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Keeping Pace: Emerging Treatment Considerations in Metastatic Urothelial Cancer

Announcer:
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Dr. O’Donnell:
Urothelial cancer, primarily in the bladder, is the sixth most common malignancy in the United States. Treatment of metastatic urothelial cancer has historically been limited to platinum-based chemotherapy. However, the majority of patients will relapse. Immunotherapy has recently offered survival benefits to patients. However, those with locally advanced or metastatic urothelial cancer don’t always respond to immune checkpoint inhibitors.

Welcome to CME on ReachMD. My name is Dr. Peter O’Donnell, and I’m joined today by Dr. Daniel Petrylak to discuss recent advances in the treatment of metastatic urothelial cancer. Welcome to the show, Dr. Petrylak.

Dr. Petrylak:
Thank you, uh, Dr. O’Donnell. How are you today?

Dr. O’Donnell:
I’m well, thank you. To get us started, Dr. Petrylak, what first-line treatments are available for patients diagnosed with locally advanced or metastatic urothelial cancer? And in addition, could you comment on how you choose between them?

Dr. Petrylak:
Well, first-line treatments are based upon the patient’s eligibility for cisplatin. As we know, bladder cancer is a tumor that is induced by tobacco as well as other chemical carcinogens, and the patients do tend to be older. So, they can often have comorbidities, which can influence the renal function and their ability to tolerate cisplatin. Other issues include neuropathy, as well as congestive heart failure, or the inability to be hydrated as well as hearing loss. So, about 30% of patients are not eligible to receive cisplatin-based chemotherapy. So, the first thing we determine is whether patients are eligible to receive cisplatin-based chemotherapy, and if they are, the treatments include either gemcitabine and cisplatin or MVAC (methotrexate, vinblastine, doxorubicin [Adriamycin], cisplatin). If they’re they are not eligible to receive cisplatin chemotherapy, then we have a choice based upon their marker status for PD-L1. If they’re PD-L1 positive, they would then receive pembrolizumab, a checkpoint inhibitor, or atezolizumab. The difference being that 1 is a PD-L1 inhibitor and the other is a PD-1 inhibitor. Or they could go on to a clinical trial. If they have negative staining for PD-L1, then chemotherapy, generally carboplatin plus gemcitabine—are administered to the patients.

Dr. O’Donnell:
Great. Could you compare or give us a sense of how effective say platinum-based chemotherapy is versus if a patient did have PD-L1 and used immunotherapy in the front-line setting?

Dr. Petrylak:
So, in a platinum-ineligible patient, if we look back from some data from Europe, the median survival is fairly dismal with the combination of gemcitabine and carboplatin. It is only about 9 months, and the response rates are lower than what you would expect with cisplatin-based chemotherapy. In phase 2 studies, we're seeing better survivals with either pembrolizumab or atezolizumab. Generally, the survivals are about 15 months overall, and so that was one of the things that led to the accelerated approval of these drugs in this setting.

Dr. O'Donnell:
Great, and 1 other point we should make about cisplatin or carboplatin-based therapy even though response rates are generally the majority of patients, or at least half or higher numbers of patients will respond to cisplatin-based therapy, could you just remind the listeners about immunotherapy response rates? While we're excited about durability, that it's actually a subset of patients that will even respond?

Dr. Petrylak:
Exactly, and really the driver in survival with immunotherapy is the duration of response. You may sense, overall see a lower response rate, generally about 20%, with immune therapy, but we know that these responses in some cases could be durable for years, but generally, they are fairly durable responses compared to chemotherapy where you may have an improvement in progression-free survival over immune therapy, but the overall survival does seem to be comparable.

Dr. O'Donnell:
Great. So, let's move from front-line to now a patient progressing beyond first-line therapy, and could you talk a little bit about now what the options are for patients that progress after whatever front-line therapy you're choosing?

Dr. Petrylak:
So, for second-line therapy, if a patient's had primary chemotherapy, there are 5 checkpoint inhibitors that are approved for this clinical state. These include avelumab, atezolizumab, pembrolizumab, nivolumab, and durvalumab, and they all seem to have similar overall response rates. The difference between these agents is the fact that pembrolizumab is the only agent that has shown a survival benefit over standard-of-care chemotherapy in a phase 3 setting. There has only been 1 other phase 3 trial that's been with atezolizumab, and that did not show a survival benefit but we really can't tell what the real reasons for the failure were, but, nonetheless, pembrolizumab is the only drug that has phase 3 data that supports its, its use.

Dr. O'Donnell:
So, let's let us talk now about patients that traditionally might get chemotherapy, platinum-based chemotherapy front-line, they move to the checkpoint inhibitor second line. Oftentimes, these patients are still have uh, uh, inadequate performance status to consider third-line therapy because the immunotherapies are so well tolerated in the second line. So, could we touch on what the options now are available for that post-platinum, post-immunotherapy space?

Dr. Petrylak:
So, enfortumab vedotin was recently approved by the Food and Drug Administration (FDA) through an accelerated approval mechanism based on a response rate that was a little bit more than 40% in patients who had received either chemotherapy or checkpoint inhibition therapy. The survival was approximately a year in these patients, which is much better than what you would expect with historical controls.In fact, most of the chemotherapy trials that have been reported have been in the second-line setting. This is in the third-line setting, which I think is even more impressive. So, one of the things I think is really unique about enfortumab vedotin is the fact that you tend to see responses in areas where you never really saw great responses with chemotherapy, particularly in the liver. If you look at the overall stratifications in the different subgroups of patients that were analyzed, patients with liver metastases did just as well as patients who had lymph node-only disease. So, there were responses around 40% percent seen in this group of patients as well. I think what's remarkable about the enfortumab vedotin is that it's almost a carbon copy of the data we reported in phase 1. Response rates are similar, the toxicities are similar, and I think that only strengthens the case of the data for this particular drug.

Dr. O'Donnell:
It is a very exciting drug. Ive also used it in a number of patients during the clinical trial development, and the impressive activity in this third-line setting really almost acts like a first-line drug as far as activity.

Dr. Petrylak:
In fact the only drug that has shown a greater than 40% response was paclitaxel in the first-line setting given as a 24-hour continuous infusion. Bruce Roth published that a number of years ago. So, the fact that we're seeing this response rate in a third-line drug is remarkable.

Dr. O'Donnell:
Those are great points. Could you just briefly speak to those other trials that are going on because of the accelerated approval status?

Dr. Petrylak:
So, the phase 3 trial would, if it's positive, which we're hoping it will be, will elevate enfortumab from accelerated approval to a full approval, and this is a trial that was being done both in the United States and Europe, randomizing patients same in clinical characteristics as we saw, uh, with the phase 2 study prior chemotherapy and prior checkpoint inhibition therapy.These patients are randomized receiving enfortumab or a standard-of-care chemotherapy, which could be a taxane or vinflunine in Europe.

Dr. O'Donnell:
One thing maybe we should backtrack to as well is this is an antibody-drug conjugate, and clinicians may be familiar with some other antibody-drug conjugates that are on the market. Could you remind us about the specific target of this drug? I'm often asked, "Is there a test that we need to do to qualify patients for receiving these drugs?" So, could we talk about that?

Dr. Petrylak:
Well, nectin-4 is a, the target of the drug. It's a cellular adhesion molecule. It's expressed in 90% of urothelial carcinoma specimens, and when we first started the trials in phase 1, we had a requirement for patients having nectin staining to enter, and, in fact, every patient stained positive for nectin. So we dropped that particular requirement. So, it's a targeted therapy that does not require that you look for the target, which I think is actually a big advantage for our patients because they can go right on study, and you don't have to wait for molecular tests to tell them whether it's appropriate to receive the drug. So the way the drug works is nectin is the target, as I mentioned before. The antibody binds to nectin, and MMAE, which is an antitubulin agent, is then incorporated into the cell. Its cleaved, and that hits its target, which is tubulin. So, it does cause direct cytotoxic effects on the cancer cell, and the theoretical advantage is that you're delivering high doses of MMAE to the cancer cell and sparing some of the normal tissue.

Dr. O'Donnell:
Excellent. That leads me to ask about expected toxicities of the drug. What could we highlight for clinicians that may be using this drug for the first time?

Dr. Petrylak:
Well, as all antitubulin agents, we see neuropathy, and in the trial, we basically did not permit patients to have grade 2 or greater neuropathy to enter, and we actually hold doses for grade 2 or greater neuropathy.We sometimes have to dose-reduce the patients. We sometimes use Lyrica to help overcome some of the side effects. So, there are ways to manage neuropathy either by dose reduction or skipping doses in a given situation, but that is one of the side effects we tend to see that is known for the antitubulin agents. Other side effects that we've noticed with the drug or noted with the drug include rash. These are generally self-limited. It's usually a rash that is different from a checkpoint rash in that you don't give oral steroids. You treat this rash topically with steroids. We also see neutropenia, and we also see hyperglycemia. So, it's important to check glucose levels prior to patients starting therapy, and in fact, you have to monitor these carefully and be sure the patients don't become hyperglycemic. We are still unsure as to what the mechanism of hyperglycemia is in these patients.

Dr. O'Donnell:
Great, and maybe the last point we'll make is we've seen such a dramatic change in the landscape of treatments for urothelial cancer. We've highlighted the FDA-approved therapies, including enfortumab vedotin, in this space. One we didn't mention, which has sometimes for patients a confusing similar name, is erdafitinib. Could you talk about how you might think about that in this third-line space, and the fact that it has a restricted population?

Dr. Petrylak:
So, erdafitinib is FDA-approved in those patients who have FGFR3 positivity. This represents about 10 to 20 percent of patients with metastatic urothelial carcinoma. Interestingly, if you're FGFR3 positive, you tend not to respond to checkpoint inhibition therapy, and so, again, this is another avenue for those patients who are refractory to treatment. The response rates are approximately 40% in patients who have this particular genetic marker, and the overall survivals are approximately 11 months. So it does seem to be a similar response rate in survival to what we see with enfortumab. Again, you can't compare these because these are completely different trials, but there are patients I've used both drugs in sequence. The question really is is what's the right sequence to use?

Dr. O'Donnell:
Those are great points. Unfortunately, our time is running short now, Dr. Petrylak. Why don't we wrap up by just sharing some key takeaways from our discussion today? Could you go first?

Dr. Petrylak:

The key takeaways from our discussion is the fact that we are light-years ahead of where we were 5 years ago in the treatment of metastatic urothelial carcinoma. Before the approval of checkpoint inhibition therapy, we really had no agents in the second line. Now we have 5 approved agents for second-line therapy. We have targeted agents, including erdafitinib as well as enfortumab, and we are clearly seeing an improvement in survival as well as quality of life for our patients based upon these new findings.

Dr. O'Donnell:
I couldn't agree with all of that more, and I think really the interesting aspect going forward will be how do we start combining some of these therapies? How do some of them actually get moved even earlier in the treatment course for these patients? Even into the perioperative setting? Those are exciting questions to come. So, that brings us to the end of our discussion today. I'd really like to thank Dr. Petrylak for joining me to talk about these recent advancements in the treatment of metastatic urothelial cancer. It was great speaking with you today, Dr. Petrylak.

Dr. Petrylak:
Likewise.

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