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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Keeping Pace in Bladder Cancers: All About Sequencing in Locally Advanced or Metastatic Urothelial Carcinoma

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Keeping Pace in Bladder Cancers*: All About Sequencing in Locally Advanced or Metastatic Urothelial Carcinoma*" is provided by Prova Education.

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Dr. Petrylak:
Treatment sequencing is increasingly complex and nuanced in second or subsequent lines of therapy for locally advanced in metastatic urothelial carcinoma, or MUC. This is largely due to multiple patient and disease factors and evolving clinical trial data that must be considered. Are you selecting and sequencing the most appropriate therapeutics for your patients?

This is CME on ReachMD, and I'm Dr. Daniel Petrylak.

Dr. Siefker-Radtke:
And I'm Dr. Arlene Siefker-Radtke.

Dr. Petrylak:
So let's jump right in, Arlene. It's critical that we select and sequence the appropriate therapeutics to provide our patients with the best possible outcomes. Can you give us an overview of the different patient and disease factors we need to consider when managing patients with MUC who have progressed after first-line therapy?

Dr. Siefker-Radtke:
Certainly, Dan. This is certainly a complex and developing field. So a lot of what we talk about, there isn't definitive data on how we should select subsequent lines of treatment. And there's a whole host of factors that can contribute to the decisions that we make when faced with an individual patient. There can be patient-related factors such as overall physical condition, performance status, other medical factors, such as the presence of peripheral neuropathy, or autoimmune conditions that can impact their treatment, and also disease-related factors. Where is the tumor? And how aggressively is that tumor behaving? There may be susceptible alterations of various genes that might predict for a particular therapy or guide us toward additional treatment. So there's really a lot to think about.

What do you think about, Dan, when you think about sequencing?

Dr. Petrylak:
Well, I think very, very similar to what you've just described. In fact, we look at the duration of the time from the initial platinum therapy to the time that the patient may relapse. If they are more than a year, we may consider these patients to be potentially re-inducible with their primary treatment. We also look at the types of therapies they may have received previously. We now have maintenance avelumab that's FDA-approved in a patient who has metastatic disease who has responded to first-line therapy. We also have an FDA approval for nivolumab as adjuvant therapy in patients who've undergone a radical cystectomy. That's for both patients who've had neoadjuvant

therapy as well as patients who have not.

So I like to look at molecular markers, including FGFR3. I am not a big fan of PD-L1 expression, especially in the second line. It's not really going to help you to determine what to do next. But as you had said, looking at disease sites, the time of the relapse, and also the overall clinical characteristics of the patients. How fit are they? Can they undergo treatment?

Dr. Siefker-Radtke:
You know, Dan, I was really struck by your statement about the duration of benefit. And this is something that is recognized in the field. And I think it's important for people who are treating patients to know about this. It's really the impact of neoadjuvant chemotherapy and how if a patient relapses within 12 months of their last dose of neoadjuvant or adjuvant chemotherapy, they are really ready for second-line therapy. As you pointed out, you may not want to give additional cisplatin if their relapse duration was a short interval.

Dr. Petrylak:
Agreed. It may only add toxicity and not benefit the patient.

So let's take a deeper dive into the therapeutic options for second and subsequent lines of therapy. Arlene, what can you tell us about the latest phase 2 and phase 3 clinical trial data?

Dr. Siefker-Radtke:
So there are certainly many immunotherapy options that can be given in patients who've already had frontline systemic chemotherapy. For instance, we have pembrolizumab in the second-line data with level one evidence suggesting evidence of clinical benefit, response rates that were improved compared to single-agent taxane, and improved toxicity profile and improved objective response rate compared to single-agent taxane.

We also have evidence for nivolumab with a single-arm trial, CheckMate 275, showing similar response rates and similar clinical outcomes, although it was not compared head-to-head with single-agent chemotherapy in that second-line setting, but certainly an option that appears very reasonable as well.

But there's other treatments to consider outside of that immunotherapy option. Certainly agents such as erdafitinib, which has been approved in patients who've received prior platinum-based chemotherapy and then had progressive disease. With the erdafitinib data, this was an accelerated approval based on phase 2 data, a single-arm clinical trial enrolling approximately 100 patients which showed an objective response rate of around 40% and even more patients, up to 70% of patients, having at least some evidence of clinical benefit with reduction in size of their tumor or disease stability, and a median overall survival of around 1 year. Which, again, at the time this type of data was presented, we hadn't seen the second-line options with such high response rates.

But erdafitinib is not the only regimen that has a good response rate. We also see in enfortumab vedotin, which is an antibody-drug conjugate targeting nectin-4 expression, which is found in a very high percent of patients with metastatic urothelial tumors. For this, we have single-arm data in patients who receive prior immunotherapy; we don't really have a lot of data in a "post-platinum prior to IO" cohort.

We also look at patients in the post-immune checkpoint inhibitor setting. And in that setting, we actually have a lot of options to consider as well, which are pretty similar to the post-platinum options. We have enfortumab vedotin, where post immunotherapy, we now have level one evidence, a randomized clinical trial showing that enfortumab vedotin had an improved response rate around 40% compared to single-agent taxane and a median survival, again, around 1 year. Much better than what was observed with that single-agent taxane. So now level one evidence in that post-immunotherapy setting for this new antibody-drug conjugate.

We still have chemotherapy as an option such as gemcitabine and carboplatin. And there's other doublets that have been used and still remain on the NCCN guidelines. And we also have erdafitinib in patients who've received prior immunotherapy as well. Of course, with erdafitinib, that's an agent that targets FGFR3 alterations. And you have to have documented an FGFR3 alteration or fusion. And some of these are fusions of FGFR2 to show evidence of potential for benefit in order to treat patients with erdafitinib. So we have a lot of options to consider in patients who've had prior therapies. And there's even more data with the use of the antibody-drug conjugates, such as enfortumab vedotin.

So, Dan, what do you think about the additional clinical trial data with enfortumab? I know you've been highly involved in this research.

Dr. Petrylak:
Well, thank you, Arlene. I have been involved right from the beginning. I think that it's a drug that really shows some very, very, very consistent activity. In fact, if you look at the phase 1 data from the EV-101 trial, the phase 2 data from 201, and the phase 3 data, across the board, we see a 40% response rate. But what's most impressive is that response rate is conserved throughout all subtypes or all anatomical sites. So you can see responses in liver in 40% of patients. Also impressively, you can see improvements of bone pain. And

in fact, you see it fairly rapidly when patients are being treated. So it's a drug that has significant activity but needs to be monitored very carefully from the standpoint of neuropathy.

So what I like to do in these patients is I like to be sure that we check them every time they receive a treatment to ensure that they have not had significant progression of any neuropathy that they may have. Dose reductions or holding doses early in the course can actually spread out the treatment of enfortumab.

The other thing about enfortumab which I think is very interesting is that the responses are fairly rapid. In fact, the trials show about a median time to first response of approximately 2 months.

There are other ADCs that are now approved by the FDA; sacituzumab govitecan is a different drug. It's a different ADC. So as opposed to targeting nectin with enfortumab, it targets a Trop-2, which is another antigen. It delivers a topoisomerase, SN-38, rather than an antitubulin agent, such as enfortumab does. Sacituzumab govitecan in a phase 2 study demonstrated a 27% response rate in heavily pretreated patients.

So the real question is how do we optimally sequence sacituzumab, erdafitinib, and enfortumab in patients who are being treated in the post-platinum and the post-checkpoint state? And I think that we have a lot of work to do in terms of developing molecular markers and other ways of sequencing our therapy.

Dr. Siefker-Radtke:
I have to agree, Dan. Isn't it wonderful to have so many new choices and so many options to consider? I think it really does enhance our ability to treat that patient, especially in a variety of conditions. You know, for instance, if you have a patient who received prior chemotherapy and they progressed, and, unfortunately, they progressed with rapidly progressive liver metastases, while I know second-line immunotherapy is an option, would you consider enfortumab or erdafitinib or even sacituzumab for that patient who may need more cytoreduction than we could achieve with immunotherapy alone?

Dr. Petrylak:
Absolutely. When we look back at our checkpoint data – this was actually published in the phase 1 experience with atezolizumab – the patients who do best are those patients who have nodal disease and have good performance status. Hepatic metastases don't necessarily respond as well to immune checkpoint therapy. That's why I think that these newer agents are so exciting in their responses in visceral disease.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Daniel Petrylak, and here with me today is Dr. Arlene Siefker-Radtke. We're discussing the importance of selecting and sequencing novel therapeutics for patients with advanced and metastatic urothelial carcinoma.

Dr. Siefker-Radtke:
So now that we've talked about a lot of these single-agent strategies, of course, the natural progression is to combine them with therapies that are tolerable and have an alternate target. We're certainly seeing a lot of combination trials with immune checkpoint inhibitors, and particular interest in enfortumab vedotin with pembrolizumab with some exciting early data. Can you tell us more about that, Dan?

Dr. Petrylak:
So this was a phase 1 study that evaluated in, initially, a dose-finding cohort and then 40 subsequent patients afterwards with the combination of enfortumab plus pembrolizumab. So the dose of pembrolizumab is the same that's used for second-line therapy, every 3 weeks, 200 milligrams; however, the dose of enfortumab was attenuated to be given on a Day 1/Day 8 schedule at 1.25 milligrams per kilogram. There are several things that are very impressive about the data. Overall, there's a 93% rate of tumor shrinkage of any sort with this particular study. And the median survival that was reported at ASCO GU this year was 26.1 months with a median duration of response of 25 months. This is in platinum-ineligible patients and that, in a single trial, to my knowledge, is the longest median survival we have seen.

Dr. Siefker-Radtke:
So with that survival, Dan, it really does seem we have the potential to overcome that cisplatin-based chemotherapy which has been that standard of care for over 30 years.

Dr. Petrylak:
We still have a lot of work to do to determine the best sequence to determine molecular markers. And also, now we start thinking about the word cure in our patients with metastatic urothelial carcinoma.

Well, this has certainly been a fascinating conversation. But before we wrap up, Arlene, can you share your one take-home message for

our audience?

Dr. Siefker-Radtke:
I think the biggest message is that we now have more options for patients than we ever had before. And we're starting to treat populations of patients who were not eligible for the typical standard of care cisplatin or carboplatin-based regimens. And as a result of these effective and sequential therapies, we are seeing that extension of life that is really exciting in this modern, targeted era.

Dr. Petrylak:
And extension of life with a good quality of life, which is so important for our older patients who want to enjoy their retirement, who want to see their grandchildren graduate from college or from high school. And I think that that's really an important gift to all of our patients that we can give. But all our patients should know they should seek out clinical trials; they should seek out the most up-to-date treatments. And that because you have not responded to the first treatment given, that doesn't mean there isn't hope and that there are other the treatments available for you.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening to us. And thank you, Arlene Siefker-Radtke, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Siefker-Radtke:
It was my pleasure as well, Dan. And I hope the whole audience enjoyed our thoughts and that it will help them in how they choose the sequential therapies for their urothelial cancer patients.

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