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Antibody-Drug Conjugates in Bladder Cancer: Guideline Updates and Adverse Event Management

Announcer:
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Dr. Plimack:
Hello. I'm Dr. Elizabeth Plimack, Deputy Director here at Fox Chase Cancer Center in Philadelphia, Pennsylvania. And I'm joined by Dr. Shilpa Gupta at the Cleveland Clinic in Cleveland, Ohio. Welcome to this educational activity entitled, “Antibody Drug Conjugates in Bladder Cancer: Guideline Updates and Adverse Event Management.”

Let's begin with our discussion of the expanding role of ADCs in the treatment of bladder cancer. Let's start with a clinical case. This is a 67-year-old man with metastatic urothelial carcinoma involving liver and bone and diagnosis. He was immediately started on enfortumab vedotin with pembrolizumab. Let's look at the data underlying that treatment decision.

EV-302, or KEYNOTE-A39 is a randomized phase 3 trial of patients like the one I just presented, who present with metastatic urothelial carcinoma. They had to be eligible for platinum and enfortumab vedotin and PD-L1 inhibitor naïve. Patients were randomized 1:1 to get EV with pembrolizumab or chemotherapy, which was cisplatin or carboplatin plus gemcitabine, for a maximum of six cycles. The dual primary endpoints of PFS and OS are listed here.

I'll turn it over to Dr. Gupta to go over these results.

Dr. Gupta:
Thanks, Dr. Plimack. So this was the pivotal trial that set the standard for enfortumab vedotin and pembrolizumab as the preferred frontline therapy. We saw in the initial data that was presented in 2023 that compared to platinum chemotherapy, the progression-free survival was doubled with EV/pembro, 12.5 months versus 6.3 months. Overall survival was also doubled. The response rates were 67% versus 44%. And complete responses were 29% with EV/pembro versus 12.5%. And this was really very impressive data.

And just recently we saw the longer follow-up on this study, and progression-free survival and overall survival benefit was really beautifully maintained with the curves remaining separated. As we can see here, the median progression-free survival was 12.5 months with EV/pembro versus 6.3 months with chemo. And the median overall survival was 33.8 months versus 15.9 months.

And this regimen really does not, you know, set apart what eligibility we need, regardless of whether patients were cisplatin eligible or not, the EV/pembro performed superiorly, as we can see here, cisplatin eligible and ineligible groups. Now it may seem that, you know, the benefit is more in cisplatin ineligible, but that's primarily because carboplatin underperforms, you know. So this is really a regimen that does not need any eligibility. And I want to highlight that PD-L1 really has no role as a biomarker to select this regimen. It works regardless of PD-L1 expression.

And more importantly, we know that liver metastases are a sign of poor prognosis for our patients. And immunotherapy by itself doesn't really work well. But with EV/pembro, we see that there is this really great activity that we see in liver metastases and any other visceral sites or lymph nodes as well. So this is very reassuring to see that, you know, in visceral metastases, which put a patient in high-risk category, they do really well.

Dr. Plimack:
Okay. Thank you, Dr. Gupta. You showed the data beautifully, and I think this is why now EV/P is standard of care in frontline therapy, a really definitive advantage over what we had before, which was chemotherapy followed by maintenance immunotherapy.

So this puts us in a new sort of era where we don't yet have trials in the second-line space after EV/P, but certainly patients do ultimately progress on it. A few right away, but some over time. And so again, I thought, Dr. Gupta, you and I could maybe discuss how we work in this data-free zone today, where we have our patients all starting on EV/P, but then in the second line, we kind of have to figure it out as we go. What's your approach to the patient, for instance, who progresses right through EV/P, for instance, at first scan?

Dr. Gupta:
Yeah, those patients really, you know, are a challenge to treat. And Betsy, on the EV-302 study, patients who were progressing got subsequent platinum, around 30% of them with around 30% response. And that is my practice. And I've actually seen that patients who are rapidly progressing on EV/pembro, we are able to stabilize with subsequent platinum. So I think that definitely platinums are not over and out; they do have a space in this setting, and we need to generate prospective data with that.

But also a reminder for our audience to make sure patients are being tested. Their tumors are being tested for genomic sequencing, so we know if they express FGFR 2 and 3, which we have therapy, as well as HER2 expression on IHC. So I think all those are important to line up for subsequent therapies. But I would say somebody progressing on EV/pembro, platinum is my go-to drug, provided patients don't have bad neuropathy, in which case we would use carboplatin. Otherwise, cisplatin is fine as well.

Dr. Plimack:
I totally agree. We tend to practice the same way, and we're aligned on that. We do feel like platinum was a powerful first-line therapy until we did better with EV/P, and so certainly offering it to patients, even though it's in the second-line, where we don't have data as to how it performs after EV/P, makes sense. I'm glad you, anecdotally, have seen good responses. I have as well, so that's nice to see.

Can I ask, when do you send the testing for targeted therapies, at what point in a patient's journey?

Dr. Gupta:
I do send it when we see patients with advanced disease or metastatic disease, because sometimes, you know, we can't really wait for so many weeks to get the results back, so I tend to do it sooner than later.

Dr. Plimack:
Right. Me too. I think that's good. It's good to be prepared and then be able to plan.

Okay, let's go back to the clinical case. So as you recall, this was a 67-year-old man presented with liver and bone metastases. Received EV/P, and then, unfortunately, he was in the rare 11% or so of patients who had disease progression at first scan. We did start gem/carbo. He received five cycles with a partial response, but it was really poorly tolerated for him. And at that juncture, we brought in palliative radiation for some of his painful bone metastases, and gave him a little bit of a treatment break. In this particular case, we actually got a fresh biopsy during this treatment break, one, because we had time, and two, because sometimes, you know, genomics - tumor makeup can change and the biomarkers can change over time. And that liver biopsy showed no FGFR mutation, but low PD-L1, and ERBB2, fortunately, which was IHC 3+. So HER2 was 3+ for this gentleman. So we were excited to see that. This makes him a candidate for trastuzumab deruxtecan. I'll walk through the data that we have so far.

So trastuzumab deruxtecan is an antibody drug conjugate targeting HER2 with a payload of DXd, a topotecan derivative. And it was tested in a basket study across multiple tumor types that you see listed here. The bladder cancer cohort included 41 patients total, and of those 16 were IHC 3+, and the response rate in that group was 56.3%. And also, I would say the one disappointing thing about these data so far is that the responses don't seem to be that durable. But again, I emphasize, this is early, with a very small sample size. Based on this entire study, trastuzumab deruxtecan got a tumor agnostic approval based on IHC 3+ for HER2.

Okay. So this patient started on trastuzumab deruxtecan. On his first scan after three cycles, the MRI reported that previously seen hepatic lesions are no longer visualized. There was only residual scar. His bone metastases were stable. His pain had improved, and he had no new sites of disease. So now he's 20 months since his initial diagnosis, and continuing on to his second scan on trastuzumab deruxtecan.

So let's move to another ADC that sort of has come and gone, but is worth discussing. And that's sacituzumab govitecan. Dr. Gupta, can you take us through this story?

Dr. Gupta:
Yeah, thank you, Betsy. Great to see that your patient did well with the T-DXd, and great to see so many options, especially with antibody drug conjugates.

So TROPHY-U-01 was a multi-cohort, open-label, phase 2 study in patients with metastatic urothelial cancer. It had, like, you know, multiple cohorts. But we'll focus on the key cohorts. These were the patients who had post-platinum and post-immunotherapy setting that is the same as monotherapy for EV, this was the cohort 1. And for our audience, sacituzumab govitecan targets TROP2, and the drug is, you know, irinotecan derivative. And in this we saw some encouraging initial activity, like we do in single arm trials, 28% responses. And in the US, we had FDA grant accelerated approval for patients who had prior platinum and prior immunotherapy. And later on, you know, EV had become approved, so that was our standard. So this was really kind of fourth-line treatment.

And that phase 3 study, TROPiCS-04, was a global study, primarily ex-US. And this was a phase 3 study comparing sacituzumab govitecan with dealers choice salvage chemotherapy, which could be vinflunine in Europe, or docetaxel in the US. We recently just saw the data for this at ESMO Asia, and this was just published hot off the press. This was a negative trial. Not just was sacituzumab not better than the chemotherapy, but it was even more toxic. There were toxic deaths on this study from neutropenia, which is really, you know, disappointing in today's day and age. So this drug was voluntarily withdrawn from the US market, and like you said, it came and went, but we learned a lot from this. So for future drug development with these kind of ADCs.

Dr. Plimack:
Thank you. Yes, I think everything you said reflects our experience with it here. It was very difficult to give and I think at the time, we weren't quite sure if it was the line of therapy or the individual patient. But seeing these data in aggregate and seeing the toxicity signal does not surprise me. I don't know if you had a different experience.

Dr. Gupta:
I think, you know, our practice is that I was using preemptive growth factors, and never really had that problem. But that was not mandated on the protocol, and I think that's where we could have probably seen less toxic deaths.

Dr. Plimack:
Yeah, yeah. No, I think growth factors would help. We did use that also. It was more platelets and hemoglobin that were a little more challenging. But in any case, we always try to optimize efficacy, but also tolerability. And in that sense, I'm glad we have new options.

Okay, we're going to shift gears to muscle invasive bladder cancer. So these are patients we're trying to cure. Their bladder cancer has advanced into the muscle wall of the bladder, and we are hoping ADCs make their way into muscle-invasive disease. Again, this is an earlier stage of disease where we're going for cure. Neoadjuvant chemotherapy has been the standard of care for some time for this disease. We do know that neoadjuvant, giving chemotherapy to shrink the disease we see and that that we don't, has led to improvals in overall survival, even using the oldest versions of chemotherapy that we have. So dose-dense MVAC preferred or cisplatin/gemcitabine as alternative.

So right now, we're in the midst of a whole series of perioperative trials. There are six that I know of, large, randomized, phase 3 clinical trials in muscle-invasive bladder cancer. They all have similar designs. I like to call it a sandwich design, where patients are enrolled, they receive novel therapy as neoadjuvant, they all get cystectomy, and they all receive a similar therapy as adjuvant, and usually the control has been gem/cis, or gem/carbo, mostly gem/cis, I guess, for this population, unless they're cis ineligible, followed by cystectomy and then followed by placebo, but not adjuvant therapy. And so fortunately, we've made some progress in this space. Adjuvant therapy with nivolumab is approved and is an option, but the, I think, experimental arms are of interest, and we'll learn a lot from these.

So on this slide are four of the six trials in development. The ones on the left, I'll draw your attention to those involve antibody drug conjugates. This is leveraging the EV/pembro combination to achieve better results at the time of cystectomy, and then it's followed by EV with pembrolizumab after surgery. And then at least EV-905 has a pembrolizumab alone arm as well, with pembrolizumab single agent sandwich. And then KEYNOTE-B15 looks at EV/pembro versus gem/cis, this is for cis eligible patients, sandwich approach versus gem/cis followed by observation. So hopefully these will read out soon. I kind of feel like we'll learn the results all at the same time.

One sandwich design study durvalumab plus gemcitabine/cisplatin did read out. And there's a lot of excitement around those results. And I'll turn it over to Dr. Gupta to briefly walk us through those.

Dr. Gupta:
Yes, thank you, Betsy. There's certainly a lot of excitement going on in the space, and we'll see where EV/pembro finally moves. You

know, if it does move in the earlier space.

But it was nevertheless exciting to see the first chemo IO combination study read out. As we know, there's this durvalumab and chemo. We also have nivolumab and chemo trial, ENERGIZE trial, we've not seen data from, and then we have the durvalumab trial. So this was the first trial that led out. This was MIBC patients who were randomized to either gem/cis or gem/cis and durvalumab, and then patients who got durvalumab also continued that in the adjuvant setting. Now this trial completed accrual 5 years ago when we did not have standard of care immunotherapy approved for adjuvant setting. And we saw the data last year at ESMO that this study improved event-free survival significantly compared to chemotherapy, the triplet was better and even met its overall survival endpoint. Now, the pathologic complete response, which was a primary endpoint, was not met, but we also saw that the chemo arm underperformed than usual. And it makes us wonder if with the immunotherapy addition, we really need to focus on path CRs anymore, or focus more on the durability of the response. So I think this is very exciting data. This regimen is not approved in the US yet, but hopefully we will have this approved for our patients who are getting gem/cis in the neoadjuvant setting.

It also has some key highlights. You know, historically, cisplatin eligibility was around 60 mils per minute of creatinine clearance, but this trial actually used a lower cutoff of 40 mils per minute where you can use split dose. So that is an important message. It also included patients with various variant subtypes. So I think this was a very progressive trial, and certainly, if we are planning to give platinums in the neoadjuvant setting, need to add durvalumab to it.

Dr. Plimack:
Yeah, I think definitely kudos to this team for really broadening eligibility to reflect the patients we see. I think that's really important. We're all glad they did that.

Great. Okay, so just to cover muscle-invasive bladder cancer, the ADCs are coming. We don't know where they'll fit. We'll see. Usually when things work really well in the metastatic setting, we see that parlay into the MIBC setting, and I hope that's the case for enfortumab vedotin and pembrolizumab. But more to come.

We're going to move to talk about antibody drug conjugates and managing the adverse events. Obviously, we treat for efficacy but manage for toxicity. And the management strategy for these ADCs is new to a lot of folks who aren't used to using them. And Dr. Gupta and I will sort of go through both the AEs that are commonly seen with ADCs and how to manage them.

So first, I'll start by going through the various AEs that we see enfortumab vedotin and pembrolizumab. Just consented a patient this morning to this treatment. And the three things I highlight are the skin reactions, hyperglycemia, and peripheral neuropathy. So skin reactions are one of those places where EV and pembro overlap. Both can cause rashes. Together, the rashes can be really bad. In the worst case, they can advance to mucosal involvement, which can be dangerous. But most of the time, they look like the picture here, erythematous, scaly and pruritic. The other thing that we watch for is hyperglycemia. This occurs in 13% of patients treated with EV/P. Usually happens early. Highest risk in diabetics. So we check an A1c, it should be less than 6.5. And we think the mechanism it's insulin resistance. And the last one doesn't usually happen immediately, but happens to almost everybody if they have enough cycles of EV along with their pembrolizumab, and that's peripheral neuropathy. It can be both motor or sensory. Motor, it obviously impedes function significantly. Sensory can as well. It is the second most common AE that patients get with this regimen. And again, by about 6 months, almost everyone has a little bit of it, if not a lot of it. It is the most frequent reason to have to discontinue enfortumab vedotin.

Moving on to some less common AEs, but ones to be aware of. Pneumonitis can happen with both pembrolizumab and EV; it tends to be more severe with pembrolizumab. But of course, when you combine, you can't always tell what's causing it. Diarrhea seen in 21 to 38% of patients treated with EV/P, but mostly mild. And as you know, doctors who are experienced in treating chemotherapy side effects, we're used to managing diarrhea in our patients. Fatigue kind of is par for the course. Severe fatigue, you would want to work the patient up for hypothyroidism or adrenal insufficiency, which can result from pembrolizumab, but standard sort of chemo-type fatigue comes along with this. This is, oh, Dr. Gupta will talk about managing it. And then ocular disorders. This is something new with EV. With EV, the ocular disorders are more surface and dry eye. They're typically mild and managed with drops but sometimes do require ophthalmology follow-up.

Alright, I'll turn it over to Dr. Gupta. I told you all the things that could go wrong on these treatments, and she's going to tell you how to manage them and help our patients through them.

Dr. Gupta:
Thank you, Betsy. So as you mentioned, you know, the skin reactions can be a mild rash, but it can also be life threatening. And in the earlier trials, we did see toxic deaths with this regimen. So we have to be very careful. Of course, you know, pembrolizumab can cause a rash, EV can cause a rash, so it becomes confusing many times. So what I do is, I always, you know, depending on the severity of the rash, first we make sure it's not Stevens-Johnson or anything severe. Obviously, the first thing to do is hold EV and pembro both. If this

is so severe, start with steroids. You know, if it's mild, then do topical steroids. But don't hesitate to do systemic steroids. And there's really no rush to go on treating through these rashes, you know, till it's resolved. And if it is felt to be EV, once you hold it, it will get better eventually, and then we should strongly consider a dose reduction. Also refer to dermatology to make sure patients are taken care of.

But this brings us to the point that it is important to do a skin exam. You know, we have to be good doctors and not just go by what the patient is telling us. Because, in my experience, patients many times underreport their symptoms on this regimen because they are benefiting.

For hyperglycemia. You know, my experience has been, Betsy, that it's not really the diabetics who we worry about; it's like catastrophic complications in patients who are not known diabetics, where you can end up in diabetic ketoacidosis. But having said that, you have to make sure their blood sugars are, at any given point, less than 250. To give EV if they're, you know, in the study, they excluded patients with HbA1c less than 8. So if there's somebody who's a poorly controlled diabetic, it would be prudent to just start to intensify their diabetes management before embarking on this regimen.

And neuropathy is, again, a very, very severe complication, which we don't want to really overlook. And it can be even more than neuropathy. You know, many times patients will say, no, we don't have any neuropathy. And then their partners will tell us they're having falls at home, and when you make them walk, they have this wobbly gate. So I think again, very important to say that do a physical exam, do a grip test, make the patient walk. And if the neuropathy is grade 2 or higher, do not give EV. And this can take a long time to recover, over 7 months. And that brings us to the question of, you know, do we really need so many doses of EV/pembro? And I know, Betsy, your group, and we have talked about it so much, I don't think they do. And even when you hold the EV, patients continue to derive benefits. So it's very important not to keep, you know, giving this drug boldly through somebody struggling, because they can get debilitating neuropathy, and quality of life can really suffer. And of course, what we usually do for neuropathic pain, we should use that. But key here is to do a good physical exam and history taking.

And again, for pneumonitis, we all know, we've been doing this for a long time, and both EV and pembro can cause that. So start steroids for more severe ones, hold the doses. And then, depending on if it was grade 1 or 2, you might want to rechallenge later if needed. But for grade 3 or higher, I would not rechallenge.

And GI symptoms, like you said, Betsy, nothing major, so just use the common management.

And ocular disorders. Again, we are lucky to have ophthalmologists at our center, but with EV really, we don't see severe ocular toxicity. It's always superficial. You hold the drug and it gets better. You can give, you know, eye drops and things. It's not like some of the other drugs where we get retinal toxicity. So that has not really been a bad issue for us.

Dr. Plimack:
So in general, Shilpa, when you're managing someone, let's talk about EV/P, for instance, because you brought up, you know, how many cycles of EV do we really need? The neuropathy is almost always dose limiting in patients. And because it's so effective, people are on it for a long time, it's sometimes hard to convince doctors or patients that stopping because of toxicity may result in a preserved response. Have you seen patients who stop EV and either continue pembro or stop both and maintain their response off of it?

Dr. Gupta:
Yeah, absolutely. I have many such patients on. In fact, one patient did not need any treatment for 1.5 years, and only when we saw some things progressing, we just gave few doses again of EV, and they did really well. So you know, this intermittent approach, if you will, I think is very effective. And I think in the study, originally, EV did not have a stop date only because we didn't really know how much we needed. But you know, pembro does have a stop date. So I think we now really need to discuss induction regimen followed by maintenance pembro. So in my experience, mostly patients maintain their response off EV.

Dr. Plimack:
Yeah, I would say that our experience here is reflective in that too. And I think when you get the courage to stop, and you see that response continue, you then get the courage to stop maybe a little sooner, before the neuropathy is truly dose limiting and forces you to stop.

Dr. Gupta:
It's a constant discussion with the patient, you know. We say, okay, you know what, we'll move the scan up a little bit for reassurance, and then patients also get more and more reassured, and they are recovering from their side effects. It's pretty good.

Dr. Plimack:
Yes, absolutely.

Okay. Let's move to trastuzumab deruxtecan. This is a new drug to the GU world, but it's been in breast cancer for a very long time. So the side effects are listed here, and these are really side effects we're used to because they occur with chemotherapy. So nausea and vomiting, neutropenia, infusion-related reactions, alopecia, and fatigue. So I think using the standard tools that any medical oncologist experience with chemotherapy has for these is helpful. For neutropenia, you can use prophylactic G-CSF. For nausea and vomiting, of course, antiemetics, both preventive and then for treatment. And then, you know, alopecia, we just warn patients in advance, lot of them have very nice hats that they come in with. And of course, the fatigue is just something to be managed with graded activity and those sorts of strategies. But the interstitial lung disease, or pneumonitis, is a hallmark potential AE with trastuzumab deruxtecan. It is not common, but it can be severe, and so we'd like to just go over some principles of management of this particular adverse event.

So Dr. Gupta, what do we do if we see ILD/pneumonitis?

Dr. Gupta:
So I think, you know, our community is already aware of how to deal with pneumonitis from immunotherapy. So the principles are the same anytime you're suspecting clinically or on radiologic findings, just like this index case here. Symptoms could be hypoxia, cough, dyspnea, chest pain. And T-DXd, Betsy, like you said, is pretty well known to cause this. So it's very important to hold the drugs, start systemic steroids, and do not rechallenge if it was a severe case. And if it is mild and we need to, then that's a constant discussion with the patient. But I think key here is to stop it as soon as we see signs of pneumonitis.

Dr. Plimack:
Right. Exactly. Just be aware, ask, check pulse ox at every visit, and stop when in doubt. Yep, absolutely.

Well, I think we covered a lot today, Dr. Gupta. This was really fun talking to you. It's so exciting that we have so many new developments in bladder cancer. We're really moving the needle in metastatic disease. We expect that to translate into muscle-invasive bladder cancer. We're already seeing that.

Any final thoughts you have for our audience?

Dr. Gupta:
Thank you, Dr. Plimack. Always great, discussing with you and aligning our practice and insights. I think, you know, the final thoughts are as we are moving these very effective drugs early on, we really need to start thinking about how much is enough, right? Even in the muscle-invasive setting, I don't think giving this as a blanket approach, if they were to get approved, to everybody adjuvantly would be very, very realistic, right? So we need to see the data and the safety and the toxicity to make those decisions for us.

Dr. Plimack:
Thank you for joining us for this educational activity entitled, “Antibody Drug Conjugates in Bladder Cancer: Guideline Updates and Adverse Event Management.” Please continue to complete the post-test and evaluation to receive credit. Thanks for joining us.

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