every other kind of lymphoma, we look at LDH. LDH is not useful in this disease.

And then the second thing is that PET/CTs have become the standard diagnostic, and I'll explain that to you a little bit more. These are young patients, so we do want to talk about fertility if we can.

Here's a case, a 30-year-old male presented to the ED, typical scenario, 2-month history of fevers, cough, night sweats, 8-pound weight loss, so that's B symptoms right there. Had a prior splenic laceration, so we learned last night about abdominal and chest imaging you see there's something missing on the left side over here, right? So we learned, you know what, there's not a spleen over there. And we do this chest x-ray and you see this very wide mediastinum, so there's this big chest mass. You then follow up with a CT in this case because he's in the ED and you see this very large mediastinal mass and you also see in the axilla there that adenopathy. So he has a CT-guided biopsy, it's fibrotic and nondiagnostic, he's referred to Heme-Onc because of the suspicion for Hodgkin disease. We get a PET scan and you see the PET-avid masses there, so you can differentiate the heart from the actual tumor here, whereas in the right image you see that it all looks black. I always take the opportunity when I'm sharing PET scans with our patients to verify that they have something going on in their brain, there's a little activity up there; they always find that a little humorous. I said I can vouch that you have something going on up there.

So diagnostically we see this very characteristic Reed-Sternberg cell, and then we see this morphological signature that we come to know in lymphomas. But you can also see the sed rate, so keep that in mind, 79. Very important. Classic Hodgkin lymphoma, and a few years ago we dropped the "S", so

Hodgkins, it's no longer Hodgkins, it's Hodgkin, so that's the other thing that's changed. But classical Hodgkin lymphoma is the most common, and there are four subtypes there: nodular sclerosing is the most common of those subtypes. We also have this thing called nodular lymphocyte predominant Hodgkin lymphoma, and this behaves very differently and we're going to talk a little bit about that. We treat this much more like we treat follicular lymphoma or diffuse large B-cell lymphoma. So here comes the part—and this is where really understanding staging and risk stratification has become the norm in hematological malignancies in general—and Hodgkin lymphoma has become really pretty complicated when you look at that, and so we'll go through that a little bit more in detail.

Keep in mind early-stage favorable, you know the typical staging system where stage—the Ann Arbor where stage I is above the diaphragm one side, stage II is two sides, but above the diaphragm, stage III above and below the diaphragm, stage IV is extranodal disease, right? So if you have a positive bone marrow, you're already a stage IV. So stage I-II, no unfavorable factors, early-stage unfavorable is I and II, any unfavorable factor, and then advanced stage III and IV. Those unfavorable factors are these very bulky chest masses, so greater than 10 cm or something else that we call a mediastinal mass ratio where basically you have greater than a third of the internal transverse diameter at the level of T5-6 and that has to do a lot with those surrounding structures. Then if we have extranodal involvement and if we go back to that image, you'll see this young man had some bone involvement in the femur.

Here's a sed rate greater than 50, so our case was 79. This young man has many adverse factors, unfavorable factors, he also had B symptoms, the weight loss particularly. Here's how that risk stratification looks now so you get a IA, a B being with B symptoms, and you can see even with one nodal site and any ESR, you're really already stage unfavorable just by virtue of having those B symptoms. You can have a IB, and that's actually worse than IIA when we look at that prognostically, and then basically as you add in greater nodal sites or an elevated ESR, that risk goes up. So keep this in mind when we start looking at how we stratify these patients for treatment. Here's the internal prognostic score for advanced-stage disease. So this is already advanced stage. Now we know they have advanced stage, but we are going to look at additional factors.

One of those would be a lower albumin just less than 4, so most places 3.5 is the lower end of normal. Hemoglobin less than 10, we are beginning to affect other cell lines. Being male over the age of 45, stage IV disease, elevated white count or a low white count, and you look at the number of factors here and look at the difference that makes in 5-year progression-free survival. Thankfully we see a large number of people with fewer of these factors, but when you get down to greater than 5, you have 42% progression-free survival where in most cases for Hodgkin lymphoma, we believe we can cure these people. It's one of the diseases that we think, yeah, well, "we think we can cure you a lot of the time." That's beginning to change now, and the idea here is really looking at who's at risk for early relapse. Here's back to our case, and again you can see these distant metastases that are in the femur there, the left femur in this patient,

so he has these extranodal sites, a sed rate of 79. We use bleomycin in this disease routinely and so we have to worry about bleo lung toxicity, and so we are going to do a diffusion capacity. It's important to always know that you have to correct for hemoglobin. We argue with our pulmonologists regularly about who's job that is. There's a mathematic equation. I've tried it a million times, there's an app, there's a site, and I'm like, I don't know what that means, right? So we argue, and my attending called them up and said, "That's your job to correct for hemoglobin." But you do need to correct for hemoglobin.

We are also going to use anthracyclines, and so you need to get an echo. Even in a young patient, it's very important. Think about that mass where you have this wrapped around these structures and abutting the heart. Here's standard ABVD, which is something that you guys are all probably familiar with, but there are very specific concerns or potential risks with these individual drugs, so I won't go through this in detail, but it's very now standard to not only do a baseline PET, but do a PET after two cycles, and why that is is we now have this PET-adapted therapy. Here are some of the other potential toxicities. One of the things we struggle with now is that now there are certain individuals who have early-stage favorable disease where you may only give two cycles of ABVD, and if they're PET negative after two cycles, they're not going to get any more chemotherapy. So when we look at whether to put a line in or not, that becomes a big conversation with people because you're only going to give four treatments basically, so because of the vesicant nature of doxorubicin and vinblastine and DTIC or dacarbazine being an extreme irritant, vein access can be an issue for

these patients. So now we talked about PET-adapted therapy. These are the Deauville criteria; it's a five-point scale, and the idea here is we want to maximize cures while minimizing toxicity. We don't want to give excess drug if we don't have to, so we don't want to under-treat and we don't want to over-treat to reduce those toxicities. Here are the definitions here. Importantly you want to be three or less after that two-cycle evaluation. And here's a study that looked at this; so these are randomly assigned roughly 1,400 patients, the German Hodgkin Study Group.

But this is looking at four cycles of ABVD, limited involved-field radiotherapy, different intensities, versus two cycles, and you can see really for the 5-year overall survival, there's really no difference in those two groups. Again, early-stage favorable disease. This began to say, you know what, we don't need to give these people that much treatment, so very important there. And less toxicity certainly with the two cycles. Radiation is a big deal, and particularly when you know we used to do the mantle radiation, wear the old-fashioned swimsuits, we would treat the entire person, and we found a lot of people having bad heart disease and secondary cancers, breast cancers, in their 40s and 50s, and so we need to, now we have a better or refined radiotherapy modalities. But still in younger patients you can leave some lingering effects, particularly young women. So it's a conversation that you really need to have with those patients, weighing the risks and benefits of more chemotherapy or should you just do the limit-stage radiotherapy. Here's BCOP, which is another regimen. We don't use this hardly at all. Does anybody use BCOP for their

Hodgkin patients? So there are regions that still use this. There's nothing wrong with that, but in older patients you can see that the treatment-related mortality goes up substantially with that regimen. Now here's where it gets a little shifty, and you've got to really think this through. We bring this chart up frequently in our clinic to try to remember what all this data said, but if you just pay attention here to look at the EORTC Hodgkin Disease 10 trial and you can see stage I2 favorable, a large number of patients, two cycles of ABVD, interim PET negative in a large percentage, not 100%, didn't really do the Deauville criteria, but basically when you look at should we do one more ABVD and radiotherapy versus two more ABVD, it's 100% versus 94.9%, so there's some difference. But then if you look at the other arm here, two of ABVD versus four of ABVD, there was—basically they were equivocal.

Then the other one I want to call attention to is this RATHL 2 study, which is also stage II, but with adverse factors. You can see here they got two of ABVD, 84% were PET negative after those two cycles, three or below in the Deauville criteria, and they compared giving ABVD versus just AVD, leave out the bleo, and there was really no difference in those two arms. So the other thing we are doing now is we're taking out the bleo. So if you meet that PET criteria after two cycles, we're taking out the bleo in selective patients, particularly the older adults where bleo raises that risk considerably.

We're back to our case. Here's this young man, he's had a very nice response, but it's not 100%. He was Deauville 3, but because he had so many adverse factors, so you have to account for all of that in the equation, you can't

just go by the picture, you have to say, you know what, he had all these adverse factors in the beginning, he did not want radiotherapy in anyway, so we committed to six cycles of ABVD.

The other thing you're going to do is you're going to repeat those PFTs and you're going to repeat that echocardiogram, particularly in the older patients so that you don't end up—you know, if we cure you, but you end up with cardiotoxicity that's life altering, if you attended the cardiovascular session, you know we haven't really done you any favors. So again, we want to be smart about the intensity of therapy. In older adults, again, we might leave that bleo out right from the get-go because there is substantial toxicity. We can now add in brentuximab vedotin, put the other B in there in some cases, if they're high risk we have that conversation. Relapsed or refractory disease becomes a whole different ball game. These patients tend to not do as well, if they are young, we are going to try to get them to transplant, and there are other kinds of options that are available to them. So let's talk a little bit about this. This is a 20-year-old, again, a college student, stage IIIB, but also has extranodal advanced disease, so higher-risk disease. She had ABVD times six, PET CR after two, but again, very high-risk factors. Relapsed 8 months later, so not good. Biopsy was consistent with the initial diagnosis. You can see she's CD30 positive, CD15, CD45 negative, and Pax5 positive was just one of the immunohistochemistries that are there. She got ICE chemotherapy, when to transplant. These are the regimens that can be used for relapsed/refractory Hodgkin lymphoma, and so I'm going to focus on some of the newer ones.

I know you've heard a little bit from Dr. Harvey today and I know you've heard a lot about the immunotherapies, so I'm just going to touch on some of these key principles. You do want to consider the pattern of relapse, how long has it been since their initial treatment? What kind of initial response did they have? What shape are they in? if they're not in a CR, they have a less favorable outcome. You have to have honest conversations. In some of those patients, if they relapse after an auto, we're going to take them for an allo, and then we're going to talk about the role of brentuximab vedotin in maintenance therapy. We also have nivolumab and pembrolizumab for relapsed or progressive disease following a transplant and post-transplant maintenance therapy. So let's talk briefly—here's that microenvironment getting us used to these pathways and targets. You can see over on the left here the—you know all of those inflammatory cells, mast cells, the eosinophils, macrophages, fibroblasts, so, very inflammatory disease, but you can see here the CD30 marker here and then you can also see the PD-L1 sites of opportunity. These are some of those novel agents that are currently either recently approved or in trials looking at a lot of these different elements, and so we'll touch on brentuximab vedotin. This is an anti-CD30 antibody approved in 2011, so again, auto failure and ineligible after failure of at least two multiagent chemotherapy regimens and then also high risk for relapse or progression as a post-autologous consolidation. It's dosed every 3 weeks; it's given over 30 minutes, so it's really not too hard on the patients in terms of receiving that. There are criteria for hepatic function and it is

contraindicated when used with bleomycin, so you aren't going to give the two Bs together basically.

This is what the maintenance looks, or consolidation, looks like after an auto transplant. So this was based on 329 patients who were either randomized to placebo or brentuximab. They get a total of 16 cycles, so it takes about a year, a little more than a year to complete that. It's every 3 weeks so you know it's a long time, but considering they're at risk, it's something that most of them are willing to do. There is neuropathy associated with this drug, so it is something that you have to monitor closely in these patients, but you can see that there is statistical difference between those two groups. The other drugs are nivolumab, again, a PD-1–blocking antibody approved for this indication in March of 2016. Again, relapsed or progressed after an auto transplant and or post-transplant brentuximab. You guys have heard a lot about these drugs, so I'm not going to spend time on that, and I'll give the podium here to Ann in a moment, but it's every 2 weeks until disease progression or unacceptable toxicity. So that's a big commitment, and if they're really high risk, we may start with this; if they're young enough and healthy enough, we may try to get them to another transplant. I'm going to skip over the drug-related AEs because this drug doesn't really care what disease you have, it's going to be similar to everything that you've been hearing about the 'itises, so those still apply.

The other drug then is pembro, or pembrolizumab, again, a PD-1 inhibitor approved very recently in March of 2017 for this indication. And again, adult and pediatric patients with refractory classical Hodgkin lymphoma after three or more

lines of therapy. This is 200 mg every 3 weeks, so again, a little less intensive. And more recently there's this KEYNOTE trial. So there's three cohorts to find: progression after an auto transplant, failed salvage therapy after a transplant, failed a transplant, but no brentuximab after transplant. They have the different cohorts there, and at a median follow-up of 9.4 months, overall response rate was 69%. Even in these patients with heavily pretreated and high-risk disease, they had a good number of responses in those patients. These are just the same, the outcome data I'll skip over that, AEs again, 'itises. I think this is something that's a pervasive thing throughout this meeting, which is good because these drugs are crossing over all tumor types, and so we do need to become very familiar with what to look for, how to prevent, and how to treat promptly these toxicities.

One thing that's a caveat because of where this drug is approved is that there is a new warning and precaution for complications after an allo transplant. Think about what this drug is doing and what you learned about immunotherapies and how they're interacting with that immune system over time, including T cells, and think about what happens in graft-versus-host. Have a competent marrow that's taken—moved into your body as a house and you now have a drug that's manipulating that transplanted marrow, and so people can develop very severe hyperacute GVHD and veno-occlusive disease, and that needs to be monitored carefully. In those patients, you have to really think about whether this is the right thing to do.

So I'm going to skip over the 'itises because you guys have heard that, and I will just summarize that you know you need to really pay attention to the diagnostics, the risk stratification, and then PET-adapted therapy in these Hodgkin patients. Ann, I'll let you take it over.

MS. MCNEILL      Good afternoon. We're going to switch gears. We're going to talk about chronic lymphocytic leukemia and the epidemiology is on the slide. This is a pretty rare non-Hodgkin lymphoma. You can see the new cases per year is about 18,900. Death rate is there. The median age of diagnosis is 71. This is a disease of the older person. The 5-year overall survival rate has tremendously increased recently, it has gone actually from about 67 to high of like almost 82% now. This disease is pretty rare in the young person; it is more common in whites and more common in men as with a lot of hematologic malignancies. There are some issues with the epidemiology that we'll talk about in further slides. There are three entities that I want to just compare here. MBL is monoclonal B-cell lymphocytosis, CLL is chronic lymphocytic leukemia, and SLL is small lymphocytic lymphoma. Basically CLL and SLL are two forms of the same disease, but you can see the criteria for diagnosing each of these entities. The big difference I want to point out between CLL and SLL is the peripheral lymphocytosis. In CLL, we do have a peripheral lymphocytosis, and in SLL it is absent. And then the monoclonal B-cell lymphocytosis is that benign condition that we call watch-and-wait and patients call, of course, watch-and-worry.

We have a case study here. This is a 72-year-old female. So let's go over this pretty quickly. She presents with recurring pharyngitis, low-grade fevers,

progressive fatigue, adenopathy, abdominal pain, greater than 10% weight loss. Her past medical history is listed here, hypertension, she does have an exaggerated reaction to insect bites, which we do see quite frequently in CLL. On physical examination, she has extensive adenopathy in the cervical, axillary, and inguinal regions. She has splenomegaly. Some of her lab values are listed here. What's really important on the bottom of the slide is to please be aware that she is tested for FISH, so she does have that peripheral blood sample sent for FISH studies and she is 17p deleted in 46% of her cells. So again, all of her labs are there, we'll go through this.

Clinical staging predicts outcome. There are two staging systems for CLL. The Rai system on top is the more common one used in this country; Binet is more commonly used in Europe. And basically we have four stages: 0 stage, we have lymphocytosis in the blood and marrow only with normal evidence of lymphadenopathy and no evidence of splenomegaly. And then as we go into the higher states, you can see in stage I and II, lymphadenopathy and splenomegaly and/or hepatomegaly are also present. And then when we get to stages III and IV, we do see the effect on the marrow. We see the cytopenias occurring as well, and you can also see the prognostic value of the staging with the median survivals listed on the slide as well. So we have prognostic indices for all of our lymphomas, IPI, FLIPI, MIPI, and now we have a CLL international prognostic index as well. We look at the FISH, serum beta-2, Rai stage, *IGHV* mutation status, and the age of the patient. We appropriately assign points and then the risk category is on the bottom. If they are high risk, which is 7 to 10 of those

points, obviously the 5-year overall survival decreases. So based on your risk profile, we can predict your—we have a prognostic indicator of overall survival. Some of the genetic alterations in CLL that are important are listed here. We have 13q, 11q, 17p and we have whether it's favorable or unfavorable. What I want to point out here is 17p deletion is probably the poorest prognostic variable we can assign to someone with CLL. 11q is also an unfavorable prognostic indicator, 13q is a favorable one. What's not on the list is also the *IGHV* mutation, unmutated is unfavorable, that's an easy way to remember it. We also do a couple of—doctors also and physicians and APNs also will look for other prognostic variables, ZAP-70 you might be aware of, but these are some of the genetic alterations we encounter in CL. And actually by looking at some of these alterations, you can see the median time to progression and survival overall is affected by the presence or absence of these mutations.

I do want to point out that elevated white count alone is not a significant adverse prognostic factor. And I think from all of us who have treated patients with CLL, we do have patients with very, very high white counts and lymphocyte counts possibly in the hundreds of thousands that have been that way for a very long time and they are living life happily with that. So again, alone the WBC count is not a significant factor if it's used alone. So what are the indications for therapy then, because that's kind of hard to explain to a patient, right? They see a white count of 100,000 and they're like, "Oh my god, but this paper says my white count should be 10,000 or lower," and we're saying, "Oh, we don't have to treat you," and they're like, "Oh my god." Right? So some of the indications for

treatment are the B symptoms. Again if you're a lymphoma practitioner, you know the B symptoms are the night sweats, the drenching night sweats, the fever, unexplained fevers with or without infection, severe fatigue, the unintentional weight loss, the generalized pruritus, tumor burden. How big are their nodes? Are they presenting with lymphadenopathy? How big is the spleen? How big are the nodes? Bone marrow failure, a big one. So are we affecting the other blood counts? Are we seeing the progressive anemia? Are we seeing thrombocytopenia? Are we seeing autoimmune cytopenias that are poorly responsive to steroids and that would be an indication for treatment?

Going back to our 72-year-old female, she's a Rai stage III based on her presence of splenomegaly, the adenopathy, the lymphocytosis. Her IPI score, she is high risk, she's 17p deleted. We do need to treat this woman; she does have progressive or symptomatic lymphadenopathy, she has fevers without infection, so she really is showing us from a lab standpoint and from a clinical standpoint that we do need to treat her. So what are the FDA-approved drugs to treat CLL? There's a whole range of drugs that are approved to treat CLL; they are listed here. The generic name, the brand name and the class. I'm not going to go over every one because we're going to talk about them in future slides, but there are quite a few drugs indicated for treatment for CLL. For frontline therapy, and I think we're all familiar with the go-go, slow-go and no-go patients based on their performance status and how fit they are. So we do not treat patients with stage 0 disease, but if we're looking at patients who need treatment, active disease, if they are not 17p deleted, we traditionally will go with

chemoimmunotherapy, and a lot of practitioners will go to the FCR or BR chemotherapy regimens—the fludarabine, cyclophosphamide, rituximab or bendamustine, rituximab and also ibrutinib is indicated here as well. If they are 17p deleted, we know that conventional chemotherapy is not going to be effective, and we will go to other agents. Ibrutinib is listed here with alemtuzumab. Then if they're a poor performance status, so we call them the slow-go patients where their performance status is a little bit less so they have more complex comorbidities. We are thinking of other agents. Again we are looking at monoclonal antibodies in combination with agents; we are looking at ibrutinib as well, and again, the anti-CD20 agents. And again, I just pointed out for the 17p deleted patients, we are not going to be using traditional conventional chemotherapy; it is not effective. Fludarabine in CLL very quickly, it's been around a long time since 1991, it does remain a preferred regimen for younger and fit patients, it does work well in combination with rituximab, good response rates. We do have to be very aware of some of the hematologic and infectious toxicities. Again, we listed the response rates here, but I think it's very important that there is a long-term depletion of CD4-positive T lymphocytes in this population, so we are going to be very aware of how we are affecting the bone marrow with the use of this agent.

Ibrutinib, so ibrutinib is an oral tyrosine kinase inhibitor used for CLL based on two studies: the RESONATE and RESONATE-2 trials. RESONATE was for previously treated CLL, and RESONATE-2 was for treatment naive, the newly diagnosed who have never been treated and basically much better. The

RESONATE was comparing ibrutinib with ofatumumab, which is an anti-CD20 monoclonal antibody, and in the RESONATE-2, we looked at ibrutinib versus chlorambucil in the treatment-naive patients. And in both cases, in both studies, we did see a significant improvement in overall response rates, progression-free survival, and overall survival in the ibrutinib arm. What's very interesting is that we do see this lymphocytosis with ibrutinib, and it's very important for us to not only know about it ourselves, but to kind of impart that knowledge to our patients as well. So we do see this treatment-related lymphocytosis that is very common after ibrutinib dosing. It is related to moving the lymphocytes out of the lymph nodes into the peripheral blood, so getting out of their cozy environment and going into the peripheral blood.

It usually occurs within the first month after ibrutinib dosing, but it resolves relatively quickly, usually within 8 months. There have been some patients that have gone on about a year and still have this lymphocytosis, and I do want to make sure that we do all understand that this persistent lymphocytosis in the absence of any other symptom does not represent a clonal evolution or progression of disease, and the PFS is not inferior for these patients who do experience this prolonged lymphocytosis versus those who just have a traditional response. I think it's really important for us as practitioners to impart that knowledge to our patients because as you know with CLL, patients are very aware of their white count and their lymphocyte count. Especially if you have an engineer patient, a patient who's an engineer, they have Excel sheets that will go through their whole white count over 10 years, so if you give them ibrutinib

because you need to treat them and they see their white count going up, they are going to be very nervous, so we do have to make sure we educate patients that this may happen and why it happens.

What kind of toxicity or safety profile do we see with ibrutinib? We have common adverse events on one side of the slide, and then we have some of the common non-heme adverse events. I do think that we have to be aware of fatigue. I see this in my practice, fatigue, cytopenias, diarrhea, which are very manageable, generalized musculoskeletal arthralgias, myalgias, the pain. And then we do have to worry about some of the other non-heme or non-common. We are going to talk a little bit more about AFib, some bruising and bleeding issues. But again, it's a very well-tolerated drug in general, and we are going to go into more of the toxicities.

So ibrutinib and atrial fibrillation. The risk of AFib and AFlutter is there. Patients with cardiac risk factors are more prone to this. Patients who have a history of AFib obviously are more prone to more exacerbation of this. We do monitor closely for AFib anybody with a new symptom palpitations, lightheadedness, whatever it may be needs prompt intervention to determine the etiology of that symptom. If it's symptomatic, we can consider discontinuation of the drug. I think this is, again, a healthcare team decision. It doesn't necessarily mean we do have to discontinue the drug, we may have to use other drugs. It may have to be dose reductions, but again, this can occur and we should be aware of the potential for AFib and AFlutter. Ibrutinib and bleeding risk: there have been in the studies incidences of grade 3 or higher bleeding events, GI

bleeds, subdural hematomas that have occurred in about 6% of patients. Bleeding events of any grade have occurred in quite a higher percentage of these patients. The mechanism for these actual bleeding events is not clearly understood. Of course, the ibrutinib bleeding risk can be exacerbated in patients receiving antiplatelet or anticoagulation therapies, and I do want to tell you that in our practice it's very important to note that bruising, the easy bruisability is more common than the bleeding, so definitely be aware of the bleeding. It is important to recognize symptoms of bleeding, but the bruising issue is much more common and easier to deal with again. We do consider the benefits and risks of holding the drug as we do in any situation with any side effect with any agent, and also what's really important is if a patient is having a procedure.

One of the things that the advanced practice nurse and the whole team should really be telling patients with regards to education is if you're going for a procedure, whether it's a tooth extraction or colonoscopy, a more serious surgery, I'm having my gallbladder out, whatever it may be, if it's an elective procedure that is planned, they do need to let us know. We do have to stop the drug at least 3 days prior to and after the procedure. For more intensive or involved procedures, it may be up to 7 days preop and post-surgery. Obviously if it's an emergency situation, we don't have the luxury of doing that, but patients should be aware to tell us about any planned procedures.

So let's go back to our case study. We have determined that she's high risk, she's 17p deleted. We determined that she was definitely a person that we had to treat based on her clinical presentation and her labs, so the treatment

selection here, again, she's 17p deleted, we are going to give her ibrutinib. We do know that FCR, BR, the traditional chemotherapies are not efficacious in this kind of situation.

Let's talk about relapsed/refractory disease. What is the definition of progression of disease? So we are looking at lymphadenopathy. If we see an increase of greater than 50% of the lymph node enlargement, hepatomegaly, splenomegaly, but then we're looking at the blood lymphocyte count as well. We are going to look at an increase of over 50% over baseline, we're looking at the platelet count, and we're looking at the hemoglobin. Relapse, again, we all know the definition of relapse: evidence of disease progression after a period of 6 months or more following an initial response. And refractory means there's a quick relapse. We are actually giving them active treatment or we've stopped treatment, and within 6 months, they're showing evidence of progression of disease. Clonal evolution and relapse in refractory CLL. So clonal evolution is of course we've all heard that buzzword with other heme malignancies. The acquisition of new cytogenetic abnormalities during the disease course. So I do want to spend just a little bit more time on this slide because it's really, really important for us as advanced practice nurses to know that it is critical to know that the disease at the initial presentation and initial diagnosis can be very different at relapse and actually at each relapse. There are mutations that are acquired throughout a patient's journey with this disease that drives the relapse, of course, so I think it's very important for us to realize that it's critical to test for 17p, do that FISH, do the flow, do those blood—it's a blood test, it's a peripheral

blood sample, do it if we suspect relapse and really know what the patient's report card is. I always tell patients, they're always asking why we're taking so much blood especially at initial diagnostic evaluation, we are taking tubes and tubes, right?

We want to get this report card of the patient, and that gives us an idea of how the disease will behave statistically. We really want to look for 11q, 17p, because these are associated with poor prognosis and inferior overall survival. And again, I want to point out that very few patients at initial diagnosis are 17p deleted, less than 10%. As they go along their journey with CLL, the incidence of them acquiring the 17p deletion becomes much greater. It's over 50%. And actually at each of their relapses, so each individual, their second relapse, their third relapse, fourth relapse, and so on—if they are not 17p deleted, the chance of them becoming 17p deleted at each relapse becomes higher. Richter's transformation is not clearly associated with no mutations. I'm not going to discuss that in detail, that's a whole 'nother lecture. Very few patients are really Richter's transformation, about 5% of CLL patients, that is a very aggressive form of DLBCL that is diagnosed by pathology, an actual tissue biopsy, and that's associated with an extremely poor performance status.

Second-line treatment for CLL. Again, we are looking at the very fit patients, the slow-go patients. We have standard therapies, alternate therapies, we're looking a refractory or progression within 2 years. Again we are looking here, we have ibrutinib, we have a lot of other agents here, we have idelalisib, we have venetoclax, we have chemoimmunotherapy, allogeneic stem cell transplant.

If your patient is fit and young, that is also an option. I did fail to mention that clinical trials at relapsed and refractory disease are always an option; we should definitely recommend clinical trials. We can, if the progression is after 2 years, we can consider repeating first-line therapy, although most practitioners know with all the new novel agents, we probably would go to one of the newer agents and treat the patient. There are some alternatives here; we have lenalidomide, we have a lot of other combinations of drugs with the CD20 monoclonal antibodies, but lots of new therapies out there for relapsed/refractory disease. Idelalisib is a PI3-kinase inhibitor, and actually this is one of the drugs that is an oral agent. It's approved for relapsed/refractory CLL. Again, it was compared to rituximab and placebo used in combination with rituximab I failed to mention. The overall survival, the overall response rate, the survival, the progression-free survival, all of those endpoints are significantly better in the idelalisib arm versus the placebo arm. There are some adverse events listed here; I'm not going to go through all of them, but again, we do have fatigue, we have some GI—actually with this drug, I do want to point out that one of the things we are looking at educating patients about is diarrhea, and we are looking at the chemistries. We want to make sure we are aware of the liver function tests because there can be some issues with the liver function tests. And on this slide it does show you the considerations for patient management. Any kind of skin rash, any kind of respiratory symptom can indicate a side effect. So we are going to look at possible pneumonitis or dermatitis related to the drug that we have to evaluate, but we are looking at the bilirubin, the ALT, AST, looking at those values very

closely and considering whether or not we are going to continue drug or dose reduce the drug. Again, diarrhea is also a very important side effect because it can be life threatening if patients don't report it and they are not being well hydrated and so on.

Venetoclax is one of the newer agents approved in 2016 for relapsed CLL with deletion 17p. This is a BCL-2 inhibitor. The BCL-2 family are very important regulators of the programmed cell death process in the cell. There were studies done with venetoclax in patients with relapsed CLL, and again, the overall response rate is much higher for these patients and in the phase I trials and the phase 2 trials. What's really important to note about venetoclax is that we can see very, very quick tumor lysis with this drug, and for that reason, there is a risk-based TLS prophylaxis that we use. Again, the drug is titrated up slowly, it's a 5-week ramp up; it starts at a low of 20 to a high of 400, so it's 20, 50, 100, 200, then 400. The reason we do this slow ramp up of the drug is because we are lowering the incidence of significant tumor lysis syndrome while debulking the patient slowly in the beginning with the earlier doses. So again, the primary endpoint, secondary endpoints, are much improved with this drug. This drug has a very nice response, and if we can manage the early debulking and the risk of tumor lysis syndrome, it's very well tolerated.

There was another phase II trial in CLL with deletion 17p and overall response—this is monotherapy—overall response was 79% of good progression-free survival, and again, we do see some patients with—all patients have to be assessed for tumor lysis syndrome, so this is a big issue with venetoclax, big, but

manageable. We do have to be aware of it and properly manage the dose ramp up phasing with venetoclax. And we do have venetoclax. The adverse events: what else do we see besides monitoring for tumor lysis syndrome? What other kind of safety issues are we looking at with grade 3 or 4 neutropenia? We do look at the CBCs quite frequently, we may need to use growth factor support, we may need to use antibiotics, we do have to encourage our patients to report fever, what fever and when and how to seek medical attention. We can see diarrhea, we can see upper respiratory infections and we can see nausea.

Again, good education, good communication between the practitioner and the patient helps to manage these appropriately. The tumor lysis syndrome risk stratification I'm going to go into—actually the next slide I want to show you the ramp up. We look at is the patient low risk for tumor lysis, medium risk or high risk? So the patients who are at low risk for tumor lysis syndrome, they can possibly or it can be monitored on an outpatient basis. It's very important for us to get allopurinol, these uric acid-lowering agents, but they should have the ability to understand the need for adequate oral fluid intake and adequate hydration, they need to drink 1 and a half to 2 liters daily, they are going to come to the clinic two days in a row, what they usually do is come in, they take their drug, we wait a few hours, they get baseline labs, they take their drug, we wait 6 hours, we get another set of labs. If we don't think they're drinking enough or they're having an issue, we give them IV hydration, but usually they are able to drink enough fluid, and then we have them come back the next day for the 24 hour labs. So very important to have these labs done at the predetermined intervals.

Medium tumor burden. What am I looking at for the tumor burden? We are looking at the lymph nodes and the actual absolute lymphocyte count. Medium is a little bit bigger lymph node, but less than 10 cm, less than 25,000 ALC. These patients may be done in an outpatient setting, we may have to consider hospitalization for these patients that may have impaired renal function; again oral hydration is important. Allopurinol. And we also do the baseline labs 6 to 8 hours after and then actually 24 hours later. So there's a couple of visits to our office to check the labs. The high tumor burden, the high-risk patients, these are patients that are hospitalized for their first two ramp ups, the 20 and 50. Very important for them get a lot of labs, we do IV hydration, they get more frequent labs, they might even get rasburicase if their uric acid is elevated. There are some studies being done with venetoclax in combination with other agents with some of the anti-CD20 agents, and that's listed here. We have seen some good results and actually at ASH this year the top one, there will be some data on venetoclax and rituximab. We are actually now looking at studies combining ibrutinib and venetoclax, and some of the studies are listed here. Second-generation bruton kinase inhibitors, so we do have acalabrutinib. And I don't know if you all know, but you probably do, last Tuesday on Halloween, acalabrutinib was given FDA approval for the treatment of mantle cell lymphoma, so it is another BTK inhibitor that is now actually indicated for mantle cell lymphoma and may have some other indications in the future.

Ofatumumab is a CD20 monoclonal antibody approved for patients with refractory CLL or CLL refractory with fludarabine and alemtuzumab. Again, it's a

monoclonal antibody. I think we're all familiar with how to manage monoclonal antibodies with the appropriate medications and the close monitoring especially at the first infusion. There is no black box warning, but again we are looking at infusion reactions, cytopenias, PML, which is something that we are aware of, that neurologic syndrome or infection with monoclonal antibodies, and the hepatitis B reactivation, which is potential with all the monoclonal antibodies. The side effects again are here. Again, very well tolerated. Neutropenia we do need to be aware of on CBCs and some of the other ones listed here. I always point out that infusion-related reactions are what we have to educate patients about as well. Obinutuzumab, chlorambucil versus rituximab, chlorambucil versus chlorambucil alone, a nice study that treated patients with—previously untreated patients with CLL, SLL with some comorbidities, and the overall response rate was a lot better in the obinutuzumab arm as you can see here. So another combination that is used, or another drug combination that is used for relapsed/refractory CLL.

So what kind of adverse events do we see? The most common are, again, the infusion-related reactions. Obinutuzumab, like ofatumumab, is an anti-CD20 monoclonal antibody. We do see cytopenias and we do see possible infections, and pneumonia is the most common. Ongoing trials, so we do see some new agents out there being studied for CLL. Duvelisib, another PI3-kinase inhibitor, acalabrutinib, which I just mentioned, which is now approved for mantle cell, which is being studied in CLL, pembrolizumab the PD-1 agent, and CAR T, which is very exciting; as we all know some of the newest approvals recently have been

for some of these heme malignancies with CAR T. Thank you very much. I think we are going to open it up for questions.

MS. MCNEILL        Yeah, is there any questions?

MS. KURTIN        If there's any questions, we do have a microphone that's available. You're all experts in CLL and Hodgkin. Oh.

FEMALE            In the CLL patients on ibrutinib, what I've read is that the average time frame for relapse with that is around 3 years, but are we seeing patients living—responding longer than that?

MS. MCNEILL        Yeah, that's an excellent question, and I'm sure Sandy can confirm with me as well. I have patients who are on the drug more than 3 years. I run a support group for CLL patients; there's actually a gentleman in the group that's been on the drug 5 years, but we do see quite a number of patients. If they're doing well with tolerability of the possible side effects and there's no evidence of progression of disease, we keep them on the drug and they do fine. But yes, very long-term disease control. Very long term.

MS. KURTIN        Any other questions? No, one more.

FEMALE            On your Hodgkin patient when you could see on the PET that you had bone marrow involvement, did you do a bone marrow still?

MS. KURTIN        We did not, so that's a very good point. Thank you for bringing that up. I didn't mention that, but that's the other beautiful thing is that if they are PET negative in the marrow, we don't do marrows anymore. So that's really great for the patient not to have to do that. Back in the day, we used to do bilateral. How many of you used to do bilateral? I know I'm getting old. But we

used to do bilateral marrows on these poor young patients, and now we don't do any because the PET is actually a really sensitive way to look at the marrow. So thank you for bring that up.

MALE                    We've been having a lot of struggle treating patients with CLL who have ibrutinib resistance. So I just wondered what you guys were doing at your institutions of treating ibrutinib-resistant CLL that have progressed?

MS. MCNEILL        There never used to be good choices for these patients, but now we do think of venetoclax as a possible treatment option for those patients, and then there are clinical, I mean, I work in a research center and so does Sandy, and so we do consider, any time a patient has a relapse, we do consider the possibility for eligibility in clinical trials as well. But venetoclax is definitely something we would consider for that patient.

MS. KURTIN            Yeah. That would be probably what we would do too depending on how healthy that person is and what else they have going on.

FEMALE                Hi. You alluded to with ibrutinib the risk of bleeding, and obviously if the patient develops AFib, and you are going to address the AFib, you might consider putting them on an anticoagulant?

MS. MCNEILL        I knew that question was coming. I knew it.

FEMALE                So do you have a preferred anticoagulant, or how do you have that discussion with your patient so now they get that risk/benefit ratio?

MS. MCNEILL        Every institution's different, and I know that warfarin is not one of the preferred agents, so we do not like warfarin, but all of the agents, there's the potential of increased risk. So we do look at the risk versus benefit

analysis, and the physician team that I work with patients who have AFib or who need anticoagulation therapy for whatever reason, they are not taken—we don't take ibrutinib off the table. If they must have anticoagulation prophylaxis, we just monitor these patients more closely and educate them about what to report as far as bleeding and so forth. But the only thing that we don't use—and I'll let Sandy speak as well—we do not use warfarin. But some of the other newer agents whether its Xarelto or whatever we do use these agents. We would love to use Lovenox, but nobody's going to want to stick themselves for 3 years, 4 years, 5 years, and no insurance company is going to like me if we prescribe Lovenox. So that's the one thing that—I don't know if Sandy you have any other...

MS. KURTIN            Not, that's true. There's actually a really good paper that was just—it's in *Clinical Leukemia Lymphoma Myeloma*, and they did a medication analysis of all of the different trials and looked at risk of bleeding, risk of AFib. And so it's not an absolute contraindication, it is something that you have to talk with the patient about and also the cardiologist because, depending on what's going on with them in addition to their AFib, their cardiologists do say "I have to have Coumadin, right?" These newer drugs—we're getting more data about the newer drugs being used in valvular disease and that thing, but it takes a conversation with a cardiologist and it takes a conversation with the patient to let them know there is a risk. My experience has been similar to Ann's in that the bruising, like people look like they have tattoo sleeves of bruising in some of these patients. It's not painful or anything, but it can be pretty extensive in some of those patients.

FEMALE Thank you.

MS. KURTIN Anybody else? One more over here.

FEMALE This is regarding the CAR T-cell therapy. Earlier they were talking about age restriction less than 25 years old, and given that CLL is a disease of the elderly, is there any concern about that?

MS. MCNEILL So I'm not sure what lecture you attended.

MS. KURTIN It was Dr. Harvey, it was a drug update, and that's the approval for that drug was in a younger population. But there are many trials that are being studied in older or a broader age range, and so you do have to do a risk analysis about whether or not they are an appropriate candidate.

MS. MCNEILL Yes, I agree. We had a lot of CAR T studies, and the age—most of our patients are over 25, so we did have many, many patients, but again it's a risk versus benefit analysis of age as far as other factors. But many of our patients were older and enrolled in the study. So it's a very interesting concept and we'll see a lot more of it coming up.

FEMALE So that approval was for ALL, not CLL.

MS. MCNEILL Correct.

MS. KURTIN Right.

FEMALE For the CAR T. She was talking about CLL.

MS. MCNEILL Yes. Yeah.

MS. KURTIN Right.

FEMALE Okay. I did want to be sure.

MS. KURTIN            But there are trials going on across heme malignancies, yes. But the approval that he mentioned was in ALL; a more recent approval was diffuse large B cell, which included people that were much older. But again, it's that risk analysis that has to be done for any therapy really. But particularly the neurotoxicity that can be seen in the older patients can be pretty severe with CAR T.

FEMALE                Okay, thank you all very much, enjoy your evening.  
Megan has a couple announcements.

MEGAN                 Thank you both for that wonderful talk.

**[END]**