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Introducing Novel Agents Into the Armamentarium for Triple-Negative Breast Cancer

Announcer Introduction:
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Dr. Sims:
Welcome back for another great session here in the PC Oncology Winter Conference. I'm Karen Sims, and I'm happy to introduce our last session, which is introducing novel agents into the armamentarium for triple-negative breast cancer. And our expert speaker today is Dr. Laura Spring, who is an Assistant Professor of Medicine at Harvard Medical School, and an Oncologist at Mass General Hospital in Boston, Massachusetts, and welcome Dr. Spring.

Dr. Spring:
Thank you for having me. Thanks, everyone for joining today.

Dr. Sims:
I'll just remind the audience, here's Dr. Springs disclosures, and here are our learning objectives for today. Differentiate among appropriate treatments for patients with TNBC based on current guidelines and clinical trial evidence, use individualized management strategies for AEs experienced by patients on therapy for TNBC, and integrate patient education and feedback to optimize patient experiences during treatment and survivorship.

Let's turn it over now to Dr. Spring to talk about the overview and epidemiology. Dr. Spring, welcome.

Dr. Spring:
Thank you. So to start, we'll review the landscape of triple-negative breast cancer. So it represents about 10 to 15% of breast cancer overall, it's generally associated with poorer outcomes compared to the other subtypes. So generally, it can see a more aggressive clinical course, both in the early and metastatic settings, it tend to be a high-grade tumor, typically grade 3. It is more responsive to chemotherapy though because it is high-grade. And also we see earlier and more frequent distant recurrence. And on the right here, you see the 5-year relative survival by subtype. And of course, data like this is always a little out of date because fortunately, there's consistently new treatment options.

Lets turn it over now to Dr. Spring to talk about the overview and Epidemiology of TNBC. Dr. Spring, Welcome.

Dr. Spring:
Thank you. So to start the overview the lanscape of triple negative breast cancer, so it represents about 10% to 15% of breast cancer overall. And it is generally associated with poorer outcomes compared to the other subtypes. So, generally can see a more aggressive clinical course in early and metastatic settings. Tends to be a high grade tumor typically at at grade 3. It is more responsive to chemotherapy though because it is high grade.

And also we see it earlier and more frequent of distant reoccurance. On the right here you see the five year relative survival by subtype and of course data like this is always alittle out of date cause fortunatley theres consistently new treatment options. But as you see,

triple negative breast cancer goup is in the yellow, which does have the poorest survival. In terms of epidemiology, this subtype is more prevalent in black women than others. It does contribute to excess breast cancer-related mortality among black women, but is not the sole explanation for that. Black women are also more likely than others to carry a TP53 mutation and tend to have breast cancers with higher Ki-67 index as well. Also, the instance of pathogenic germline BRCA mutations is about 16% in TNBC with the vast majority being BRCA1. And there's also a disproportionate affect on younger women, premenopausal women, and women with BRCA mutations. So as what you reviewed before, a decent percentage can have a germline BRCA mutation, with more being BRCA1. And TNBC is present in about 70% of premenopausal BRCA-positive women with breast cancer. And here on the right is some data on the prevalence of TNBC among different groups.

Now I'm going to talk a bit about the patterns of distant recurrence that we see with this disease. So in some reports, distant recurrence can occur in 34% of the time, versus 21% of patients diagnosed with non-TNBC. More likely to have visceral metastases, some metastases to the lung and brain, liver, compared to other subtypes. And we also see a shorter meantime to recurrence compared to non-TNBC. Local recurrence 2.8 versus 4.2 years, to distant recurrence 2.6 versus 5 years. And you can see that here on the right with TNBC represents it in the blue, and you see essentially almost all recurrences are happening in those first 5 years, compared to non triple-negative breast cancer, particularly hormone receptor-positive breast cancer, where we describe a low but persistent recurrence risk.

In terms of some risk factors, many of these also relate to risk factors for breast cancer in general, but some are – appear at an early age, so under 12 years old and/or a later menopause, black and Hispanic ancestry, BRCA1 mutation as we reviewed, and family history is also a factor. In terms of risk factors that are modifiable, obesity in premenopausal women, moderate or high alcohol consumption, low physical activity, exogenous hormone use, and young age at first pregnancy.

So just to review some important facts about TNBC for this section. So TNBC is a breast cancer subtype that accounts for about 10 to 15% of breast cancer overall, generally is associated with poor outcomes versus other breast cancer subtypes, it's more prevalent in black women, it is more likely to metastasize to visceral organs and the brain than other breast cancers, and the modifiable risk factors for TNBC include obesity, alcohol consumption, physical activity, hormone use, and age at first pregnancy.

And an action item, be aware of the modifiable risk factors and know that maintenance of a healthy lifestyle may reduce the risk of developing TNBC.

So next, we'll move on to the biomarker and molecular genetic test section. The first in this section, we'll discuss the subtypes of TNBC. So like all cancers, and breast cancer as well, TNBC is a heterogeneous disease, there is distinct genomic subtypes and, in general, we think of as overlapping, but it's not perfectly synonymous with what we describe as basal-like breast cancer. And these molecular subtypes are based on gene expression, and about 75% of TNBCs are categorized as highly proliferative basal-like subtype. And the basal TNBC subtypes are more likely to be seen in younger women as well. About 20% of TNBCs are highly enriched in tumor infiltrating lymphocytes, or TILs, and immune checkpoints, such as CTLA-4, PD-1, and PD-L1, and this group actually has a better prognosis.

In terms of the impact of the subtypes on overall survival, this summary here, there's several different classification systems that have been explored, but this is a common one here, which is basal-like 1, basal-like 2, luminal androgen receptor (LAR), and mesenchymal. And these have different overall survivals that have been observed, with the worst prognosis being basal-like 2. Now to say clinically we aren't testing for those subtypes, but we do think we can get a sense of them sometimes just looking at some of the pathologic features on the report. So if it's a high-grade tumor or not, you can get a sense of which subtype it might be.

So a bit more about the recommended biomarker and molecular testing. So of course any patient with breast cancer we need to know ER, PR, and HER2. HER2 with the IHC is equivocal if it comes as 2+, then we do a confirmatory dual probe ISH assays or FISH to determine if it's considered HER2 amplified or not. So at recurrence for TNBC it is important to check PD-L1 expression using IHCs to determine the CPS, or the combined positive score, with a score of 10 or more considered positive, as we'll see in a bit that does impact how first-line treatment's approached. It's also important for anyone with advanced disease to have genetic testing, particularly for BRCA1 and 2 performed if that had not previously been done. And that would be germline or hereditary testing. At the same time, sequencing on the tumor or in the blood can be done to assess for actionable somatic mutations that are directly cancer related or part of the cancer itself. So the ones here, NTRK fusion, RET fusion, these are on here because we now have disease agnostic approvals for certain agents, so they're now approved NTRK inhibitors, there's an approved RET inhibitor, and the qualification is advanced disease with one of these fusions, and these are quite rare but they are actionable. There are also disease agnostic approvals for immunotherapy with an MSI-high status or a high tumor mutational burden.

And who should be tested for BRCA1 and 2? In the advanced breast cancer setting, it's easy; everyone who hasn't had recent genetic testing should have it. In the localized breast cancer setting, there are some more nuanced guidelines that are summarized here, but I

will say in general the field is moving towards testing more and more, particularly for triple-negative breast cancer, we're testing almost everyone now. Other kind of must-test situations would be lobular breast cancer with a personal family history of gastric cancer as well, any male breast cancer, and then other factors would be age 45 or younger, and then it gets a little more complex after that as with other agents it depends much more on the family history of history of other cancers.

So to summarize, molecular testing and biomarker testing in triple-negative breast cancer is important. It's a heterogeneous disease, there are distinct genomic subtypes, accurate hormone receptor and HER2 assessment are crucial to avoid risk of false negatives and missed opportunities for effective endocrine or HER2-directed treatments. So with a recurrence, we always, if possible, want to biopsy and confirm receptors again. PD-L1 testing is needed at diagnosis, so if triple-negative metastatic breast cancer, to determine eligibility for immunotherapy, and all patients with MBC should receive genetic testing if not previously performed. And that's because, again, that is actionable due to approval of PARP inhibitors, which we'll review later on.

And an action item, ensure appropriate biomarker and molecular assessment at diagnosis and at time of recurrence or metastasis to guide optimal treatment decisions.

So next, we'll move on to discussion of the treatment of early-stage triple-negative breast cancer. So a key study in the last couple of years is the KEYNOTE-522 trial. And this is the trial that explored immunotherapy with pembrolizumab in the early breast cancer setting. I think it's important to take a moment to review a summary of the eligibility criteria for this trial, because that helps inform us in clinic who should get pembrolizumab or not. This trial included patients 18 or older with newly diagnosed T1c, N1-2, or T2-4, and 0-2 triple-negative breast cancer. So one way to think about that is with any lymph node involvement, we would think of the patients being eligible for pembrolizumab. Without clinical lymph node involvement, it's reserved for patients with a tumor T2 or greater. And tissue was looked at for PD-L1 but it was not part of being eligible or not. So unlike metastatic triple-negative breast cancer, PD-L1 testing is not required for early breast cancer. This study was comparing immunotherapy with chemotherapy, so it was carboplatin and paclitaxel, followed by Adriamycin and Cytoxan, and the pembrolizumab carried on throughout. And then after surgery, pembrolizumab was continued for an additional 9 cycles, and that was regardless of response at the time of surgery. And the primary endpoint was both pathologic complete response and event-free survival, so the dual primary endpoint. This required a larger study, but with past studies looking at pathologic complete response as the primary outcome, the question was always, well does that translate to improvement in event-free survival? So with this study design, they had a dual primary endpoint, so they were able to report on those closer together than we typically see, and the study was powered for event-free survival as well. As we reviewed, pembro was for a full year, so it was in both the neoadjuvant and the adjuvant study, and so with the addition of pembrolizumab, significantly more patients achieved a pathologic complete response, and that was independent of nodal status. There was also significant reduction in progression, recurrence, or second primary tumor.

So here is a summary of the PCR data for pembrolizumab versus placebo. In all patients, the improvement of path CR was 13.6%. And then as we always see, PD-L1 positive tumors do have a higher PCR rate than those that are not PD-L1 positive. But as you see here, with pembrolizumab, PCR rates were higher in both the PD-L1 positive and PD-L1 negative groups. And the delta was actually larger, and the PD-L1 negative group 18.3% versus 14.3%. So that's a key point of why we don't have to test for PD-L1 in the early breast cancer setting because this approval is not based on PD-L1. And as many know there are different ways to give pembrolizumab. So in the study, it was given at 200 mg every 3 weeks, but it can also be given at 400 mg every 6 weeks.

And here are the event-free survival data. So there was a significant improvement in EFS independent of PD-L1 expression, so the EFS made a 36-month overall survival was 89.7% versus 86.9%. And that data is still immature. But you see overall, this blue line is the pembrolizumab group, significant improvement in EFS with a hazard ratio of 0.63. The trial did not include other adjuvant treatments like capecitabine or olaparib, but in practice, that combination is often being done for patients with residual disease.

And so speaking of olaparib, here's the OLYMPIA study. This was the study that explored adjuvant olaparib for patients with triple-negative breast cancer with a BRCA mutation. So these patients eligible for this study had already completed their chemotherapy, had to have at least 6 cycles or more and had to be considered a high risk of recurrence. And there's a variety of criteria whereby patients could meet eligibility for the study, and patients were randomized to olaparib 300 mg twice a day for 1 year versus placebo. And the primary endpoint was invasive disease-free survival. And here on the right, the primary endpoint is shown here with a significant improvement 85.9% versus 77.1% with olaparib versus placebo.

And so to summarize this section, in the KEYNOTE-522 trial, the addition of pembrolizumab to chemotherapy significantly improved event-free survival and pathologic complete response rate regardless of PD-L1 status in high-risk early triple-negative breast cancer. Pembrolizumab reduced progression, recurrence, and second primary tumors and improved event-free survival and PCR rates. In the OLYMPIA trial, adjuvant olaparib improved invasive disease-free survival, distant event-free survival, and 3-year overall survival compared with placebo for patients with BRCA1 or 2 mutated HER2-negative high-risk breast cancer.

And so an action item is to remember the adjuvant pembrolizumab can be given concurrently with olaparib for patients with high-risk

early TMBC with a BRCA mutation with residual disease after neoadjuvant therapy, because that's a situation that's come up a bit in that prior to the approval of pembrolizumab, we had options to do capecitabine for 6 months for residual disease, or more recently if a patient has a BRCA mutation to olaparib for the year. So there was some uncertainty early on about combining these therapies. But there are safety data from the advanced setting, so a lot of practices have started to do that.

Alright. So next we'll look at novel and emerging strategies for advanced triple-negative breast cancer.

Dr. Sims:
So here's another case, Emily, she's a 50-year-old, black woman presenting with concerns about self-detected lump in her left breast. Her BMI is 25. She's a nonsmoker, moderate alcohol use. Three children, the first was born when she was 20 years old. She has a large tumor on physical exam with an axillary node involvement. She's diagnosed with stage 3 TNBC and treated with adjuvant chemotherapy. Two years later, follow-up imaging shows uptake in the right breast and metastatic lesions in the lung, two, each are less than 5 mm, and in the liver, one, that's less than 3 cm. Her family history is negative for breast or other cancers on her mother's side. Her father had low-risk prostate cancer diagnosed at age 70. Her test results show PD-L1 CPS greater than 10, and BRCA1 and 2 negative. She receives pembrolizumab and chemotherapy, and she has a clinical response to therapy. Treatment is well tolerated.

At a follow-up visit 11 months after starting pembrolizumab and chemotherapy, scan showed disease progression in Emily's lung tumors.

Dr. Spring:
Here's a summary of the current recommended approach for metastatic triple-negative breast cancer. As we reviewed in the first line, the key is what is the PD-L1 status. Is the combined positive score greater than 10% or not? If it is, then a patient's eligible for pembrolizumab combined with chemotherapy. If not, we tend to continue to treat with chemotherapy, often single agent, sometimes we will use combination therapy if very symptomatic or immediately life-threatening disease, and sometimes we'll start with that combination and then remove one of the agents and continue with single agent. When there's progressive disease, the BRCA status is, again important because if there's a BRCA1 or 2 mutation, again, more likely to be BRCA1, a patient is eligible for a PARP inhibitor. And technically PARP inhibitors can be used first-line also but now with immunotherapy, a lot of patients are receiving that in the first line if eligible. And then from there, if there's no BRCA mutation, other considerations are what is the HER2-low status? So that is an entity that's now very important to understand. We used to think of HER2 as positive or negative, but there's been recent work, and we'll review it, looking at HER2-low, and there's an approval for trastuzumab deruxtecan now in that setting, so very important to know the HER2 status fully. And then another option would be the antibody drug conjugate, sacituzumab/govitecan. And of course, there's other chemotherapy options too. So we'll review some of the data behind this flowchart.

So here's the final analysis of KEYNOTE-355. So this is the pivotal study that led to the approval of pembrolizumab for metastatic TNBC with a combined positive score 10 or greater, so positive PD-L1. In the final analysis, the improvement in overall survival, the median overall survival was 23 months in the group with pembrolizumab, versus 16.1 months with chemotherapy alone. So that was quite significant. Median progression-free survival was also improved, 9.7 months versus 5.6. And the response rate was also higher in the group with immunotherapy.

In terms of chemotherapy backbone, so there were different options in this study, and those included nab-paclitaxel, paclitaxel, or gemcitabine with carboplatin. And there's some suggestion that perhaps those with receiving a taxane did better than those on gem/carbo. And there was a lot of interest early on in nab-paclitaxel, because it doesn't require steroids. But with time, I think there's been more comfort with using steroids with pembrolizumab. And so, sacituzumab/govitecan is a really exciting agent, an antibody drug conjugate. It includes a payload. The active payload is SN-38, which is part of irinotecan, which was a topoisomerase inhibitor, and this is linked to an antibody. And the antibody for this agent. It targets Trop-2, which is an antigen expressed in many epithelial cancers, including about 88% of triple-negative breast cancer. And really, regardless of Trop-2 status, we still see efficacy with this drug, which again, is why Trop-2 status is not needed to give this drug. And importantly, this agent does have a bystander effect. So in acidic tumor microenvironment, the SN-38 is released from the anti Trop-2 antibody, and therefore, can diffuse into neighboring Trop-2 negative cells. And that's in part why the degree of Trop-2 positivity is not something that we look at to decide if someone could have this agent.

And so the ASCENT trial was the confirmatory phase 3 study of this drug. It had already received initial improvement based on a single-arm study. But this was the randomized confirmatory study. And so, it was for patients with metastatic TNBC with 2 or more prior treatments. And here we're looking at the outcomes in patients without brain metastases as well as in the full population. So as you see in both groups, the group that receives sacituzumab did much better than chemotherapy alone. So median progression-free survival was 5.6 months versus 1.7. And then the full population 4.8 months versus 1.7. And even though this was for patients with 2 lines or more, there was some variability there in how many lines of treatment a patient had, so some heterogeneity in these results. The response rate was also significantly higher in those patients who receive sacituzumab compared to chemotherapy. So the overall

population, 31% versus 4%.

And here are some results again, looking at progression-free survival among patients without brain metastases, again, the sacituzumab group did much better. And looking at overall survival among patients without brain metastases, and the sacituzumab group did much better, 12.1 months versus 6.7 months. And here is the overall survival data specifically for patients with 1 prior line of treatment in metastatic setting and progression 12 months or more after they received therapy and that localized breast cancer setting. And here's your overall survival. Again, improvement with sacituzumab.

In terms of the FDA approval for this agent, so it's FDA approved for patients with unresectable locally advanced or metastatic TNBC, who have received 2 or more prior systemic therapies, at least one of them for metastatic disease. And so that's important. There's some confusion about what line this agent's approved for, but it's important to note if they have already received a line of therapy for localized breast cancer that could count towards the 2 lines. And as we reviewed, assessment of Trop-2 expression is not necessary prior treatment with this agent.

Now moving on to talking a bit about HER2-low and the approval of trastuzumab/deruxtecan. So this was the DESTINY-Breast04 study that looked at trastuzumab/deruxtecan versus chemotherapy for HER2-low MBC. So to review how this is defined, so HER2-low is currently defined as IHC 1+, or IHC 2+ FISH negative. So essentially, everyone who isn't HER2 positive and whose tumor isn't HER2 IHC-0. And this could be based on the tumor from the early breast cancer setting or from the recurrence. And it's important, there's some centers that only have had sent FISH before. So as we're thinking about this agent, it's important to look at the past results and understand was HER2 assessed with IHC or not? Because if not, it's hard to determine if a patient does have HER2-low breast cancer. And so that's just a couple thoughts on why that's so important. But essentially, in this study, all patients had had at least 1 line of prior chemotherapy, so overall 1 to 2 lines of prior chemotherapy in the metastatic setting. Also, if a patient was hormone receptor-positive, because we see HER2-low with both HR positive or with triple-negative breast cancer, they have to have 1 or more lines of endocrine therapy. Stable brain metastases were allowed, and patients were randomized 2:1 to receive trastuzumab/deruxtecan, at standard dosing of 5.4 mg/kg every 3 weeks versus chemotherapy. And the primary endpoint was progression-free survival, specifically in the hormone receptor-positive population, but a key secondary endpoint was PFS overall, including HER2-low TNBC patients.

So here is the analysis looking at the hormone receptor-negative HER2-low patients, because that's relevant to our discussion today. So looking at PFS on the left, you see a significant improvement with trastuzumab/deruxtecan, 8.5 months versus 2.9. The blue line being trastuzumab/deruxtecan. Often early on in studies, we may not see yet an overall survival benefit as that data is not mature yet. But here, even at an earlier assessment, we've already seen overall survival benefits. So with T-DXd, 18.2 months versus 8.3 months with chemotherapy. Again, significant improvement. We're looking at the response rate with this agent, which again was much higher with T-DXd compared to chemotherapy. The approval is by the FDA for patients with unresectable or metastatic HER2-low breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence 6 months or less after completing adjuvant chemotherapy. So essentially, we're thinking about this agent for patients with HER2-low breast cancer who have already had 1 line of chemotherapy in the either advanced breast cancer setting or if the recurrence happens quite soon after treatment for localized disease, and that can count as the one line of chemotherapy.

And so moving on to PARP inhibitors. So, PARP is an enzyme that helps maintain DNA integrity during DNA replication. So when cells lack BRCA1 or 2, which are proteins involved in homologous directed repair of DNA, PARP inhibitors disrupt DNA damage repair mechanisms in the tumor cell, so kind of like a second hit, and it may lead to cell death and potentially reduction or stoppage of tumor growth. And therefore, it was thought that these agents could be helpful in patients with BRCA mutations.

The trial here, OLYMPIA, had looked at olaparib versus chemotherapy in patients with BRCA mutations and metastatic breast cancer. And so there were significant improvement in progression-free survival with olaparib versus chemotherapy. And at this time, there has not been a difference in overall survival. But this agent is approved as well as talazoparib, so there's a trial looking at the PARP inhibitor, talazoparib, called EMBRACA, and that also compared the PARP inhibitor to chemotherapy. And again, with the PARP inhibitor, there was significant improvement in progression-free survival, but at this time point, no difference yet in overall survival. And then specifically in TNBC, in this study, there was again a significant improvement in progression-free survival and the clinical benefit rate. No overall survival benefit has been seen at the time of the final analysis, but importantly, improved quality of life was seen with the PARP inhibitor versus chemotherapy.

And so to summarize, optimal treatment of metastatic TNBC. So first-line treatment of metastatic TNBC is determined by the PD-L1 status. Sacituzumab/govitecan is the first antibody drug conjugate that targets Trop-2 to deliver potent cytotoxic topoisomerase-1 inhibitor in it to receive approval and locally advanced or metastatic TNBC after 2 or more prior systemic therapies with 1 or more being for metastatic disease. Trastuzumab/deruxtecan, another antibody drug conjugate, is an option for unresectable or metastatic HER2-low breast cancer after a prior chemotherapy for metastatic disease, or after recurrence 6 months or less of completing adjuvant

chemotherapy. And olaparib and talazoparib are options for patients with BRCA1 or 2 mutations in metastatic TNBC.

So an action item, performing germline testing, especially for BRCA1 and 2, and obtaining HER2 and PD-L1 IHC in all patients with metastatic TNBC is crucial to making the optimal treatment decision.

So next we'll talk about immunotherapy-related adverse events. So there's, as I think this group well knows, a broad spectrum of immune-related adverse events that can be seen, essentially could impact any organ with some being more likely to be impacted than others. So at this point, there's no current way to predict who will develop these versus not. Onset is typically 2 to 3 months after starting therapy, but can occur for up to 2 years after therapy completion. So it's very important to ask patients to contact their oncology team if any symptoms develop, if they're admitted to the hospital, or if they begin any new medications, just to make sure there's not impact on the immunotherapy. So any specific symptoms and signs we're looking for are severe fatigue, headache, cough, dyspnea, diarrhea, skin rash, chest pain, bloating, weight loss, severe muscle weakness or pain, bowel, vision, or mood changes. So in general, we have to just have a very high suspicion for immune-related adverse events. And it's hard because a lot of these can be signs and symptoms that we see with chemotherapy. But we just have to have a broader differential on our mind with immunotherapy.

If an immune-related adverse event is suspected, we conduct a complete workup including lab tests to rule out other causes. One of the most common IRAs we see is hypothyroidism, and that's more common in females than males.

So here's a summary of some of the adverse events with pembro and chemotherapy seen in the KEYNOTE-522 and KEYNOTE-355 studies. So overall, hypothyroidism was the most common, followed by severe skin reaction, hyperthyroidism, and then much more rare, adrenal insufficiency, pneumonitis, thyroiditis, hypophysitis, or colitis. But fortunately, the majority were hypothyroidism, which is one we can usually treat through by replacing thyroid hormone.

Here are some recommended assessments and education prior to starting immunotherapy. In terms of history, it's important to understand if they have a history of an autoimmune disorder, which can put them at higher risk for developing any immunotherapy adverse events. Also important understand any infectious diseases, if someone does have a severe immunotherapy toxicity and needs significant immunosuppression to treat that, that can allow some infectious diseases to flare. Also important to assess for neurologic conditions, endocrine disease, bowel function, and any pre-existing comorbidities that could make immunotherapy challenging.

So for patient education, dedicated education, specifically on the signs and symptoms of these adverse events by a medical professional is important, including informational booklets, reference cards, also counseling on steroid-related toxicities if indicated, and encouragement to use contraception if applicable, and discussion about fertility is important with immunotherapy as it is with chemotherapy.

Lab tests that are often checked before would be routine labs with the CBC with differential, CMP, A1c, serum cortisol, thyroid studies, if indicated, cardiac test such as EKG and troponin, and, if applicable, assessment for latent infections. And that's again in case significant immunosuppression is needed. There are certain infections like hepatitis B or tuberculosis that could act up.

In terms of on and posttreatment monitoring. So before infusions, CBC and CMP are assessed at regular intervals, we'd look at thyroid function, and especially if symptomatic, we would assess cortisol and ACTH. Physical exam includes a pretty general exam, including of the skin, and to assess for unexplained shifts in weight, which could reflect issues. Lab tests again that we're looking at pretty regularly are the complete blood count, CMP, and thyroid function.

And here is a guide to managing immune-related primary hypothyroidism. So not something we have to memorize but essentially gives guidance for where the TSH level is and how to approach that. And essentially usually for early grade, it's something we can treat through well. If someone has severe symptoms, then obviously the pembrolizumab would be held, and we'd be involving endocrine for sure.

And so this is some guidance on steroid dosing, with the message being to maintain a low threshold for using systemic steroids, especially once you hit grade 2 or more with immunotherapy toxicities. And there's general dosing guidelines and many institutions would be involving different specialists, depending on the adverse events. So if it was GI related or cardiac or derm, it's helpful to involve specialists in those areas.

As we mentioned a bit before, it can be challenging to differentiate what are the toxicities from the immunotherapy versus from the chemotherapy, especially in breast cancer where we're giving these agents together. So as a reminder, the onset is typically 2 to 3 months after starting therapy, but it can occur for up to 2 years after treatment completion with inflammatory autoimmune type symptoms and thyroid symptoms more common with pembrolizumab. It's important for us to maintain high level of suspicion for these adverse events, and to assess any changes. And then also important to provide patients with instruct them to carry and share with their healthcare providers, a wallet card or other information to detail they are on immunotherapy and what potential side effects could look

like as well as contact information for the oncology team.

And so an action item is to monitor patients regularly for these adverse events and to educate them to immediately report any concerning signs or symptoms to you.

Next, we'll discuss antibody drug conjugate-related adverse events.

Dr. Sims:
This is Emily our case again. So Emily received sacituzumab/govitecan without any need to test for Trop-2 expression, and she has been doing very well on treatment. However, she presents her cycle 6 day 8 treatment and her ANC is 850 or grade 3. She has been afebrile and she feels well.

Dr. Spring:
So here's a summary of the treatment-related adverse events with sacituzumab/govitecan. So ones of particular interest are neutropenia and diarrhea, as that's known to be expected with the SN-38 payload part of irinotecan. So neutropenia, as we heard in the case study, can lead to the need for growth factor support, sometimes dose reductions, but overall, the most common ones we see are grade 1 or 2 nausea, diarrhea, alopecia, and fatigue. So in terms of holding, we withhold S/G for an AMC of less than 1500 on day 1 of any cycle, or ANC less than 1000 on day 8. And here again, not to memorize but as a summary of the common potential severe toxicities associated with this agent and some of the management strategies for it, so neutropenia, you know, there's clear guidelines for, you know, based on the ANC, when to hold the agents, we reviewed, and you can use GCSF and dose reductions, particularly for grade 4 neutropenia, or prolonged grade 3 or really any febrile neutropenia.

And then in terms of diarrhea, there is potential as with irinotecan, for severe diarrhea. So prophylaxis is not recommended unless there's a particular history or concern. But important to educate patients about early use of loperamide at day, you know, at first onset. You know, in infusion if there was early, you know, significant diarrhea, atropine can be used. And then for late diarrhea, of course, always also important to think about any potential infectious etiologies, or other reasons for diarrhea. And like any treatment-related diarrhea, we're managing this as needed with fluids, electrolyte substitutions, dose reductions, and general holding for grade 3 or greater diarrhea.

For nausea and vomiting, this is you know, decently high risk of that, so important premedicate with a 2- to 3-drug regimen. The onset could be delayed. The median was 8 days in the study. So it's not always kind of right after treatment, so important for patients that have antiemetics at home as well. Hypersensitivity can be seen, again, there's premedication with the agent.

So in terms of counseling patients, I think important to discuss that this agent, you know, does often cause hair loss. I think scalp cooling has not been demonstrated to be effective yet with this agent, in part because it does have a long half-life. If they're interested, provide a prescription for a wig. And also important to talk to them of course about all the common side effects and also to reach out early if they're having issues with gastrointestinal side effects.

And here is a summary from the ASCENT trial looking at time to onset of the treatment-related adverse events compared to chemotherapy. So more neutropenia was seen, more diarrhea was seen, and of course neutropenia can be seen early but can get more significant as time goes on. Diarrhea, as we discussed, isn't always incident, but it can be kind of early or late. Anemia also is one that can be seen early but can get worse with time. Nausea tends to be more early, and related to the vomiting as well, but hopefully again with some good antiemetic approaches, nausea and vomiting can often be well controlled.

And now we'll move on to different antibody drug conjugate, the trastuzumab/deruxtecan. Toxicity with this agent are managed similar other drugs when we're thinking about dose adjustments or interruptions when we have to. One special adverse event to point out with this agent is interstitial lung disease. So in this study, there's 12.1% of patients in the trastuzumab/deruxtecan cohort who had ILD. So, you know, we see ILD with pretty much almost any agent, but this is much higher than we see with other drugs. So, certainly, one to be very aware of. The median time to onset was 129 days. So, you know, extremely important to educate patients about this risk and be assessing for any T-saturations, cough, shortness of breath, and have a very low threshold to assess with a CT scan of a chest.

Cardiotoxicity can also be seen as we can see with many anti-HER2 agents. So there's recommendations look an echocardiogram prior to treatment and at regular intervals. Routine labs are looked at with this agent as well and it can also cause significant nausea, so important to premedicate and have agents at home for nausea.

Here is sort of overview of management of ILD associated with trastuzumab/deruxtecan. So if it's suspected, the drugs should be held and there should be assessment with chest imaging to see if there's any changes suggestive of it. It can be confirmed with a high-resolution CT scan of the chest. Often, if it's at all more significant, we'd be involving a pulmonologist. Important to rule out infections as well. Sometimes additional testing is needed if infection's on the differential as well, so some patients may end up with a bronchoscopy,

pulmonary function test. And so as soon as it's suspected, we're holding the drug. And really it depends on how severe it is in terms of if you - if a patient may be able to be retreated with the drugs. So if it is grade 1, it's held until it resolves to grade 0. Treating with steroids early. And if it does resolve early then retreatment can be attempted, versus grades 2 to 4, the agent is permanently discontinued.

So in summary, sacituzumab/govitecan and trastuzumab/deruxtecan have different side effect profiles, and some overlapping side effects. So the most common grade 3 or 4 adverse events associated with sacituzumab is neutropenia, and that can be managed with growth factor support and dose reductions. We withhold treatment for ANC under 500 on day 1, or ANC less than 1000 on day 8. Grade 1/2 nausea, diarrhea, alopecia, and fatigue are also common with sacituzumab. Trastuzumab/deruxtecan is associated with ILD, cardiotoxicity, and neutropenia. If ILD is suspected, we must hold the agent, assess and confirm, and manage appropriately with steroids.

So an action item, discuss potential risks and benefits of S/G versus T-DXd with eligible patients with metastatic TNBC who have progression after prior therapies.

Next section is about PARP inhibitor-related adverse events. Again, a summary here, so common ones that we see are impact on the blood counts. So anemia, neutropenia, thrombocytopenia, so we're keeping an eye on the CBC. There can also be GI, renal toxicities, as well. Fatigue can be seen, and alopecia can be seen. And the onset of that is usually later compared to chemotherapy.

And here's some information on the management of the non-hematologic adverse events. And essentially, that would be by grade, with us often being able to kind of treat through early grade, but at grade 3 or more, the agent has held. And then grade 3 or 4 lasting 28 days or more at the lowest dose, the PARP inhibitor would be stopped. And some other management, so different laboratory abnormalities can be seen as well including in the liver function tests. Cholesterol can also be impacted as well. Less common toxicity would be neurologic, respiratory, and cutaneous.

And so to summarize, common adverse events with PARP inhibitors, anemia, neutropenia, and thrombocytopenia are the most common usually develop within 3 to 4 months of starting, and generally resolve within 2 to 3 weeks. PARP inhibitors are also associated with nonhematologic AEs, including alopecia and GI and renal adverse events. For grade 3 or 4 lasting 28 days or more at the lowest dose, we would discontinue the PARP inhibitor.

And so an action item is to counsel patients about the common hematologic AEs, and that they generally resolve.

Dr. Sims:
So let's move on to dosage and administration.

Dr. Spring:
Here we have a summary slide of the different agents we discussed with the starting dose and the dose reduction and the indication. So this can be more for reference.

To finish up, we're thinking about patient and caregiver education. So, overall important to manage expectations regarding potential adverse events and side effects, to educate about them, and to make sure patients are up to date on everything else they need, such as vaccinations and to support adherence with education strategies. Some of these agents are easier to take or remember than others. And then also important to educate about clinical trials if applicable.

A bit of a summary, so prophylactic interventions can often mitigate treatment-related adverse events, so primary or secondary prophylaxis can minimize effects on treatment toxicity, premedication for nausea, vomiting, and hypersensitivity is recommended for sacituzumab, manage more severe hematologic toxicity with supportive measures or dose modifications, counsel patients in advance about expected toxicities and potential remedies, and educate patients on side effects or toxicity that require immediate consult with your team.

An action item, be aware of potential toxicities and use recommended prophylaxis where indicated.

So next we'll talk about communicating with your patient. Tips here about how to implement key communication skills by addressing the patient's needs and assessing their preferences, have an open dialogue, listening, tailoring discussion, overcoming cultural language differences, raising and addressing the issue of healthcare disparities, and importantly, discussing financial toxicity of treatment.

So here is a PCE action plan. Overall, kind of action plan summary, be aware of the modifiable risk factors and know that maintenance of a healthy lifestyle may reduce the risk of developing TNBC, ensure appropriate biomarker and molecular assessment at diagnosis and at time of recurrence or metastasis to guide optimal treatment decisions. Remember that adjuvant pembrolizumab can be given concurrently with olaparib for patients with high-risk early TNBC with BRCA mutation with residual disease after neoadjuvant therapy, perform germline testing, particularly BRCA1 and 2, and obtain HER2 and PD-L1 IHC in all patients with metastatic TNBC, as that's

crucial for optimal treatment decision-making. Monitor patients regularly on immunotherapy for potential adverse events and educate them to report any concerning signs or symptoms to you. And discuss potential risks and benefits of S/G versus T-DXd with eligible patients with metastatic TNBC who have progression after prior therapies, counsel patients about common hematologic adverse events with PARP inhibitors, noting that they generally resolved within 2 to 3 weeks, and to be aware of potential toxicities and use recommended prophylaxis were indicated.

Dr. Sims:
So now let's revisit some of our questions. I'm going to push on so I can ask one question to Dr. Spring. Dr. Spring, if TNBC is more prevalent in the African American population, is there anything that can be done to proactively prevent that disease in this population?

Dr. Spring:
No, it's a great question. I think screening remains incredibly important. And right now, it's a little bit of a one-size-fits-all approach. But I think to kind of dig deeper into the epidemiology and ages and think more about screening and education communities about screening as well, thinking about MRI when we see very dense breasts, so education about that, I think with primary care teams would be important. And I think there's a lot of work going on to improving screening and I think also to really better understanding the biology of the disease to see if there might be anything else from a prevention standpoint.

Dr. Sims:
Yeah. Dr. Spring, I want to thank you for a great presentation. I'm hopeful for TNBC breast cancer patients, knowing the choices that you've outlined for us today. I've learned a lot, and I know the audience has too, and I appreciate your time.

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