Moderator: Welcome to Managing Hodgkin Lymphoma with Antibody–Drug Conjugates, a three-part podcast series presented by the publishers of the *Journal of the Advanced Practitioner and Oncology* and Harborside Medical Education. This certified educational podcast is supported by an unrestricted educational grant from Seattle Genetics, Inc. Please visit advancedpractitioner.com to view faculty disclosure information.

Ms. Goodrich: Hi, I'm Amy Goodrich, a nurse practitioner and research associate at the Johns Hopkins School of Medicine and the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. I'm joined today by Barbara Rogers, adult hematology/oncology nurse practitioner at Fox Chase Cancer Center. Thanks for joining me.

Ms. Goodrich: Today, Barb and I will discuss anticipating and managing side effects for patients with classical Hodgkin lymphoma, including the short- and long-term adverse events associated with chemotherapy, checkpoint inhibitors, and antibody–drug conjugates.

Ms. Goodrich: We're first going to talk about chemotherapy in Hodgkin lymphoma, which really remains the backbone of treatment. And to consider a patient, we've got a 69-year-old male who presents with pruritus and painless adenopathy. His biopsy and his staging workup reveals stage IIa classical Hodgkin lymphoma, and he is to receive AVBD followed by involved site radiation therapy. During cycle 3, he developed a dry cough and exercise intolerance due to dyspnea on exertion, and he's found to be neutropenic with an absolute neutrophil count of 0.3.

Ms. Goodrich: So Barb, what are you thinking about when this guy comes in? What are you worried about?

Ms. Rogers: So, first I think it's important to think about that with ABVD and Hodgkin lymphoma, we don't really pay that much attention to the counts. We notice what they are, but unless, if they're having fevers along with a low white count, we just usually treat on and it's usually one of those, okay, thanks for letting me know, continue to treat. So the neutropenia actually doesn't get me that excited. There actually have been a number of studies looking at treating patients with Hodgkin lymphoma with low white counts and shown that the patients don't have any higher risk of developing neutropenic fever than those who don't develop neutropenia. So we know we can continue on. Some of the studies included the use of some antibacterials, but not all clinicians use them when people have a low count.

Ms. Rogers: Now of more concern though for this is the shortness of breath he's experiencing, especially with the dry cough. So, while of course, Amy and I both live in the northeast, so we do see a lot of colds and flus, especially this time of year, but first thing I thought is could this potentially be pneumonitis associated with bleomycin toxicity? So, of course we've got to work that up, but again, we don't want to hold up treatment because this is a curable disease and we have to stay on schedule.

Ms. Rogers: So usually what we'll do in our practice anyway is hold the bleomycin but continue with the rest of the drug and hold the bleomycin until we can get pulmonary function tests to see whether there is any evidence of pneumonitis from the bleomycin.

Ms. Goodrich: Great, Barb. And can you talk a little bit about other baseline studies you might do with patients getting ready to start ABVD?

Ms. Rogers: So first with the bleomycin, we do pulmonary function tests right from the beginning to know what they are. It's amazing how many people have pulmonary issues before they ever start treatment, and also the disease itself can cause some pulmonary issues, so trying to figure out could this be the disease or could it be some other reason why they've got abnormal pulmonary function tests? The other thing we do, because they're going to get anthracycline with the doxorubicin, is to get either an echocardiogram or a MUGA scan. We almost rarely get MUGA scans these days because of the insurance issues, but to make sure that patients have a normal echocardiogram. In the past we've actually sometimes said, "Oh, they're young, the likelihood of them having abnormal heart issues is very low" and so some practitioners, we used to bypass it. But we've had a few patients who were young and still had some cardiac issues, so we pretty much, across the board at this point, get everyone to get an echocardiogram.

Ms. Rogers: And then otherwise, those are the main things that we do up front, except things that we normally do for staging like scans, PET scans because we're going to use that especially in this patient for looking at the response. Maybe a CT of the neck if they have lymphadenopathy there, but not all providers do that. One physician I used to work with used to say, "You should be able to feel them, so I don't need to get a CAT scan." So that's just good practice.

Ms. Rogers: And then anything else that's coming up with that patient that you've got concerns about: Do they have a history of maybe having an MI? Although this patient population usually is younger, although we do see it in older patients. So we might send them to a cardiologist, so if they've had cardiac issues before, to make sure that they're going into this without any issues that could affect their treatment.

Ms. Rogers: And we also usually make sure if a patient has diabetes, where potentially the diabetes might give them neuropathy, to make sure their diabetes is under control, because we don't want that causing neuropathy and potentially holding some drugs when it could for another reason, so we want to make sure that everything else is under control.

Ms. Goodrich: Yep, absolutely. Getting back to our case, should you use growth factors in this person? Should he be put on filgrastim or pegfilgrastim?

Ms. Rogers: So that's the big issue with bleomycin. So there is some data, although not super great although enough to give us concern, that there may be an increased risk of pulmonary toxicity with bleomycin when patients receive the neutrophil growth factors. So we do not usually give them any Neupogen (filgrastim) or Neulasta (pegfilgrastim) when they're on ABVD. However, if we have someone who is not getting bleomycin or they've had some issues in the past with their counts and developing neutropenic fever, and we're going to stop using the bleomycin, then we can add in the growth factor if they're not getting the bleomycin.

Ms. Goodrich: Right, right, but like you said, their risk of infection is not higher even though they are profoundly neutropenic for very long periods of time, sometimes. And then the other toxicities that we see with chemotherapy, like all sorts of GI toxicities, peripheral neuropathy, is there anything unique about ABVD for this patient?

Ms. Rogers: Well, there are I guess what I think about is having patients having issues with nausea and vomiting because a large number of these patients are younger, they seem to have more difficulties with nausea and vomiting, so you may need to add in additional drugs for their nausea as they proceed through treatment. I think most of us believe we should have nausea under good control with the number of drugs we have available, but I think we just have to always leave it in the top of our brain that they may have more difficulty with controlling it and we may need to add or modify their treatment regimen for the control of their nausea.

Ms. Goodrich: Right. But nothing amazingly unique like the treating through neutropenia to keep the drug going through the neutropenia.

Ms. Rogers: I think the biggest thing is keep educating the nurses why we're not going to do anything when their neutrophil count is 200 or even 100.

Ms. Goodrich: That pulmonary toxicity and making sure that you are ruling out infection as well as looking for that bleomycin toxicity. Great, okay, so that's our first case, who is found to have bleomycin toxicity and has this bleomycin dropped out of the regimen.

Ms. Goodrich: So let's go to our next set of drugs here: checkpoint inhibitors. As you know, nivolumab and pembrolizumab have been approved for relapsed/refractory classical Hodgkin lymphoma. In general, the side effect profiles have been very similar to our solid tumor folks and certainly the dosing and the scheduling is the same.

Do you want to talk about some of the things that you're looking for in these patients in general?

Ms. Rogers: I guess I'll start again with pulmonary just because this is a population that we may have other issues with them pulmonary-wise from other treatments. But we certainly have seen pneumonitis from these agents and yet, we really have to pay close attention to any complaint patients have with shortness of breath or coughing and to make sure that we can at least have an idea whether we think it's more related to the drug or are they developing other symptoms from infection for whatever reason.

Ms. Rogers: The tough part is since there is some data about some delayed pulmonary toxicity associated with bleomycin, so always kind of have in our brain what could be causing it. It's going to be real hard to know for sure, but I think for those patients on any of those drugs, we've got to use checkpoint inhibitors. We have to assume that perhaps it's from these agents because it can be pretty severe if we continue on the drug that potentially could be causing some severe pulmonary toxicity.

Ms. Rogers: The other one you see pretty regularly is the colitis that occurs and so we – obviously your hope is not around the time when you're having the GI viruses going around, but usually it's pretty distinct and pretty severe. And with the more severe episodes, you've got to stop these checkpoint inhibitors. Potentially give patients steroids until it improves and then they potentially could go back on these treatments for either of these two as long as we get them under control. But as things get more severe, sometimes we do have to stop them altogether. I have seen a patient with Hodgkin lymphoma who we were giving the nivolumab to who did develop this pseudoprogression syndrome shortly after starting the nivolumab. He was one that, because of the number of treatments he had previously, he kept pushing to get scans done and we kept saying, “No, we don't want to,” and of course finally we gave in and his disease looked like it was progressing, and then trying to explain to him, this could just be fake out, it might just be inflammatory response and it's not really progression.

Ms. Rogers: And so we continued on, and lo and behold the next scan he had showed he had a good response to treatment. So that can occur is not listed as being super common, it certainly does happen. So I think that’s a potential with any disease that we are treating with the checkpoint inhibitors.

Ms. Rogers: We also have these more rare ones, and I guess in hematology we think of the ones that affect the blood counts. We're currently taking care of a patient who doesn't have Hodgkin lymphoma, but has another solid tumor who’s seeing the hematologist because they've had issues with a what looks like an immune-related anemia and thrombocytopenia, probably associated with a checkpoint inhibitor. So we have to always pay attention to them and think could this potentially be something other than—because of their disease—could it be the drug and do we have to hold it? It doesn't happen very often, but I certainly have worked with a physician who said, "If you haven't seen all the side effects, you just haven't given enough." So you always have to pay attention, because it might happen to one of your patients.

Ms. Goodrich: Right. And I think one of the tricky things here is that both of these drugs are approved third and further lines. So these folks have been pretty heavily pretreated. My perception is they're used much sooner in the solid tumor population, so this is the more heavily pretreated group of folks.

Ms. Goodrich: Okay. And then autoimmune disorders with folks getting checkpoint inhibitors?

Ms. Rogers: It's something to consider and to pay attention to. We will usually, before starting them, talk to the rheumatologist about the severity of their autoimmune disorder and what they're thinking of and how hard has it been to control their autoimmune disorder, and kind of have a chat between hematology and rheumatology to talk about, is this too risky for us to start a drug like this in a person with an autoimmune disorder, so it has to be that give-and-take between the two groups to figure out is it okay to start and what are we going to do to more closely monitor these patients, especially with their autoimmune disorders, because potentially it could become worse on the checkpoint inhibitors.

Ms. Goodrich: And then in just thinking about grade 4 and 5 toxicities, there have been none in the studies with giving nivolumab to classical Hodgkin lymphoma patients, and it's extremely uncommon in the pembrolizumab to have truly severe toxicities. It's relatively well tolerated but definitely toxicity that you've got to be looking for and ready to manage.

Ms. Goodrich: So our next slide is a case and it is a patient who is 70 years old, and he presents with stage IIIb classical Hodgkin lymphoma. His comorbidities include a significant smoking history, COPD. He had early-stage lung cancer about 6 or 7 years ago that was treated with lobectomy and radiation. He's got hypertension. He does not have peripheral neuropathy and so this is – he was just diagnosed and the options are weighed and the decision was made to start him on brentuximab vedotin plus AVD, which is a brand new regimen to the NCCN guidelines, and this really trades the bleomycin with brentuximab vedotin to try to avoid some of that pulmonary toxicity with the bleomycin.

Ms. Goodrich: So he starts BV AVD and he presents in cycle 4 with painful numbness and tingling in all of his fingertips. He can't button his buttons, he can't pick up small items, he's unable to type on his smartphone, which really has him unhappy. Do you want to talk about neuropathy with brentuximab vedotin, Barb?

Ms. Rogers: So in my mind, this is the real toxicity we have to pay attention to with brentuximab vedotin. However, I think the thing that we're always thinking about is should we hold treatment? Should we hold treatment? But with this combination and anytime we're using BV, I think we have to always think about, what else can we do? Because we're also thinking about long-term disease-free survival, so I want to keep them on schedule as much as possible, but what things can I do?

Ms. Rogers: Thinking about modifying the dose, even doing it early so we can keep them on treatment and hopefully don't have to hold treatment, because that's when they always think about with patients with Hodgkin's, because the more you delay their treatment, potentially you're affecting their long-term outcome. So you have to think about when are they getting to this point, can we modify the dose sooner? Do we have to start lengthening the length of the cycle? Although this is given every 2 weeks, so it's a little bit hard to do that. So I always think, should we modify the dose sooner rather than thinking about letting it go a little bit longer when we may have to hold a dose? So that's one of the things in my mind. And we've been really successful at dropping down the dose, even in patients who have pretty severe neuropathy when they start treatment.

Ms. Goodrich: How severe is severe enough to reduce doses? So this is a grade 3, because he is having impact on his activities of daily living?

Ms. Rogers: So I really think that we should do it sooner, even around the higher end of grade 2. When it's just starting to affect their ability to do their usual activities, picking up things. It's interesting a 70 year old is worried about his being able to use his smartphone, but we are all different. But the importance of that – I had a patient who his main enjoyment in life was being able to fish, and when he stopped being able to cast his line because neuropathy, that strongly impacted his quality of life. And so we used that as our criteria. So the activities of daily living may be dependent upon the patient and what they consider important to them. But when they start telling you they're having trouble doing certain things, that's enough time to start thinking about at least dropping down the dose a little bit, see if we can keep them on treatment by modifying the dose that their neuropathy doesn't get too bad where they have to have their dose held altogether.

Ms. Goodrich: Right. So had this been grade 4, what would the decisions have been then?

Ms. Rogers: Probably stop treatment altogether to take out the BV and potentially even the vinblastine, because that also can affect the neuropathy. I think then you're thinking about what other options do I have, because now you're left with potentially two drugs instead of four.

Ms. Goodrich: Right. Right. And so in this regimen, this BV plus AVD, what other side effects are you thinking about when you're seeing these patients?

Ms. Rogers: So you have to think about their counts again, and so I think this is one of the things that we have to really make sure nurses are well educated about, because when we think about all we've harped on them about ABVD, we continue on treatment, we continue on treatment, we don't care what their counts are. In this study, when they started off using this combination, they didn't give growth factor, but what they found was patients did get significant neutropenic fever and so that did impact patients and so now that's part of the recommendation is to start patients on growth factor, and that has been able to

prevent patients who are on BV plus AVD from getting the significant neutropenic fever. So it's a little different between the two combinations.

Ms. Goodrich: Yes, yes. That's a great point, Barb. Is there anything else that you're thinking that we need to cover with BV AVD?

Ms. Rogers: Not that's different than the ABVD, except obviously because you're thinking of doxorubicin and cardiac toxicity and if there's any issues with administration if they don't have a central access. But really the key ones that are different for these two are what we do with the counts and watching the neuropathy.

Ms. Goodrich: Right, and then fortunately with this patient we're not as concerned about the worsening his pulmonary status. Thank goodness we finally have a better option for those patients.

Ms. Rogers: Yes.

Ms. Goodrich: Okay. Although hopefully he's quit smoking. Alright, so our next case is brentuximab vedotin in relapsed/refractory classical Hodgkin lymphoma. So this is a 30 year old who was diagnosed with stage IV classical Hodgkin. He received ABVD. He relapsed a little over a year later. He received salvage therapy with ICE, and he underwent autologous stem cell transplant. He was offered a post-transplant brentuximab vedotin, but due to his need to return to work and get back to his life—a young guy with kids—he just didn't want to put in that time in the clinic, which is certainly understandable. He declined the post-transplant brentuximab vedotin, recovered completely, comes back for this 2-year post-transplant visit, and he's got new axillary adenopathy. His CT shows that he's got adenopathy in lots of places. The biopsies confirm that he has relapsed classical Hodgkin's, and so because he was familiar with brentuximab vedotin from his post-transplant offering, and at that time there were discussions that happened about if the disease comes back, that was always still an option. And he decided to go with BV post his relapse.

Ms. Goodrich: So Barb, what are you teaching this guy and what are you worried about and what are the red flags for this very heavily pretreated patient?

Ms. Rogers: In my mind, I still go back to neuropath, because a lot of patients post-transplant where they may not exhibit significant symptoms of neuropathy, I've seen a number of patients who kind of develop neuropathy a little bit faster than what we would expect maybe with other combinations who didn't go to transplant, so I'm really careful to watch their level of neuropathy during this. Although again, trying to keep the treatment on schedule because we want to get the most benefit as possible since he's a young guy with relapsed disease. And obviously though watching his counts too because he may not have a lot of reserve in his bone marrow depending upon the quality of the graft that they were able to get from his autograft.

Ms. Goodrich: That's a perfect segue because he arrives in cycle 3, and his platelet count is 41,000, which is a grade 3 thrombocytopenia. So what are you going to do now for this guy?

Ms. Rogers: So we probably are going to have to delay his treatment or potentially start with reducing the dose and watch him very carefully. It could potentially be that that graft wasn't as good as it could've been, and so it may just be, even though they may have gotten a good response and he recovered well following the transplant. Now we're giving additional insult to that bone marrow, and so it might just be a little more sensitive to what we would see with someone who hadn't had a transplant before. And so the options are still the same: a delay or hold the dose.

Ms. Goodrich: Right. And if this had been grade 4 thrombocytopenia, which is a platelet count of less than 25,000, how would you be thinking about this differently?

Ms. Rogers: Well, potentially obviously, it went by transfusion, but again it comes down to is this because of the graft or we may need to do a bone marrow biopsy to see does he now have disease in his bone marrow? Because you have to think about – and maybe he's not responding to treatment. I always wonder, is that potentially going on?

Ms. Goodrich: Right, and then really thinking about monitoring these patients very closely who are pretreated. And then in terms of bleeding precautions, signs or symptoms, you want to talk about that?

Ms. Rogers: Obviously, patients have to be forewarned about when their counts are low, and I usually pay attention mostly when it's below, really, around 25,000, provided that they're not doing something that potentially puts them at risk like – since it is winter here, patients going on sleds. Or I had a patient who had a platelet count of 15,000 who called to tell me that he actually rode his motorcycle home from the hospital that day when he had his labs drawn. So those are the things that obviously we have to make sure they understand, when your counts are low, you can't do those things and making sure they understand those when they're really low, which usually is between 10 to 15,000. Below that level, we then also think about not using a straight razor and just anything that potentially has a sharp edge to it. No invasive procedures, just always thinking about what things they may become under risk for.

Ms. Goodrich: Yes. And no going to the dentist. That's always a big one.

Ms. Rogers: Oh yeah.

Ms. Goodrich: Everyone wants to get their teeth cleaned. So, well, great, Barb. Thank you so much. Our PEARLs here today, our takeaways, are that ABVD remains the gold standard for initial therapy for the majority of classical Hodgkin lymphoma patients. The things to remember with ABVD are treating even when patients

are neutropenic, generally not using a lot of growth factors or prophylactic anti-infectives.

Ms. Goodrich: Brentuximab vedotin is an important option in relapsed/refractory classical Hodgkin as well as maintenance therapy post-autologous stem cell transplant. And then most recently, brentuximab vedotin has moved into frontline treatment with AVD replacing the bleomycin and reducing that risk for pulmonary toxicity. Certainly with brentuximab vedotin, the most common side effect is peripheral neuropathy, which is really best managed with a diligent baseline assessment as well as ongoing assessment and dose reducing to optimize outcomes and keep patients on therapy as long as possible.

Ms. Goodrich: And although we have a growing toolbox of drugs for these patients, it's not endless. Side effects are definitely expected and common and real with all of these therapies. And expecting them, preventing them, being on them, managing them aggressively are critical to assuring our patients have the best outcome.

Ms. Goodrich: And I thank all of you for joining us today. And thank you, Barb, for this great discussion.

Ms. Rogers: My pleasure.