EVOLVING STRATEGIES TO MANAGE TREATMENT-RELATED ADVERSE EVENTS FOR PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA

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INTRODUCER Good evening, everyone. My name is Denice Economou, and welcome to our CE-certified symposium on Evolving Strategies to Manage Treatment-Related Events for Patients With Classical Hodgkin Lymphoma.

The symposium is certified by the Annenberg Center for Health Sciences at Eisenhower, and to claim your credit, please follow the instructions on the sheet you received this evening. If you didn't receive a sheet, please let one of us know, and we'll make sure the staff member will provide you one.

We have two wonderful speakers for you tonight. Ms. Amy Goodrich is a nurse practitioner in the Hematologic Malignancies Program and research nursing manager at the Johns Hopkins Kimmel Cancer Center in Baltimore, Maryland. Ms. Goodrich manages patients with various types of hematologic malignancies, concentrating on the lymphomas. She also manages the Cancer Center's research nurses and is extremely involved in research operations.

Dr. Jose Sandoval is an assistant member of Moffitt Malignant Hematology and Cellular Therapy at Memorial Healthcare System. He is a researcher whose focus is in prognostic and therapeutic aspects of lymphoid malignancies, with an emphasis in CLL and mantle cell lymphoma. His professional interests are in patient-focused care of all hematologic

malignancies, with a special emphasis in both indolent and aggressive lymphoid tumors. Please welcome Ms. Goodrich and Dr. Sandoval. Thank you.

DR. SANDOVAL Thank you.

MS. GOODRICH Thank you for joining us this evening. I know it's been a long day. Everyone's been up a long time now. Just so you know, the restrooms are this way, out this way. We're here to talk about Hodgkin lymphoma. Learning objectives – we're going to talk about adverse events, we're going to talk about emerging therapies, we're going to talk about best practices regarding adverse events, we're going to talk about checkpoint inhibitors and immunotherapies, as well as patient education.

DR. SANDOVAL Thank you, Amy, and thank you very much, JADPRO, for the invitation, and thank you for all you guys being here. And welcome to South Florida, the land of Cuban coffee and accents, so I hope you have a fun time here.

So, I'm going to start here with Hodgkin lymphoma – basic epidemiology of the disease. Hodgkin lymphoma, just for you guys to know, is one of my favorite diseases, one of my favorite patients to be seen, because it's very simple in a way. We are, nowadays, with the current treatments, we're curing about 70 plus, 80% or more of these patients, so it's one of the refreshing times of the day. However, you just heard me say around 80, 75, 80%, so there's still a fraction of patients who are not cured and actually are benefiting from the new advances of new medications that we are developing. So anyhow, let's get started here.

It's not a very common disease. Like you see it is around, like new cases in the U.S. in 2018, it would be about 8,500, and the deaths, it's around a little bit more than a thousand patients per year this year, so it's a very curable malignancy. Still, we lose some of our patients to this tumor. The age of diagnosis – it has a bimodal age. The median age at presentation is actually around 38 years old, but we have a first peak that is in the 30s, and then a second peak that is the most – actually, I would say is the most challenging population, that is a second peak around the 70s. Those are the patients with the more aggressive disease, if you may.

In general, the 5-year overall survival, by the year 2016, was more than 80%. Risk factors – they are not very well established, with a lot of hematologic malignancies, they have – socioeconomic factors have been described. Familial risks, certainly there's a cluster of families with a history of Hodgkin lymphoma that have a common predisposition and certainly, if the patient has a family member with a history of Hodgkin lymphoma, the risk increases by two- or three-fold sometimes.

EBB, Epstein-Barr virus, very important. It is related with some Hodgkin lymphomas, especially one that is called lymphocyte-rich. We see a lot of that around here in the Caribbean and Central and South America. Thirty to 40% in Europe, North America, and up in the 80% Central and South America, as you see here. Sometimes related to autoimmune disorders, tobacco use, not very strict for but important, HIV patients on antiretroviral therapy. Actually, this is not

a disease marker for AIDS. These patients actually develop more lymphoma when they have a good number of CD4 count.

It has a lot of things to do also with the bone marrow microenvironment that I'm not going to touch base on a lot of that right now. And also, two main important genetic drivers in this disease is the NF-kappa-beta pathway and the JAK-STAT pathway that is actually in the gene. We're going to talk about that a little bit later, the amplicon that is right next to this JAK-STAT pathway is our gene for PD-L1, PD-L2 as well. That is very important in this disease.

Again, 0.5% of all new cancers here in the States. A little bit more common in males than in females. We talked about bimodal age distribution. And the survival –it's quite a bit. So it is very important also the survivorship care of those patients – that's one of the main messages of our meeting today as well.

Again, the most common Hodgkin lymphoma –by the WHO, there are five types of Hodgkin lymphoma, but the most common one is what we call classical Hodgkin lymphoma. The other small portion that we are not going to talk about in this meeting is the one that we call nodular lymphocyte predominant, that I don't even know what is in this group. This looks more like a low-grade lymphoma, but that's sort of like a different category.

Classical Hodgkin lymphoma – again, most common one, four main types. One, nodular – this is how we see the cells of Hodgkin lymphoma – how we see the disease under the microscope. This is a histologic classification. Most common one, nodular sclerosing classical Hodgkin lymphoma. This is the most common one in younger patients. The mixed cellularity one usually has a

characteristic that it usually involves a little more the liver, and it's also more common in older folks as well, the lymphocyte-rich classical Hodgkin lymphoma, and that is also more related to EBB, and the most rare category is the lymphocyte-depleted classical Hodgkin lymphoma, most common in HIV patients.

A little bit about the staging of the disease. Again, from Ann Arbor staging, not with a modification of the Lugano classification, so – mainly Hodgkin is divided into a limited-stage disease and an advanced-stage disease. Limited-stage disease, stage I and II. Advanced, stage III and IV, and on those, especially important for limited-stage disease, we have unfavorable risk and favorable risk. Talking about unfavorable risk for limited stage, you can see bulky disease.

For your information, bulky disease in most publications is referred to as diseases or masses that are more than 10 cm, in Hodgkin lymphoma. Like you see here, large mediastinal adenopathies that take more than one-third of the internal transverse diameter of the thorax. Also important – higher risk is when they have extranodal involvement and also when they have more than three, especially four or more nodal sites of disease involvement. Most common site of extranodal involvement, now in the PET era, actually with a site from the – more common than the bone marrow is actually bone involvement, and then bone marrow.

As a tip, Hodgkin lymphoma very rarely involves the bone marrow. Other areas is the lung, liver, and muscle. The ESR, or erythrocyte sedimentation rate,

when it's elevated, especially more than 50 with no B symptoms, is a high-risk factor, or when you have B symptoms or constitutional symptoms, and when the ESR is more than 30. Here are the classic B symptoms for you guys to review. I'm not going to go through that one. I'm going to go to the next slide.

This is one of the most common prognostic scores that we use in Hodgkin lymphoma. That is called International Prognostic Score, or IPS. One thing that is important for the IPS: it is only validated for stage III and stage IV Hodgkin lymphoma. You can count, it's one point for each factor. There are eight different factors. Any zero is excellent. More than five factors, actually, is a very high-risk disease. But again, you can see the difference. You can see the spread out course. If you see the course from the publication, there are very nice Kaplan-Meier curves there, but even patients that are five or more – more than 40% of patients are considered cured by 5 years.

So, Amy, do you guys use this classification of this staging when you meet the patient initially?

MS. GOODRICH We do, yeah. We definitely do, because it gives patients – they think this is the good one, right? There is no good one. Right? But – you know, we do talk about these risk factors with patients so they understand where they sort of stand on our benchmarks.

DR. SANDOVAL Absolutely. And this is important also for a couple of new interventions that nowadays have been approved for the treatment of Hodgkin lymphoma in the first line that we will talk a little bit later. But also, something that I want to point out, these are very sort of like bedside

measurements that actually you can do. With a complete metabolic panel and with a physical exam, and a CBC and a physical exam, you can determine these factors of risk for patients. What we're missing here that are very important prognostically nowadays? PET scans, okay? PET scan is extremely important in Hodgkin lymphoma. So next slide here.

I'm going to start talking about first-line therapies of classical Hodgkin lymphoma. These are the usual –I would say the first one, first-line here, is the one you guys probably are very familiar with, that is ABVD. It's like my ABC. And usually, we use between two to six cycles, depending if it's early disease or advanced-stage disease. And the medication, A for doxorubicin. B for bleomycin, dreaded bleomycin, vinblastine, and dacarbazine. Probably dacarbazine is one of the only aside from – in the past, in stage IV melanoma, is probably one of the only malignancies that we use dacarbazine. The Stanford V – an old regimen. I actually have never used it myself. I was talking with Amy that I guess I'm too young to have used the Stanford V.

MS. GOODRICH I'm not too young, but –

DR. SANDOVAL But it's a very heavily treated – heavy uploaded treatment that the main thing about these is that it has a medication that is called mechlorethamine. It's very related to a lot of second cancers, and it's also related to infertility. And also these schema also has – embedded on the schema itself, radiation therapy. So that's one of the main different factors for this Stanford V.

BEACOPP is a German protocol. It is between two to six cycles, and we know it as BEACOPP or escalated BEACOPP. We will talk about it a little bit,

because it had very interesting results, but it's a very heavy chemotherapy regimen, related a little bit more than ABVD with secondary malignancies and so forth. I don't use it a lot. I have used it, but I don't use it a lot. But if you have used it, you'll see that it's not for everybody, okay? It's only for the very hard.

Involved site radiation, one of the things that I want to tell you guys is that radiation is very nonpopular here in the U.S., but I believe it's very, very, very important, especially for patients who have limited-stage disease, but especially males, and especially the things that are not around your chest or mediastinum. But otherwise, it's extremely important in my point of view.

And then brentuximab vedotin is one of the new kids on the block for front line, recently approved by the FDA, with a combination of AVD. We will talk maybe about it a little bit later. It's approved for stage III and stage IV disease and patients with IPS more than four. That's what I was telling you, that it's important in that sense. Brentuximab vedotin, we will talk about that medication a little bit later on. Doxorubicin, vinblastine, and dacarbazine. Just a tip for you guys – never ever, ever use brentuximab with bleomycin. That's what you don't ever see, because the pulmonary toxicity is prohibitive. Okay? That's why we don't use it in that regimen.

Next, back to you, Amy.

MS. GOODRICH Okay. So, ABVD. Who treats Hodgkin's patients in here? Okay, so most of you. So, you know ABVD, right? You know the schedule, it's every 2 weeks. Day 1 and 15, but all of these patients, any patient you have with lymphoma really needs a good workup initially. Certainly all of the HIV and

hepatitis testing applies to all patients. For these folks, again, that bimodal distribution, fertility considerations are very important for that first peak of folks that you're going to see. Not so much for the 65 year old, although it may be. And then, as you've seen, all of these regimens have an anthracycline, so you need to understand people's cardiac function, and for the regimens that use bleomycin, certainly getting PFTs with diffusion information is important. There are some dose adjustments here for creatinine clearance. Or for creatinine clearance, you're going to stop the bleo if there's any suspicion of lung toxicity, and then you're going to adjust for liver function studies.

And then the dacarbazine, you guys know this, it's very irritating. Most patients that I treat don't need lines, but occasionally you get somebody who just can't tolerate it. So, adverse events, again, you're seeing these patients. Lots of nausea with this regimen, and I don't know if you're seeing this, but in my younger patients, they tend to have a lot of anticipatory nausea and vomiting, which lorazepam works beautifully for, but in sort of a unique issue with them, and not so much the older folks. Infusion reactions, we don't give test doses of bleomycin. Does anybody give a test dose? Do you have a test dose, Jose?

DR. SANDOVAL Yes.

MS. GOODRICH You do?

DR. SANDOVAL Still give it in the -

MS. GOODRICH Yeah, we don't do that. I guess that's a preference thing. Again, you guys are giving this regimen, so you know that many times they're coming in, they're neutropenic, they're due for their treatment, you treat

them, their counts come back up, and they have very little trouble with infections or neutropenic fevers, which is very nice.

Again, don't give oxygen with bleomycin. Hopefully everyone knows this. And when we talked about the brentuximab with AVD, that's a great option for your patients who come in on oxygen for some reason. Usually the older folks. We've got lots of them who come in with their oxygen tanks. That's a great regimen for those folks to avoid the bleomycin. So, you're looking for cough and these can start out very subtly, just cough, a little dyspnea on exertion. Steroids usually take care of this, but you're going to look at PFTs and chest scanning, and then you're going to get rid of the bleomycin if there's any question that it is bleo toxicity.

So nausea and vomiting, again highly emetogenic regimen. You're going to do the right thing. I'm sure you've all got a cookie cutter regimen of antiemetics that you're using. But it's not uncommon for these people to have to get stepped up or need to get some lorazepam added for their anticipatory nausea and vomiting. Hydration, hydration, hydration. Patients always want to know what they can do. I say, wash your hands and hydrate. Right? That's the two things they have control over, and really, you're just trying to make sure they're not dehydrated.

And then, the counts that go up and down, like I said, very little neutropenic fever. They can be anemic and thrombocytopenic. Very few of these people are going to end up needing transfusions. Occasionally, you have a one-off, but they're rare. And you're just going to be watching their counts, and you're

going to be doing the right thing and you need to educate them on what they're looking for, and you need to be doing your part here.

The other thing, and this is more for older folks, these vitamin deficiencies – don't ever forget about those, because that can be a very common cause of anemia in our patients. And then, same thing for thrombocytopenia. We get lax with this sometimes, but the men need to—and the women—get rid of your razor. Just those practical sorts of things.

DR. SANDOVAL Before I advance, I want just to see a couple of arms. Who of you guys who treat patients with ABVD always include growth factors? That protocol? Raise your hand. Okay, not a lot. So, another tip that I want to give you guys, that the main – the secret ingredient for ABVD and the cure for lymphoma is two-fold. One, the biology of Hodgkin, of course, that I would gladly – we can treat and we can cure it in a large portion of our patients. But also the treatment intensity as well. Okay, so fair enough, it's completely normal, and actually we should encourage not to use a lot of growth factors in these patients, especially if you're using the ABVD, okay? Bleomycin and growth factors, like Amy just pointed out, it's been related to more pulmonary toxicity, and also we really don't need to use growth factors in these patients, just as such. Even in patients that are neutropenic, we should go ahead and treat them, regardless of those counts. However, you should use growth factors if the patient has any sort of febrile neutropenia. That's a different story. I just want to make that clear.

MS. GOODRICH Yeah.

DR. SANDOVAL Okay. German Hodgkin lymphoma study group HD10 is a very important trial. You don't have to remember the name of the trial, but it was a very large phase 3 trial in Germany, were like the fine one of our algorithms and were standards of care for early-stage Hodgkin lymphoma. They compare all those different groups of ABVD, two cycles versus four cycles, but those involve field radiation therapy. And I can tell you the gist of it is that patients with good prognostic early-stage Hodgkin lymphoma had the same 5-year overall survival when they received two cycles of ABVD versus four cycles of ABVD, and we incorporate 20 Gy of radiation versus 30 Gy of radiation. That's the good prognostic patients.

If, however, you have patients with a bulky mass, or who have unfavorable disease that is very localized, you can go ahead and do four cycles of ABVD and radiation. Here in the United States, I don't think we're going to talk about that right now. What we usually tend to do nowadays, especially with PET-guided therapy, if you have bad prognostic early disease with bad prognostic features, we can use between four to six cycles plus or minus radiation therapy for bulky masses, or if you have localized disease with good prognostic features, we follow—I believe we're going to talk about it a little bit later—but three cycles. You see the PET-negative – one more cycle of radiation. Do you understand? So, a little bit different, the focus, when you're here than in Europe. But remember, if you want to use for an early-stage Hodgkin patient with good prognostic features, only two cycles of ABVD plus a low-dose radiation, it works really, really well, and you can see the table there.

I'm just going to breeze through it. Stanford V, I don't know if you guys – somebody still uses it, it's a very, I would put it, challenging regimen, and believe me, it's very hard for the fertility of our young patients. Okay? So, I mean, we don't use it in our institutions. I don't know at Hopkins, they use it, Amy?

MS. GOODRICH No.

DR. SANDOVAL BEACOPP. Very important for us here in the United States, very important salvage regimen. I can tell you in Germany they use it quite a bit. They have two different sort of flavors of BEACOPP. One that is escalated BEACOPP, and the other one is the standard BEACOPP. The difference is on the doses of the etoposide, the doxorubicin, and the cyclophosphamide. Okay? So, in patients that are high – well, sort of the scenarios that I have used this protocol is when patients – for example, high-risk patients with stage III or stage IV disease, they undergo two cycles of ABVD, and they still have very clear positive PET scans, okay? I don't know if you guys remember, the way we quantify these PET scans are something that is called Deauville score or DS score, from zero all the way to five. So, if we have a score of four or five after the two cycles of ABVD, so the patient is clearly positive from the PET scan point of view, sometimes one of the things that you can do is to escalate therapy with BEACOPP. The escalated or standard BEACOPP.

I only use it—like you see in the left column, to my left column—I only use it in patients that are young and they have good performance status. It's also a hard therapy to use, and do not use it in patients with immunosuppression status,

like HIV patients. It was not approved and not validated in that context. Do you guys usually use a lot of that protocol?

MS. GOODRICH We use it when we have to, right? Because you can see this treatment-related mortality is really quite startling for your older folks, so these are patients, again, younger, and when you give two cycles of ABVD and the PET is still positive, you don't give six cycles of BEACOPP, you give four, so you get away with a little less toxicity than is reflected on this slide. But only when you have to, because it is not an easy regimen.

DR. SANDOVAL And also, yes, last point about this slide, these patients also have a little bit of longer-term toxicities, like second malignancies, myelodysplastic syndrome, CML, and so forth, and actually the procarbazine has been related to other malignancies, things like we didn't even expect, but there are very large Dutch registries have been related to, for example, stomach cancer, lung cancer, and so forth. So it's very effective, but it has its own implications, yes.

So continuing to talk about first-line therapies for classical Hodgkin lymphoma. The majority of classical Hodgkin patients will be cured with initial therapy, 80% or so. However, we still have that 15 to 20% of folks that are sort of like the – those diseases that are the bad players. All regimens are toxic, and we need to respect them, and they have potential for significant side effects during and after therapy, and ongoing improvements in the prophylaxis and treatment of therapy-induced side effects may – many will be guideline driven. The best thing

in a lot of these side effects is prevention, okay? Prevention, prevention. Choose the right patient with the right comorbidities to give XYZ treatment.

And all you guys, nurse practitioners or advanced practitioners, they play a very important role in educating the patients and families, especially on the first time that you see the patient, diligent monitoring of all the side effects and symptoms, effective management of side effects, and assuring optimal treatment outcomes of these patients.

MS. GOODRICH Yeah. So, these are commonly used second-line therapies, and in the bold are the ones that are most common. So DHAP, ESHAP, BeGEV, you know, other gemcitabine-based regimens, ICE, is very common. Brentuximab vedotin plus chemotherapy, autotransplant comes in here as well after second line, and then allo is typically third line and beyond. So the general principles for relapsed/refractory Hodgkin – so you are considering the pattern of relapse, what drugs did you use before, really how long was that first remission? That is really a very telling, you know, timeline for patients. Certainly, those who have primary refractory disease have a very dismal prognosis, so allo stem cell can be considered after auto, if you can get somebody into remission third line or later. BV is a treatment option if auto has failed or if two prior multiagent regimens have failed. So again, nivolumab and pembro as well are options for patients after second line, third line, and beyond. So, those are our key points here. Brentuximab. Great drug.

DR. SANDOVAL Let's talk about this molecule that is very, very interesting. I don't know if you agree, Amy. So, brentuximab vedotin is one of the

first, it's not the first, but one of the first of this class of antibody-drug conjugates. Definitely the first one in our realm of malignant hematology. It is an antibody that targets CD30 that is expressed on these classical Hodgkin lymphoma cells that are called the Reed-Sternberg cells. It targets CD30, that is a member of the TNF family, and it is expressed on all the Hodgkin cells. And it combines a potent anti-tubulin agent that is called monomethyl auristatin E with CD30 can make monoclonal antibodies. So mainly, you see here to my right side of the slide, the antibody has a payload, like generally four-part – four molecules of this MMAE. Anti-microtubulin agent is say like vincristine or vinblastine, but in a very miniature size. And it's attached by a linker. The linker is the key here. Because this company works a lot of times in trying to make the good linker for that toxic molecule to be attached and not disseminate in the body and cause extra toxicity. And then when it binds to the CD30 receptor on these Hodgkin lymphoma cells, it gets internalized in the cell through the lysosome, the lysosome goes into a vesicle, then it attaches to a lysosome. The lysosome gets rid of the linker, and the monomethyl auristatin gets released into the cell and attacks the tubulin complex.

One thing that I will tell you is that, you have to remember that inside, let's say, a lymph node of a Hodgkin lymphoma patient, there's only about 1% or less of these Reed-Sternberg cells. It's all a milieu of immune cells and fibroblasts, and a lot of different components, but only about 1% or less actually are these tumoral cells. So this therapy also has some other sort of effects around the microenvironment of the Hodgkin tumor as well. So very interesting component.

MS. GOODRICH Sure. So brentuximab, it's been around now since 2011. The current indications are failure – after failure of auto, so in transplant-ineligible patients who are heavily pretreated and post-auto in people that are at high risk for relapse after transplant, and so you see the dosing 1.8 mcg/kg. There's some dose reductions, and it's contraindicated concomitantly with bleomycin, which has already been mentioned.

So when you look at side effects of brentuximab, it's all about counts, right? But then look at the second one down. So, peripheral neuropathy, if you add the sensory plus the motor, that's 60%. So 60% of your patients are likely to develop some degree of peripheral neuropathy. Fortunately, only 13% will be severe, but that is definitely the most common side effect of BV, and then the fatigue issue is real, pyrexia, nausea, diarrhea, bowel changes. You know, none of this is out of the realm of what we're used to, but that's a really high peripheral neuropathy rate.

In looking at BV after transplant – so this is a study that looked at folks who were high risk for progression post-auto, and they were randomized to either get BV maintenance or placebo. And so, as you can see from this slide, the progression-free survival is improved for patients who got BV, but the overall survival, there's no difference. So, you really need to choose carefully which patients – these have to be your really most high-risk patients that you're worried about relapsing. These can't be people who have baseline peripheral neuropathy. But, you know, they – go ahead, Jose, I know you wanted to make some comments here, but you know, it's kind of a hard sell to patients, so you

have to spin it just the right way for your most high-risk patients. Because they get done with that auto, and they just want to get on with their life, right? They don't want to be coming back and getting strapped down to IVs again in your clinics, even though they like all of you, right?

DR. SANDOVAL Especially young adults, right?

MS. GOODRICH Yes.

DR. SANDOVAL And they don't want to be bothered.

MS. GOODRICH Yeah.

DR. SANDOVAL Anyways, yeah. A couple of points about – this trial is a famous trial in our field. It's called the AETHERA trial. Initially published here in 2015, and yes, indeed, it showed a PFS improvement for 16 doses or 1 year of brentuximab vedotin maintenance after transplant for – on the criteria for how to choose the patients for this, their three main criteria – one of them, early relapse, meaning that the Hodgkin lymphoma came 12 months or less after the patient was in remission. The other one is primary refractory Hodgkin lymphoma, and the third one is a relapse with extranodal disease, okay? You have to have one of those criteria to be included in the trial. Actually, the update of this trial was just published last month in – no, actually early this month in *Blood*, in October in *Blood*, and it still shows just a benefit of PFS. So, we did therapies that we have right now for Hodgkin lymphoma. I don't think we're ever, ever going to see an improvement in overall survival in this population.

So, like Amy was saying, just to make the point, I really choose the patients that I want to put on this treatment. There are some other centers that

are more liberal, and they say, like, I will put almost every single patient on this treatment. But really, the people who it works the most is in patients that have one of those criteria, okay? So again, people who relapse less than 12 months after they were in initial remission, patients who relapse with extranodal disease, and patients who actually relapse – who have primary refractory disease. And if you go to the nitty gritty of the data, actually the people who got the best of all are the patients who have two or more factors – two or more of these risk factors. And it has certainly side effects, right? Like peripheral neuropathy, a lot of my patients cannot finish this treatment because especially the peripheral neuropathy is involved in that.

MS. GOODRICH Okay. So peripheral neuropathy, we all know about peripheral neuropathy. It is very common in our Hodgkin patients because of the neurotoxic drugs that we're giving them. It's most commonly sensory, and as you all know, this can last for days, months, years, and people can be left with peripheral neuropathy permanently. I think the hard part about these people with Hodgkin's, like we keep talking about, this is a curable disease, and so, you know, pushing through and giving full dose and dose density and all of that really is important, so you have to be assessing very carefully and peeling off and dose reducing very carefully for these patients, because we know it has a really horrible impact on their quality of life. And so, the best thing we can do is assess and dose modify appropriately.

So, management of chemotherapy-induced peripheral neuropathy – so, prevention. When somebody cracks the nut on this one, we are all in for a treat,

right? But think of our patients too. We, meaning collectively, are all in for a treat. There have been countless things studied trying to prevent peripheral neuropathy. Nothing has worked, and so there is no prevention for peripheral neuropathy other than early detection and appropriate management from there. I'm really looking forward to somebody fixing that.

When we look at third line and beyond, again bolding the common ones – so, brentuximab – bendamustine comes to the scene, and this is where we get our checkpoint inhibitors, but you can also see, again, there's lenalidomide there, everolimus, there are some different drugs that come into the scene third line and beyond. And, you know, when I started in oncology, nobody got to third line and beyond, and now we have a whole buffet of options for these patients, which is really great.

DR. SANDOVAL Okay, so, you know, coming to the third line and coming soon, second line and maybe even, you know, first line, the microenvironment of Hodgkin lymphoma is a rich microenvironment for the development of new therapeutic options for our patients. Like, tailoring the therapy to the tumor biology of the patient may improve outcomes. That is – I wouldn't say it's wishful thinking. Actually, it's a reality that is probably going to come sooner rather than later. You see, that's a very busy picture there, but it's a very nice review paper, actually, of all the potential pathways that we could target in these patients. Especially the ones that we are very interested on and one that we are already exploring is that pathway here –for example, you direct your attention to the PDL1/PD1 pathway. These Reed-Sternberg cells are enriched

with expression of this PDL1/PDL2 receptors. So, it was a great, great story of translation of research that went to our patients that has been extremely successful.

Also, the JAK-STAT pathway, with our JAK-STAT inhibitors, that I think they are in their infancy at this moment in time, and a lot of other things that we can use – immunomodulators and so forth and so on. We're just going to concentrate right now on these checkpoint inhibitors that you guys that also treat solid tumors are very familiar with. But I can tell you one thing: the cancer that has the best response to checkpoint inhibitors is Hodgkin lymphoma.

But anyway, some other new agents that are coming soon to this realm and some of the ones that are pointed up here, actually we are already using, like, for example, brentuximab vedotin, that is an antibody-drug conjugate targeting CD30, nivolumab and pembrolizumab, PD1 inhibitors.

Okay, rituximab in Hodgkin lymphoma. Some of the Hodgkin lymphomas express CD20, that is – that were target for rituximab that is very common in low-grade and high-grade non-Hodgkin lymphomas, and people have used actually rituximab in Hodgkin lymphoma, but I can tell you, there's a recent randomized, phase 2 trial from MD Anderson that used ABVD with or without rituximab; they don't really work. So I wouldn't recommend it at this moment in time. However, you're going to see some other experts that they still will recommend for some patients this antibody.

Galiximab is an antibody in development in CD80. All the microenvironment-targeting therapies, lenalidomide, immunomodulator, of

course, you guys know, very famous in multiple myeloma, MDS, and other therapies. Also nowadays in relapsed/refractory diffuse large B cell lymphoma, has some activity in Hodgkin lymphoma, as usual between 20 to 30% of response rates, but it's definitely not a home run there.

HDAC, or histone deacetylase inhibitors, like panobinostat, they are also in development, but we don't have a lot of information right now. And other inhibitors of signal pathways, for example, mTOR inhibitors, everolimus, me myself, in my opinion, I believe those medications are dirty medications. They don't really target very well the pathway. They have some activity, around 30% of response rates in Hodgkin lymphoma, but not very effective. And Akt, MAP inhibitors, I really don't have a lot of information from that, because they're still in development in these malignancies per se.

MS. GOODRICH Okay. So, nivolumab – so, who treats solids too? Okay, good.

DR. SANDOVAL Wow.

MS. GOODRICH So, you guys – this is great. I don't treat solids. So this was all new to me. So, you guys have a serious – do you treat solids, Jose?

DR. SANDOVAL No.

MS. GOODRICH Okay, all right. So this is all new to us. But anyway, so nivolumab came to Hodgkin's in 2016. It's indicated for relapse or progression after auto- and post-transplant BV, or three lines or more that one should include in auto, but we all have patients who will never get to transplant that we can easily get this approved for as well. You guys know the dosing, because you're

giving this to your solids. Again, this is the phase 1 study that was done, 104 patients but only 23 of them had Hodgkin's. Actually, 20 had classical Hodgkin relapsed/refractory, 78% of them were post-auto, 78% were post-bendamustine, and look at that overall response rate: 87%. You don't see that in your solids, do you? Mmm-mmm. Nope.

So, at 7 years, five progressed, five went on to transplant, and 10 are still responding. They're still in remission. So, this really revolutionized the care of these patients who really 5 years ago, we had nothing for them. So, this has been great. This is Checkmate 205. Do you want to talk about this, Jose?

DR. SANDOVAL Checkmate 205, absolutely. I love this trial. You know, it's a phase 2 trial of nivolumab, sort of like a hammering in in the effectiveness of these treatments. These are patients, very heavily treated patients, certainly most of them treated after transplant, or after two or three lines of therapies, over response rates of almost 70% and CR rates of 16% and PR rates of 53%. You can see those nice curves explaining there. Of course, like a lot of our malignancies, the all-American way, the more is better, of course. If you have a better response, a CR response, these patients last longer on remission, of course.

However, you guys have definitely more experience than us – do you guys know how tricky it is sometimes to evaluate the response – in solid tumors, to evaluate the response to a checkpoint inhibitors? With images, especially with PET scans. So, we have to be very, very, very careful about the evaluation of these patients. It is less common, for example, in lung cancer or melanoma for

that matter, that this phenomenon of cell death progression – actually, we also see it in Hodgkin lymphoma. Especially, we see a lot of inflammation. These are very inflamed tumors, okay? So, we have to be very careful with that.

We sometimes actually continue, even though you – unless the patient has new lesions, of course – even if some of the previous lesions were growing or more hot, in a way, we sometimes continue. And there are some studies that you can continue this one in Hodgkin lymphomas, some other studies in solid tumors. So, extremely, extremely active treatment. And you see a median overall survival in this trial was not reaching 1-year overall survival 92% in very heavily treated patients.

In the Checkmate 205, main side effects are similar, actually, to the ones that you see with other PD1 inhibitors. Mainly, one of the ones that we don't realize sometimes is fatigue, okay? Patients complain of remission, doing absolutely great, but they feel fatigue. And obviously, not a lot of infusion reactions. Amy is going to talk about that in a minute. And there is not a lot of discontinuation because of adverse reactions. Only 17 patients, and they were actually because of immune-related side effects, 2% because of pneumonitis. We see that more often than colitis with the PD1 inhibitors. And autoimmune hepatitis, one patient.

Serious drug-related reactions, most of them were also – not most of them but 1% was pneumonitis and the other was infusion-related reactions, not that very common. Pneumonia, pleural effusion, and pyrexia.

MS. GOODRICH All right. So pembrolizumab – again, you guys are treating your solids. You know this. This came to Hodgkin's in the beginning of 2017. So, the spin here is that it's still for folks who have multiple relapsed disease, but then the pediatric angle comes in. This is approved for kids, for those of you who have crossed paths with pediatric oncology. The dosing is the same as what you're used to in your solids. And then if you look at overall response rate from this trial, 73% for those who had been transplanted, 64% for patients who couldn't get to transplant, had progressed after BV, and then for patients who had transplanted but had not gotten post-transplant BV, 70%. So, all of those numbers are really quite impressive. Complete response rates of about 22%, PRs of almost 50%. So, again, in a very heavily pretreated patient population, these are great numbers.

Again, treatment-related adverse events, this is really typical of what you're seeing in your solid tumor patients: thyroid dysfunction, fevers. Only a little less than 5% discontinued therapy because of adverse events. There were no treatment-related deaths. So, this is just a beautiful AE profile for this drug in this patient and has great, great, great efficacy.

And so, AE associated with immune checkpoint inhibition – so it's an augmented immune response driven by T-cell activation that creates all these autoimmune inflammatory states in various tissues, and I do like this slide, because, you know, these are all the systems you're looking at, and you're looking at that in all your solids, and `we're giving these drugs like water now, but this is new to us in heme malignancies, but so be it.

Infusion reactions – so, these are uncommon, about 10% of patients, but it seems like less than that. You guys know what to do. You do the right thing, you stop the drug. Try not to use steroids if you don't have to. Have emergency equipment available. So, you also know this, because you're giving this to your solids. And this is an iffy slide, but it still is applicable to the drugs that we're giving on Hodgkin's. So, these don't happen out of the gate. They can happen weeks and even months afterwards – rash, liver toxicity, colitis. You know, all of those things that we're looking for.

So, the treatment of severe and steroid-refractory immune-related adverse events – and this is really cookie cutter for your solid tumor patients, if you've got grade 3 or 4 toxicity, you're admitting folks, you're doing the right thing, you're hydrating them, you're giving them steroids, and then in the little – oh, I guess that's gold, I don't know – goldenrod color.

DR. SANDOVAL In South Florida, it's gold.

MS. GOODRICH Okay. So, depending on which adverse event folks are having, you can use different, a little different mix of these agents. And then, really the key is, they've all gotten steroids, they're all on pretty high-dose steroids, and you just have to taper them down slowly, and if people flare, you reescalate the steroids to try to get things under control again. And then hopefully, everybody's got mechanisms to do this and, you know, this is like old hat to people at this point. Do you want to talk about immune modulating?

DR. SANDOVAL Absolutely. Mechanism of actions of these immune-modulated medications, steroids, we're very, very, very familiar with steroids.

They have multiple, multiple effects on both our T cells and B cells. They're mainly lymphodepleting agents in a way. And also through phagocytes and K cells and macrophages, they work through inhibition of transcription, interleukins, reduction of synthesis of cytokines and inhibition of neutrophil apoptosis, and reduced macrophage function. Whoo, that's a mouthful. Well, we use a lot of steroids anyway, you know.

Infliximab is a tumor necrosis factor inhibitor, initially approved for rheumatological conditions, but it is one of our key agents where we're treating grade 3 or grade 4 immune side effects for these checkpoint inhibitors. One tip as well, the only one – and I should have made that a question, but you guys probably know this better than us for solid tumors, the only immune-related side effect that you should not use infliximab on is hepatitis, all right? That one you can use mycophenolate mofetil and whatnot. Then, that is the mechanism of action of mycophenolate mofetil, MMF as well, and it's a milieu nucleotide production inhibitor on lymphocytes, and tacrolimus and cyclosporine, they're calcineurin inhibitors. Very familiar with that on our committee for transplant. Limits transcription of IL-2 involving T-cell proliferation. Mainly the ones that we use for these side effects are steroids, anti-TNF inhibitors like infliximab, and in some cases of hepatitis, mycophenolate mofetil as well.

Okay, so keys to optimal management of patients with immune checkpoint inhibitors. Time to – instead of adverse events, they're usually delayed, so we have to be very cognizant and very vigilant of those side effects. I have a personal experience of a patient that came with colitis back when I was in Moffitt

working in the emergency department. A melanoma patient came with colitis, grade 3 colitis, after I believe it was 10 or 11 months after being on combo ipi/nivo. A little bit strange, but, you know, it can happen.

Education, education, education times three of healthcare team. Patients and caregivers, very important. Subtle symptoms may be the signs of initial presentation. The patients are at the very beginning in those clinical trials, there were some fatalities, because we didn't know about these side effects, unique side effects, so rapid and timely interventions have changed the natural history of these side effects. Steroids is the cornerstone for some intolerable grade 3 side effects and any grade 3 or 4. For the grade 2s, you can start with oral steroids, of course, prednisone, and grade 3 and 4s, usually IVs, methylprednisolone and so forth, and slow taper of steroids would be 4 to 6 weeks of steroid taper.

Reinitiation of treatment may be possible, especially when you use PD1 inhibitors. You know, EP is a little bit more difficult, but especially with PD1 inhibitors, especially when the patients have grade 2, sometimes grade 3, but especially grade 2, you can reinitiate this one.

Let me see. One thing that I want to mention before I go back to Amy on this is that, especially in patients with colitis, it's not that common with PD1 inhibitors, more it is common with ipilimumab. But remember, you're entitled to have multiple things, okay? So when patients come at the very beginning, it's not right away steroids, okay? Then you have a megacolon or C. diff, and you know, you're done. So, remember, work up the patient. Okay? Some people are advocating sometimes even for sigmoidoscopies in these patients, because they

have found some features of that. For example, patients with ulcers on the sigmoid, sometimes they don't respond as well to steroids, and then you go to infliximab. There are some little pearls there, but remember, we need to see this patient as a whole, not just a patient getting a checkpoint inhibitor.

MS. GOODRICH And so my pearl here is that, when you have these young folks – because this reminds me of a patient of mine, a 20-something-year-old. He was on a trial getting ipi and nivo, and he got a terrible rash, and so we put him on steroids, stopped the ipi, and then he was just on nivo. He stayed on the study, just on nivo. He came in several cycles later, saying, "I have really bad diarrhea. And I just took those leftover steroids, and it all went away." Like, oh my gosh. And now his wife is pregnant too. So anyway –

DR. SANDOVAL Side effect of the steroids.

MS. GOODRICH He's the patient from, you know. So, pregnancy. So, again, these are young folks. They should not be getting pregnant, men or women should not be – they should all be using birth control. Make sure you're screening your young patients. I know we're all –we're used to older folks, but those younger patients – you really do need to think about them a little differently.

So, checkpoint inhibitors and allo transplant. Who does allos here? Okay, so a smaller group. So, there is this phenomenon now that is coming forth of patients who get these checkpoint inhibitors with Hodgkin's who get into remission to get to allo, which is a great thing. But there is an increased incidence of toxicity-related deaths during allo transplant, and what they typically are hyperacute GVHD, severe acute GVHD, the steroid requiring febrile

syndrome, hepatic VOD, which we really see very little of, so when that happens, it's eye-catching. And really other odd immune-mediated adverse reactions.

So, we're all grappling with how much of a washout is appropriate for these patients. The problem is—and Jose and I were talking about this—the problem is, these patients are usually third- or fourth- or fifth- or sixth-line therapy, and so you don't want to give them a huge gap, but you don't want to commit them to any of these really life-threatening side effects of transplant. So more will come on that, and those of you who are referring these patients to transplant, you really need to be aware of where this falls out so that you're doing your timing appropriately with your transplant center.

So key takeaways here, second-line and beyond therapy, we now have options, right? We never used to have options. So, we can get people into remission and get them to allo transplant, lots of trials, more patients on lots and lots of therapy. So again, all of you in the room, continuing to educate. This is really where shared decision making is critical, right? Because out of the gate, there's not a lot of discussion about shared decision making or – because there really aren't buffets of options initially, but once you get to this point, you know, you really need to be involving your patient so they can choose which therapy they think is going to work best for their lives. Looking for side effects and getting on toxicity pretty quickly.

So we're going to do some case studies here now. This is a 25-year-old female with newly diagnosed favorable risk classical Hodgkin's. So, you're thinking about her, and this is not in any specific order, but you're thinking about

fertility, right? She's 25. She's got early stage, and so we talked about radiation being a key part of the treatment of early-stage patients. So you're worried about breast radiation, you're worried about pulmonary toxicity. This is somebody who is hopefully going to live a normal lifespan. You're worried about long-term toxicities, and then this whole psychosocial thing for these folks who are young. You know, they're in college, they've just finished college, they've gotten their first job, maybe they're starting families. This is something that we don't see every day in our clinical areas.

So, fertility. The 5-year survival rate, like we talked about, is 85%. Very few females will have premature ovarian insufficiency, which is early menopause, from ABVD. About 10% of males will not have a normal sperm count a year out, so this is not a horrendous regimen for fertility. The problem is, we don't know who is going to relapse, or who's going to be refractory, right? So that's the problem here. Once they get to transplant, the rate of fertility dysfunction gets very high. Abdominal radiation for females – you know, zapping ovaries, and the same for men with testicular radiation – and really, why do we care? So there are big social and psychosocial impacts for people. This really impacts their quality of life.

So, what are options? So, for women, you can put them on birth control to try to shut that factory down a little bit while they're getting chemo. You can harvest eggs, you can do embryo cryopreservation. You can do ovarian tissue cryopreservation. The problem is, this takes time. And other than our first option there, they're invasive, right? So, you don't really have a lot of time with these

people, unless they're very, very early stage. They usually need to get through a cycle or two to get all this stuff done. You may or may not have time to do it.

With men, sperm banking. It's easy, you know, you all have a mechanism to get sperm banking done. And that's, you know, that can be done in a matter of days. But there is a lot of research going into pre-puberty boys and trying to figure out how to preserve their fertility, because there are not good options for those – unless you're in pediatrics, you don't see them.

So, what do you need to do? You need to educate. So, the risk is low, but all females should be referred. Hopefully you have a GYN that you work with who likes to see these patients. I mean, there are careers to be made in these areas for sure. Lots of papers to be written. If your young woman is getting ABVD, they're probably not going to do anything. Cryopreservation is considered if it's a much higher risk, the chemo has a much higher risk of premature ovarian insufficiency. Anybody who is going into transplant, hopefully they've had that discussion before and it's all taken care of, but sometimes you get people who come to you and no one's ever spoken to them about it. And all males should be offered sperm banking.

Pulmonary toxicity. So this is a big deal in Hodgkin's because of bleomycin. It can happen early, it can happen late. It's pulmonary fibrosis, and those are the drugs – the bleomycin is the biggest offender. But certainly the more therapy folks have had, the higher the incidence of pulmonary fibrosis. VOD, pulmonary VOD, again, very common. Commonly seen with bleomycin and busulfan, which would be more of your transplant patients. Pleural effusions with

busulfan and thoracic radiation, we certainly have a lot of these folks getting their chests radiated. And then bronchiolitis obliterans. None of these are good to have, but they happen. You need to be looking for them, you need to dose reduce, you're typically going to put them on steroids. You're going to do imaging, you're going to work this up. Hopefully, you've got good pulmonary colleagues that are going to help you too.

Second malignancies. So, these numbers are big. They were sort of shocking to me, so for patients with a history of Hodgkin lymphoma, and remember, that first slide we showed you, there were almost 200,000 Hodgkin's survivors in this country. They have a much higher risk of second malignancy than the general population. One in five of Hodgkin's survivors will develop a second cancer in the first 20 years after their treatment. The alkylators are the biggest risk for acute leukemia and MDS. And of course, the older you are, the more heavily pretreated you are, heavily treated you are, but within radiation fields, and this is where the young women come in, breast radiation below 30 is a big red flag. But patients can develop – anybody who's gotten radiation to their chest can develop lung cancer, thyroid cancer, stomach cancer, sarcomas. So this is really a big deal for these patients, and they need to know about this for long-term health planning.

So follow-up care. They should be avoiding smoke at all levels. Women who do get chest radiation before 30, and really in my shop, there are radiation oncologists essentially will not do it. But you can find somebody who'll do anything, right? So, women treated with chest radiation before the age of 30

should get early breast cancer screening. And this is really important for these women to know. So, 5 to 8 years post-radiation or age 25, breast exams, mammograms, and yearly breast MRIs. So, this is really an important part of their survivorship care plans and their primary cares, their GYNs – I don't know that GYNs know this. I don't know that they even know this if we're not telling them.

So, the patient gets ABVD, no radiation, tolerates it well, complete response. So hopefully she's one of those 85% that are disease-free in 5 years.

DR. SANDOVAL Okay. Let's try to see if we can get through these other cases. This actually is a little bit more challenging population. The 68-year-old male treated with ABVD for classical Hodgkin lymphoma 3 years ago and arrives for a regular scheduled follow-up visit. That's a thing that actually young adults, they don't do a lot—follow-up. But anyway, this is a little bit different.

He remains in complete remission. However, he was recently diagnosed with high blood pressure, have to have a marginal ejection fraction, 45%, on echocardiogram, feels fatigue since chemotherapy, it's likely worsening recently, slightly elevated creatinine at 1.5, normal hematocrit, hemoglobin, and TSH. He is asking about correlation with chronic Hodgkin lymphoma therapy. So, one thing that I can tell you is that if you have not already noticed, what we are emphasizing right now in these cases, is both the acute toxicity, but the late toxicity. So, the survivorship care of these patients is extremely important. Why? Because fortunately, we're curing these patients in a high, high percentage. So we need to be very cognizant of our survivorship care plans.

So, one, cardiotoxicity. We're all familiar with the cardiotoxicity with anthracyclines. It can be all those modalities up there. It may occur during, shortly after, or years after your treatment. Often, unfortunately, nonreversible. The anthracyclines—doxorubicin, daunorubicin, and so forth is in Hodgkin lymphoma. Mainly doxorubicin. Usually when you have an accumulated dose between 450 and 550 mg per meter square, I can tell you, Hodgkin's, even if you – there's some calculations that if you give up to eight cycles of ABVD, you get a cumulative dose of 400 mg/m^2. Nobody gives eight cycles of ABVD. So, if you think about it, it's not a lot of anthracycline that you're accumulating. But you have to be cognizant, especially in older adults. Chest radiation, it does increase cardiotoxicity, but in a different way, especially chest radiation increases the risk for early or premature coronary artery disease. Valvulopathies as well. So, we need to be also watching these patients for this.

Consider – you can't – provision strategies. You can consider less toxic agents, or for example, liposomal agents, like liposomal doxorubicin. I have never used that on Hodgkin lymphoma, to be honest with you. I consider late EF monitoring. In some regimens in older patients, we can consider echocardiogram at the beginning and at the end of ABVD therapy. And there are some cardio-oncology guidelines that you can follow, and hopefully in a lot of your institutions, you have now cardio-oncologists. They're a big, big, big help for a lot of our patients.

Renal toxicity, you can have glomerular and tubular damage. Most of the time, it's subclinical but may progress to chronic renal failure. Usually, we see on

our salvage regimens that include platinums—carboplatin, cisplatin—some of the immunosuppressive agents as well. Anti-infectives—we love to use. We give like candy sometimes. That is acyclovir. Remember, you can have renal toxicity, so you have to be careful about that. And also, patients with comorbidities, long-time, uncontrolled high blood pressure, diabetes, for fourth, there are really no protective agents for these renal toxicities. And as always, of course, avoid polypharmacy, especially in older folks. Monitor their renal function. And obviously, reduce appropriate – the doses of our chemotherapies when they are appropriate.

Fatigue. Very important in survivorship of these patients. Up to 67, almost 70% of patients with Hodgkin's – survivors of Hodgkin lymphoma, they complain about fatigue. It's a higher incidence in older patients. No correlation with any other risk factors.

Common things are common, and obvious things are obvious. Encourage physical activity. These patients will get better with physical activity. And evaluate also for treatment, especially. Fatigue, very nonspecific, but can be one of the signs of disease progression or relapse, so we need to keep that on our radar. And also evaluate for other psychosocial, psychiatric issues. Only, it could be just depression of the patient.

In this case, the patient was evaluated by Cardiology. He was started on an ACE inhibitor, beta blocker, and diuretic. Sodium-restricted diet, blood pressure was under control; creatinine stayed the same. Energy was low but it

was back to baseline, so it's just to point out that – the care of these patients in the long run.

MS. GOODRICH Okay. Case Study 3. It's a 57-year-old male. He's receiving BEACOPP for stage IV newly diagnosed Hodgkin's. His IPS score is 5, so he's over 45. He's a man, stage IV, low hemoglobin, and low absolute lymphocyte count. So his 5-year survival is 42%, which is why he got stepped up to a more aggressive regimen. He presents on day 8 with a low ANC and a fever. He's orthostatic. You're going to admit him. I'm going to whip through this. All of you are treating these patients. You know what to do. Hand washing, watch their counts, safe food handling, appropriate use of growth factors and anti-infectives, and the difference here is that he's getting BEACOPP, so growth factors are definitely more enfolded into that regimen, as well as the anti-infectives that ABVD – everybody should get their flu shot and their other age-appropriate vaccinations. Antimicrobial prophylaxis, I'm going to let you guys read this. Antibacterial, antiviral, antifungal. Follow your guidelines, follow your ASCO guidelines, your NCCN guidelines. You guys know how to do this.

So, he gets admitted for febrile neutropenia. Empiric antibiotics are started. No source. Fever resolved. You know, the typical – discharged on orals, and he's got no further fevers.

So, let's go to Number 4. I'm going to whip through this. This is a 42-year-old male with multiply relapsed Hodgkin's, including auto. Working full time remotely from home. Three little kids at home. He's getting pembro. He's got an excellent partial response and he is getting worked up for allo at your transplant

center. He arrives for his infusion, everybody has a GI virus. They're vomiting, they have diarrhea. No, they're not vomiting, they have diarrhea. They're nauseated, they have diarrhea. You culture him. His vitals are good. You're going to hold his treatment and let him ride out this virus. He's going to contact you if anything strange is going on, and he comes back in a week.

Cultures are negative. He's now having 10 watery stools a day, and you know, 42 is like the new 18, I think. This is grade 3 colitis. He's hypotensive and tachycardic. He's got a little cough. You're not treating him. He's going to get admitted. But he has to get to transplant. He doesn't want to get admitted. He doesn't want anything to throw him off. And you know, they're like this, these men who think they're invincible are like this. So, you talk to him, and you talk to him about the life-threatening potential of this toxicity he's having. He needs to be hydrated beyond what your clinic can support him through. And he needs to get worked up so you can get this turned around. And then, really, there's a real rate of interruption for toxicity, and I think if patients understand that out of the gate, then they're not so frightened and they're not so reluctant to tell you what's really going on. His wife tells him, get in the hospital.

He gets a colonoscopy done, steroids, rehydration, it all turns around, it's deemed an immune-related adverse event, and then because he was in a very good partial response, he was ready to go to allo. We didn't have to give him any more pembro before his allo. So he got a little washout period. He is now – or at the time, he was 60-days post-transplant. He's farther than that now. Little bits of

skin GVH. Really did fine, did not have any of those horrific toxicities. He tolerated it well. He's working part-time from home. He's very happy.

So, we have a minute and 23 seconds left. So, follow-up. I'm just going to do bullet points here. So, TSH, if radiation, you're only repeating PET scan, if the PET scan was positive, that's the only time you're gonna repeat them and do serial PET scans. Once you get a negative PET scan, don't go back to them. You're just looking for false positives.

Counseling. Okay, screening. This COG, the COG, chest x-rays, PFTs, in patients who have gotten lung radiation or any of those high-risk alkalators, bleomycin, yearly pulmonary exams. Again, get your flu vaccine. Cardiovascular symptoms can occur at a very young age. Again, this is where your primary cares come into play and those survivorship care plans become so important, because look at these, stress echos, carotid ultrasounds. I mean, these are not things that you're doing with a 35- or 40-year-old. Lipids, TSH, breast screening.

So, this annual breast screening, this is for women who are over 30 who have gotten chest radiation or axillary. So even your older women who get chest radiation, they do need different breast screening. Again, MRIs. Referring them to someone who sees these patients all the time is a great idea.

And then they need to get their other routine screening done, especially these younger folks. They seem to think the cancer card hit them once, it's not going to hit them again. And they become very complacent with their follow-up. They feel like they've had their lifetime of doctors' visits and they're done.

And then survivorship clinics. Who has a survivorship clinic or runs a survivorship clinic? Yay. Okay, good. These are perfect referrals. Do you refer these people to your survivorship clinics? Who does that? Good, okay. Wonderful. Yup. Yes, we should all have a survivorship clinic.

So, in summary, Hodgkin treatment side effects are expected. They're potentially severe. There are immediate, late, and long-term side effects that we really need to be aware of and focusing on for these patients. Diligent management at all phases really helps reduce the severity and the impact on quality of life for these patients. Their education is critical. The sooner they're reporting things, the less severe they become. Good communication with primary care providers and other specialists is critical. And all of us in this room are really in a unique position to get into that inner sanctum of that patient and figure out what's happening with them, but then also referring and making sure that everybody on their care team is aware of the red flags that need to be monitored long-term.

DR. SANDOVAL Just one or two things. A couple of things to think about Hodgkin lymphoma in your own practice. I want to close up with these take-home points that I believe are very important. One of them – remember, guys, we're curing 80% plus of these patients. So it's an excellent time to be treating these patients and to follow them through treatment. This is the type of patient that you can see them in college, graduating, making a family, and so forth. So it's very gratifying to treat the patient when they go well. But the 20% of patients, remember, there are still patients that are very challenging.

Second of all, do not – in a healthy young patient, do not – even if they have persistent disease after salvage therapy, even half of those patients can get cured without a transplant. Okay? So, remember to refer the patient early on for an allo transplant in the salvage setting.

Third of all, patients that progress after transplant or they're not eligible for a transplant, they go on to receive brentuximab or checkpoint inhibitors, these patients do really, really, really well.

Third of all, we don't know when to stop checkpoint inhibitors in patients that are doing really well, but allo has never been done in this disease. And last thing, if you have difficult patients, especially male, talk to the wife, all right? That will help. Okay, now it's your turn.

MS. GOODRICH Does anybody have any questions?

DR. SANDOVAL Question over there.

MS. GOODRICH And I just want to thank all of you for hanging in here. And you all look alert. Good work.

DR. SANDOVAL Especially on a Friday night.

MS. GOODRICH Yeah, Friday night.

QUESTIONER You had mentioned with infliximab you should not give it for hepatitis?

DR. SANDOVAL So, usually, you don't give it. Sometimes it's not that useful, and actually sometimes can induce a little bit of hepatic injury. But, I believe it's not that useful. We usually use steroids, of course, you know, high-dose steroids, and we use MMF, like mycophenolate for the most part, but that's

what usually – actually in the new – oh, by the way, there are new ASCO guidelines from this year for the managing of checkpoint inhibitors. Checkpoint inhibitor side effects and so forth. And that's one of the pearls that I got from it. You know, for the only one. You know, hepatitis. That's the only one that I saw with infliximab.

QUESTIONER You had mentioned about liposomal doxy – why do we not see that used?

DR. SANDOVAL That's a very interesting question. I don't know. They have never – on the studies that I know of, on the big studies that I know of from Hodgkin lymphoma, especially front-line therapy, it has never been tested. There are some salvage regimens that they put in a big box of Hodgkin's and non-Hodgkin's patients that they later take to transplant. That has been used, but I do not believe in any one of those big, big, phase 3 randomized studies have been used with liposomal doxorubicin really. But I don't know why haven't they done that. Maybe because there's not a lot – especially with ABVD – and actually with BEACOPP as well, it's not a lot of anthracyclines that we give to that population. It's usually, like I say, usually way less than 400 mg/m^2, and they're usually younger folks. So, I think that the interest has not been there. I might have said so, but –

MS. GOODRICH I've used it once in Hodgkin's. It was an 85-year-old with an EF of about 35%. And it was before we had nivo and pembro and some of these more interesting things. This was a while back, but I – you know, when

you really are between a rock and hard place. But, I mean, there's no data, which is – it's because we're not maxing folks out.

QUESTIONER I have two questions, actually. One is about bleo and oxygen. We have used bleo and oxygen with people that pass their pulmonary function tests and their diffusion to try to get two cycles in. Do you say, never?

MS. GOODRICH Well, you used to have to do that. But now you don't have to. Now you can give brentuximab with AVD. You don't have to do it. You don't have to risk it.

QUESTIONER So you'd be better – okay.

MS. GOODRICH Yeah.

QUESTIONER And then my other question is sort of general. One of our referring institutions lets people get the zoster vaccine twice, and then stop acyclovir for myeloma-suppressed patients. What are you guys doing with the zoster vaccine in your survivors or your actively treated patients?

DR. SANDOVAL Actually, for patients who are "cured" – survivors – I really don't have – okay, let me back up a little bit. I usually don't use a lot of acyclovir in these patients, especially for my young patients, unless they have a clear history of shingles in the past. And, you know, sometimes a very bad chicken pox and things like that. But usually, I don't use it because this regimen is not a very T-cell suppressant, if I might say so. But if you want to use that, especially in the older folks, in patients who are "cured" in remission, I don't believe there's data – there's data in multiple myeloma, a little bit, but not that much. So, like, abstracts, you know? And in CLL. But in Hodgkin's? I mean, it's

hard to say. I think I potentially would use it, especially if you're a long time after treatment and so forth. But, I don't have a very solid answer for that. I think will potentially use it, but –

MS. GOODRICH Good question, thank you. Does anybody else have questions? Okay, well, thanks for coming. Thanks for spending Friday night with us.

DR. SANDOVAL Thank you very much.

MS. GOODRICH Thank you.

DR. SANDOVAL Thank you very much.

MS. GOODRICH Enjoy the rest of the conference.

[END]