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Current Standards and Future Opportunities for ADCs in Advanced/Metastatic Triple-Negative Breast Cancer

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[CHAPTER 1]

Dr. Gradishar:
Antibody-drug conjugates [ADCs] have transformed the treatment of triple-negative breast cancer with one ADC approved for this indication and others in development. Are you ready to change your treatment approach?

This is CME on ReachMD, and I'm Dr. Bill Gradishar. Here with me today are Dr. Hope Rugo and Dr. Javier Cortés.

Dr. Rugo:
Thanks so much for having me.

So let's get started. Bill, to set the stage for this chapterized course, can you tell us what the NCCN says about triple-negative metastatic breast cancer and the sequencing of ADCs, or antibody-drug conjugates? As the head of the NCCN Breast Committee, I know you're intricately involved in both the guidelines and keeping them really the most up-to-date guidelines in the world.

Dr. Gradishar:
Thanks, Hope. And as you know, we're both very much involved in this effort to develop guidelines based on evidence. And the NCCN if one examines them in the area of triple-negative breast cancer, we still see that there is a fair bit of chemotherapy that is used. But now we see the emergence of other agents, including sacituzumab govitecan, as an option, particularly after patients have progressed having received prior chemotherapy. And there's also the possibility of using other agents in select situations, such as PARP inhibitors should a patient have a BRCA mutation. Obviously if patients have a PD-L1-positive metastatic breast cancer, we look to immunotherapy as an option, an area that you've done a lot of work in. And then, of course, in select patients, which will be a topic later, there may be evidence that even trastuzumab deruxtecan may have a role in select patients with HER2-low disease.

So again, I think we have the development of many different agents that have emerged over just the last couple of years. Though chemotherapy remains foundational, we have new agents to give our patients hope.

Dr. Rugo:
Yeah, that's so interesting. I mean, I think that we thought for some period of time that we'd sort of reached the ceiling on chemotherapy after the approval of eribulin and then some data suggesting that eribulin was better than capecitabine for triple-negative breast cancer in the second- or greater-line setting. And now, you know, we have these new antibody-drug conjugates and immunotherapy as well as PARP inhibitors that have all happened since that initial publication of the EMBRACE study, and then the subsequent data looking at

eribulin versus capecitabine. So we've really sort of broken out that ceiling and, I think, are continuing to make advances with understanding where to use the ADCs, moving them earlier, doing newer ADCs as well as using PARP inhibitors earlier to try and better understand their use.

And then the immunotherapy field is huge, where we have a relatively small percentage of patients who benefit now based on PD-L1 positivity, but there's still a lot of work going on trying to expand that number of patients by combinations and even reaching outside triple-negative disease.

In Chapter 2, we'll discuss using ADCs to treat triple-negative breast cancer in more detail. Stay tuned.

[CHAPTER 2]

Dr. Gradishar:
Welcome back. We're just talking about the NCCN for the use of ADCs in triple-negative metastatic breast cancer. Now we're going to look at their use in treatment.

Hope, can you start us off by discussing the use of sacituzumab govitecan in triple-negative metastatic breast cancer?

Dr. Rugo:
Absolutely. This is such an exciting area because it was our first approved non “sort of standard chemotherapy” but still chemotherapy to treat triple-negative breast cancer. And also, we've been so excited about these new drugs and their ability to not just improve progression-free survival [PFS] and response but also overall survival.

So sacituzumab govitecan is a first-in-class Trop-2-directed antibody-drug conjugate, meaning the antibody is directed to Trop-2. There's a linker which is plasma stable, it doesn't get digested in the circulation, and then a toxin which is the active metabolite of irinotecan, a topoisomerase-1 inhibitor. And these new generation of ADCs are quite intriguing. Some of them, the 2 approved agents now, have a high drug-to-antibody ratio, or DAR, of 7.5 in the case of sacituzumab govitecan to 1, meaning there's a lot of toxins on each antibody. However, there are newer ADCs that are quite active and have lower drug-to-antibody ratios, so that's clearly not the end-all for the activity of these drugs.

So sacituzumab govitecan was first studied in an umbrella trial, essentially where a number of different cancers and subsets of breast cancer were treated with sacituzumab govitecan in the late-line setting. And in 108 patients with refractory metastatic triple-negative breast cancer, who really had received a lot of prior therapy, a median of 3 lines of prior therapy for metastatic disease, a range of 2 to 10, some of them must have initially had hormone receptor-positive disease, their response rate was about a third, 33%. And also, the clinical benefit rate was very high, and progression-free survival was quite remarkable in this patient population. We saw the most common toxicity was neutropenia and, to some degree, diarrhea. So we took that into mind when the phase 3 confirmatory study was designed. So based on this being an unmet need, from this initial phase 1/2 study, sacituzumab [govitecan] had accelerated approval for pretreated metastatic triple-negative breast cancer.

And ASCENT led to the final approval. This trial randomized patients who had metastatic triple-negative breast cancer, had received at least 1 prior chemotherapy for advanced disease, as long as they had received treatment in the early-stage setting; those who had no prior treatment had to receive at least two prior therapies. Patients were randomized to receive sacituzumab, which is given on day 1 and day 8 every 3 weeks, versus chemotherapy, a physician choice. And a total of 529 patients were randomized. Primary endpoint was progression-free survival in patients who didn't have brain metastases. There was a small number of patients who had stable brain metastases who were included in the population, but we know that that portends a poor prognosis. So the primary endpoint excluded those patients, although they were included in the secondary endpoints.

About half of the patients in this trial received eribulin, which I think is a very nice comparator, given the data from the EMBRACE and other eribulin studies, as their treatment of physician choice. And the median number of prior regimens, including early-stage disease, was 4, with 88% of the patients having visceral disease. As now we all know, progression-free and overall survival was significantly improved in patients who received sacituzumab versus those who received treatment of physician choice. And it was quite remarkable; the median PFS was just 1.7 months for standard chemo and 5.6 months for sacituzumab, a hazard ratio [0.41]. So, you know, that's a better than 60% relative improvement. And then overall survival was also improved. And that data was just updated at ASCO this year, 2022, with an almost doubling in overall survival, 6.7 to 12.1 months, with a hazard ratio of 0.48, a 52% improvement in survival. So quite nice.

I think there are several things we always want to look at when we see these remarkable results and know we're going to use agents in this setting, patients who are in the second-line setting, and I think some of us even treat patients in the first-line setting who've had very rapid recurrences, and that’s safety and efficacy based on different characteristics that might increase risk.

We saw data nicely presented by Kevin Kalinsky that the impact of sacituzumab was similar whether you were under the age of 65 or 65 or older. And then we saw similar toxicity to the original phase 1/2 trial with neutropenia and diarrhea being the most common toxicities. Neutropenia seems to be related to the amount of prior treatment and of course metabolism and can be managed, in my experience, with growth factors. You just have to pay attention to it and be aware of the risk. Grade 3 diarrhea occurs in somewhere around 9% to 10% of patients. And in those patients, either dose reduction or anti-diarrheal therapy, depending on the setting, works very well to manage the toxicity. The other toxicities I found are very well managed; a fair number of patients have alopecia as well. And there are studies looking at scalp cooling to see whether or not we can prevent the alopecia from sacituzumab, which, in my experience, works reasonably well.

Dr. Cortés:
So as we know and said by Hope before, I think that the data of sacituzumab govitecan in triple-negative breast cancer was so exciting that we were all waiting for the next generation of ADC in triple-negative breast cancer. And we knew at San Antonio 2021, the great data by datopotamab-DXd, which is a new antibody-drug conjugate, also against Trop-2. And these data come from a phase 1 study in different tumor types including non-small cell lung cancer, many tumor types, triple-negative breast cancer, and hormone receptor-positive HER2-negative breast cancer. And in triple-negative breast cancer, they treated about 44 patients, heavily pretreated. The median therapies in the metastatic setting was 3. And it's interesting to highlight that a significant number of patients received 3 or more. And regarding adverse events, it's important to remark that no cases of drug-related ILD [interstitial lung disease]/pneumonitis were reported, and the overall response rate was just amazing – 34%, so 15 out of 44 patients did experience response. And for those patients who did not receive previous treatment with a TOPO 1 inhibitor, obviously based on the ADC, the overall response rate was 52%. So very high activity, also with datopotamab deruxtecan, in the triple-negative breast cancer, highlighting the role of anti-Trop2, antibody conjugates in TNBC.

Dr. Gradishar:
So I think the comments from Hope and Javier really highlight the fact that we're going to have, in the near term, probably several ADCs available for treating patients with triple-negative breast cancer. One of the challenges, of course, is understanding how best to sequence these drugs and whether or not they'll have similar efficacy depending on the sequence that's used. And that's all the subject of ongoing research.

I know in the subsequent discussion in Chapter 3, we'll be discussing adverse events because this plays into the decision about how we choose among the different agents that are available, and it may make one more attractive than another depending on the patient.

In Chapter 3, we'll be discussing the management of adverse events associated with ADCs. Stay tuned.

[CHAPTER 3]

Dr. Gradishar:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Bill Gradishar, and here with me are Drs. Hope Rugo and Javier Cortés. We're discussing the use of ADCs in advanced metastatic triple-negative breast cancer.

Welcome back. After hearing about ADCs in development for triple-negative metastatic breast cancer, we're turning now to the management of ADC-related adverse events.

Hope, what are the common adverse events seen with ADCs in triple-negative metastatic breast cancer?

Dr. Rugo:
This is such a great question because, of course, it depends on the ADC. And one of the intriguing areas that's come up is that the toxicity seen with the new antibody-drug conjugates, so these sort of second-generation, loosely called ADCs, seems to be not only related to the toxin, the drug-to-antibody ratio, or the antibody. There's some combination of the delivery with the antibody, the toxin itself, and the number of molecules, the toxins per antibody. And this is now poorly understood.

So for sacituzumab govitecan what we see is neutropenia as by far the most common toxicity. This can be managed pretty well with growth factors. I talk to a lot of people about management of neutropenia on a regular basis. The drug, as you know, is given day 1 and day 8 every 3 weeks. In the phase 3 study, to avoid significant issues with neutropenia, we required a neutrophil count of 1,500 to start each new cycle. But now that we're using it as standard clinical practice, I use a neutrophil count of 1,000, because that's what we use for all other drugs. But we are fairly heavy-handed about growth factors. We use filgrastim on day 3 after the day 1, and then on day 11 or day 10, after day 8, depending on the patient. And then some people have used pegfilgrastim or the long-acting filgrastim after day 8 for prevention of the sort of delayed neutropenia, and then they don't give any growth factor after day 1. That allows you to use the on-body device if you want to use it as well. And in my experience, both approaches work very well. Sometimes we end up giving 2 doses of filgrastim after each infusion, and then of course, dose reduction can also be utilized.

For the diarrhea, which is the next most common toxicity, the major issue is using anti-diarrheal therapy and educating patients up front as early as possible. So this is just really critical. When we looked at the metabolism of the active metabolite, the SN-38 we found that it didn't matter whether you are a poor metabolizer in terms of diarrhea, just neutropenia, which was kind of unexpected. So for the diarrhea, what I've generally done is I educate patients, have them call in if they have more than, you know, sort of minimal grade 2 diarrhea, have them use anti-diarrheals. And then if they really have a lot of diarrhea, we dose reduce. So grade 3 diarrhea in general, for me, is a trigger to dose reduce because it means that those patients just are seeing a lot of drug and are unusually sensitive in a way that we can't measure well.

Otherwise, we also educate patients about the risk of alopecia, and many of our patients use scalp cooling. There is a study going on at Dana-Farber, looking at the efficacy of scalp cooling with ADCs. So that's interesting as well.

And then lastly, I think, you know, nausea is an issue with many of the drugs we give. My experience with sacituzumab is that this is very easy to manage. It's sort of only minimally to moderately emetogenic. We give the nausea medications, some rescue drugs. My favorite rescue drug right at the moment is olanzapine, the antipsychotic. We give it at very low doses, 2.5 mg at bedtime, but you can certainly go up to 5 and up to 10 mg. It's listed in the NCCN. And this is a very nice way for the first 2 to 3 days of preventing ongoing nausea.

But that's not the only toxicities we see with antibody-drug conjugates. So other antibody-drug conjugates that use a topoisomerase inhibitor, deruxtecan, have been associated with very different toxicities. So more nausea, for example, delayed nausea – again, olanzapine works very well – no or minimal neutropenia or cytopenias.

And then one of the ADCs, the experimental Trop-2 ADC that we just heard about in the last chapter, that one causes stomatitis, which may be able to be controlled with a steroid mouthwash that we use with everolimus.

So these are very different drugs, and some of these ADCs that use deruxtecan as a toxin are associated with interstitial lung disease. So that's also intriguing. We don't know why that is. It's not seen with sacituzumab.

And then lastly, there's even another experimental ADC against HER3 that causes thrombocytopenia – same toxin, deruxtecan. So this is clearly a very interesting area with the experimental ADCs and, I think, also one that hopefully we'll learn more about and understand better as we explore even more ADCs to treat metastatic disease.

Dr. Gradishar:
Thanks, Hope, and I think what that discussion really illustrates is that oncologists, when they first encounter a new drug, are often guided by the [package] insert and how the trial was done. The reality is once physicians start using the drug, they understand better how to overcome the side effects that patients encounter. So whether it's dose reduction or the use of growth factors, or anti-emetics, or in the case of stomatitis, mouthwashes, these are all things that physicians, oncologists deal with on a day-to-day basis, sort of with standard chemotherapy and other targeted therapies. So I think we learn as we go. And we develop a skill set that allows us to keep patients on a drug, at the same time minimizing, hopefully, the side effects that they experience.

One other side effect that patients often experience with metastatic disease, and often amplified by certain therapies, is fatigue. And I think we have to acknowledge that that is part of a patient's experience. And we have to do everything we can to minimize those kinds of side effects to maintain quality of life.

In Chapter 4, we'll touch on regional considerations in treating triple-negative metastatic breast cancer. Stay tuned.

[CHAPTER 4]

Dr. Gradishar:
Welcome back. After discussing the management of ADC-related adverse events in triple-negative metastatic breast cancer, we're going to close by taking a look at regional considerations.

Javier, can you talk a bit about challenges to testing outside of the US?

Dr. Cortés:
So I think that, you know, again, it's difficult to talk about challenges outside the United States because of the great heterogeneity across different countries. Not only the differences between the biomarkers that we can ask for, also the different techniques, even availability of different drugs. For example, in many countries, the new antibody-drug conjugate sacituzumab govitecan is not approved. In other ones, it is. So I think that there is a nightmare here. It's a very heterogenic situation. But I'd really like to highlight 3 key aspects. The first one relates to the biomarker, and it is important to highlight that in many countries, either PIK3CA mutations, the germline BRCA1 and BRCA2 mutations, and the PD-L1 expression are widely available, and this could be important for the clinical practice. Basically, in the

triple-negative breast cancer field, I would highlight the PD-L1 expression for the use of immunotherapy and the germline BRCA1 and/or 2 mutations for the use of PARP inhibitors.

The second is what about all the biomarkers with potential interest in the clinic, such as, for example, PALB2, again, a very heterogenous situation, highlighting that aspect. And finally, I would like to highlight not only the testing challenges, not only the biomarker access and assessments, but also, as I said at the very beginning, the drug approvals. It's very important to highlight that in addition to the antibody-drug conjugate, many other agents – the PARP inhibitors, also the immunotherapeutic approaches – and the new data we have seen, for example with trastuzumab deruxtecan, in a small number of patients with triple-negative breast cancer and HER2-low expression. This will be something to be considered if we would like to homogenize a little bit the treatment opportunity for the patients outside of the United States. I am not talking only about Europe. I'm talking, unfortunately, for many other countries as well.

Dr. Gradishar:
Well, this certainly has been a fascinating conversation. To summarize a great deal of data and discussion, I think we all are excited about the promise that ADCs have shown to date, as well as the drugs that are on the horizon that we may have access to. I think one of the interesting things that we have to acknowledge is that when we think about immunotherapy, we have to do testing to determine whether or not a patient is PD-L1 positive in order to decide whether that given patient is eligible for therapy. In contrast with the ADCs to date, we don't need to know the level of target that's present because in the example of Trop-2, we know that sacituzumab govitecan works whether you have high expression or low expression, so that doesn't seem to be the case. So as we go forward, we'll have to see if that holds true for all the other ADCs in development.

As noted by Hope and Javier, there are predictable side effects that occur with these agents. We know how to manage these by our experience with other chemotherapy drugs that we often use. Things such as neutropenia or diarrhea, stomatitis, et cetera, are all manageable with current strategies that we use for other things. Obviously, fatigue is something that is very important to patients, and we have to acknowledge that as potential side effects for all of these drugs.

So as we go forward, we hold the hope that we'll have other drugs that are available not only in the US, but around the world.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening in and thanking both Dr. Hope Rugo and Dr. Javier Cortés for joining me and for sharing all of their valuable insights. It was great speaking with you today.

Dr. Rugo:
Bill, this has been a great discussion. Thanks so much for including me.

Dr. Cortés:
Thank you very much again for having me today. It was a terrific – a great, great, great, amazing discussion. Thanks. Thanks, folks.

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