Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/current-and-emerging-roles-of-immunotherapy-and-adcs-for-patients-with-non-muscle-invasive-and-muscle-invasive-bladder-cancer/14553/

Released: 12/23/2022
Valid until: 01/05/2024
Time needed to complete: 30 minutes

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

Current and Emerging Roles of Immunotherapy and ADCs for Patients with Non-Muscle-Invasive and Muscle-Invasive Bladder Cancer

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Current and Emerging Roles of Immunotherapy and ADCs for Patients with Non-Muscle-Invasive and Muscle-Invasive Bladder Cancer” is provided by Prova Education.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

[CHAPTER 1]

Dr. Parikh:
Immunotherapy and antibody-drug conjugates have transformed the management of metastatic urothelial carcinoma. So how can we best utilize these treatment options to improve outcomes for our patients with advanced urothelial carcinoma?

This is CME on ReachMD, and I’m Mamta Parikh, and here with me today I’m lucky to have Dr. Daniel Petrylak.

Dr. Petrylak:
Good afternoon.

Dr. Parikh:
Hi. So let’s get started. Dr. Petrylak, to set the stage for this chapterized course, what can you tell us about current and emerging roles for antibody-drug conjugates, or ADCs, in this setting?

Dr. Petrylak:
So there are 2 ADCs that are FDA-approved for metastatic urothelial carcinoma: enfortumab vedotin as well as sacituzumab govitecan. So I’d like to review the data that led to the approval of these agents for the different clinical situations in urothelial carcinoma. Firstly, from the EV-201 trial, there were 2 different cohorts. Cohort 1 included those patients who had prior immune therapy and who had prior chemotherapy for metastatic disease. Enfortumab vedotin was administered at 1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle. And patients were then treated until toxicity or progression. The objective response rate in the EV-201 trial was 44%, which led to the accelerated approval of enfortumab vedotin in this group of patients. The EV-301 trial confirmed the observation that enfortumab vedotin’s active in this group of patients, and enfortumab was randomized against dealer’s choice chemotherapy which included taxanes in the United States or vinflunine in Europe. And a survival benefit was demonstrated for these patients, so that led to the full approval of enfortumab vedotin. Second cohort of EV-201 were those patients who were cisplatin ineligible who had received a prior checkpoint treatment. And in this group of patients, enfortumab vedotin was administered at the same schedule. An objective response rate of 52% was observed, so that also led to an approval in this particular cohort of patients.

Sacituzumab govitecan is also FDA-approved for those patients who have metastatic urothelial carcinoma who have progressed after platinum-based therapy and anti-PD-1/anti-PD-L1-based therapies. So sacituzumab is given on a day 1, day 8 schedule at 10 mg/kg. And in the TROPHY U-01 trial, which was very, very similar in design to the EV 201 study, it was found that the response rate was

approximately 30%, and the side effects with sacituzumab included diarrhea as well as neutropenia.

So I think one of the most exciting areas in research in checkpoint therapy, as well as in ADCs, is the combination of checkpoints along with an ADC. And data has been presented from the EV-103 trial, both cohort A, which has now been published in JCO, as well as cohort K, which was presented at the ESMO meeting this year. In these cohorts, enfortumab vedotin was combined with pembrolizumab, but a different schedule was used. Enfortumab was administered at 1.25 mg/kg on days 1 and day 8, and pembrolizumab given at 200 mg on day 1 of a given cycle. And the data, I think, is incredibly exciting. As we look at the data from cohort A, 93% of patients had a tumor reduction, whereas 73% had a confirmed objective response, and this was seen irrespective of PD-L1 status. What's really exciting here is the median survival – now of course, this is phase 1/phase 2 data – and the median survival that's been reported is 26.1 months with a median follow-up of about 25 months overall. That really is significantly different than what we've seen with any combination, both in platinum-ineligible or cisplatin-ineligible, as well as platinum-eligible patients.

Cohort K was designed to confirm previous observations, both with enfortumab vedotin as a single agent, as well as enfortumab combined with pembrolizumab. It was a noncomparative trial, and this looked at 2 different groups of patients, again, that were cisplatin-ineligible. And the response rates were impressive. EV monotherapy demonstrated a 45% response rate, whereas EV and pembro had a 64% response rate. Again, the same pattern was seen in terms of PD-L1 status, and the responses were not dependent upon PD-L1 overall. And the duration of response, the median has not yet been reached where – it's 65% of responders were still responding at 12 months, and the data is not yet mature in terms of overall survival and progression-free survival. But the question of course is will it parallel what we saw in cohort A? Most importantly, there's a randomized trial, EV-302, which is randomizing enfortumab vedotin plus pembrolizumab against standard of care chemotherapy for both cisplatin-eligible as well as -ineligible patients. So that will hopefully give us the answers to whether this combination has a better survival than standard of care chemotherapy.

Dr. Parikh:
Okay, great. So let me turn now to some patient factors and strategies for the management of adverse events that come with these ADCs, and there are special considerations for each of the ADCs that you just mentioned, Dr. Petrylak. So for enfortumab vedotin, we do see an increase in peripheral neuropathy, hyperglycemia, and skin toxicity, so we do need to take special care in patients that have a history of diabetes or have underlying peripheral neuropathy. And in some cases, dose reductions or interruptions are required due to that toxicity.

Sacituzumab govitecan has a different safety profile, and the adverse events that we see with sacituzumab govitecan involve GI toxicity including diarrhea and neutropenia or febrile neutropenia is also seen, so we do need to consider G-CSF support for patients that have neutropenia and consider supportive antimotility agents for patients with diarrhea or GI toxicity. And again, sometimes dose reductions or interruptions are required. So I think these are very promising antibody-drug conjugates. As Dr. Petrylak mentioned, they are approved for use for metastatic urothelial carcinoma, and there are a lot of promising combinations that are being studied as well.

So to continue on, in Chapter 2, we'll be discussing how to determine which immune oncologic agent is right for the patient in front of you. Stay tuned.

[CHAPTER 2]

Dr. Parikh:
Okay, welcome back. We were just talking about approved antibody-drug conjugates in urothelial carcinoma, and now we are going to delve into treatment selection in metastatic disease.

So, Dr. Petrylak, can you talk about what steps we need to take to identify the right agent for the right patient with metastatic bladder cancer?

Dr. Petrylak:
So there are basically 3 clinical situations that we would consider a checkpoint inhibitor for metastatic urothelial carcinoma. The first situation I'd like to discuss are those patients who are ineligible to receive cisplatin-based chemotherapy. And this can include those patients with a creatinine clearance of less than 60, peripheral neuropathy, hearing loss, as well as those patients who may not be able to tolerate hydration that's necessary for cisplatin-based chemotherapy. And there are 2 agents that are approved by the FDA in this particular situation. Those include atezolizumab as well as pembrolizumab.*

The second clinical situation where checkpoint therapy is approved is those patients who are responding to chemotherapy in the first line. For those patients who have metastatic disease, have had chemotherapy as their first-line treatment – and that includes carboplatin-gemcitabine, cisplatin-gemcitabine, and MVAC – methotrexate, vinblastine, Adriamycin, and cisplatinum. This group of patients who respond – and that's defined as stable disease, a partial response, or complete response to therapy – avelumab is FDA-approved as maintenance therapy, and the studies have demonstrated that there is a survival benefit for patients receiving avelumab

plus best supportive care versus best supportive care alone in responding patients.

The third group of patients for which we have an approval by the FDA for checkpoint inhibitors are those patients who received chemotherapy and have progressed on chemotherapy. And there are 3 FDA-approved drugs in that situation – nivolumab, avelumab, as well as pembrolizumab. And the only one that has Level 1 evidence supporting its approval is pembrolizumab, where a survival benefit was demonstrated compared to standard of care chemotherapy in the second line in those patients who received initially chemotherapy for metastatic disease.

So one of the questions that I'm often asked about the sequencing of treatments for metastatic urothelial carcinoma comes in those patients who are first line and who are cisplatin ineligible. In a patient who has PD-L1 positivity, should we be giving carboplatin and gemcitabine and then giving maintenance therapy to the responding patient, or should we give a checkpoint therapy up front, and then go forth with other forms of treatment afterwards? Well, PD-L1 positivity is clearly one factor in deciding what to do first, but I also like to assess how rapidly a patient's disease is progressing. If a patient has visceral disease, or needs their disease to get under control rapidly, I often will give chemotherapy first irrespective of the PD-L1 status, get the disease under control; if those patients respond, then give checkpoint therapy as maintenance treatment. And of course, if those patients progress, one could give a checkpoint as a second-line agent. So there are 2 ways to handle that patient who is cisplatin-ineligible, and I like to use disease aggressiveness or the speed at which the disease is progressing as a measure of how we should select our treatment.

Dr. Parikh:
So those are interesting takeaways from everything that Dr. Petrylak just mentioned. Interestingly, PD-L1 status is most relevant in patients that are cisplatin ineligible when considering immune checkpoint inhibitor therapy. But as Dr. Petrylak mentioned, disease burden is also an important consideration in considering the first treatment that a patient should receive.

In Chapter 3, we'll be discussing the current status of adjuvant and neoadjuvant therapy for muscle-invasive bladder cancer and how that affects the setting of metastatic disease. Stay tuned.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Mamta Parikh and here with me today is Dr. Daniel Petrylak. We're discussing current and emerging roles of immunotherapy and ADCs for patients with metastatic urothelial carcinoma.

[CHAPTER 3]

Dr. Parikh:
Welcome back. After discussing treatment selection in the setting of metastatic bladder cancer, we'll shift gears and talk a bit about adjuvant and neoadjuvant therapy for patients with localized disease. I'll start by discussing the clinical practice guidelines for adjuvant immunotherapy for bladder cancer.

And this is based on the results of the Checkmate 274 study, which evaluated nivolumab given for 1 year compared to placebo given for 1 year in the adjuvant setting in patients who had undergone a cystectomy or nephroureterectomy. If no neoadjuvant chemotherapy was given, patients with pT3 or higher disease or node-positive disease were considered eligible for nivolumab, or if patients had neoadjuvant cisplatin chemotherapy, patients that had pathologic stage T2 or higher or node-positive disease on their cystectomy specimens were considered for the study. And the study showed a clear disease-free survival benefit for nivolumab compared to placebo in the intention-to-treat population. So Dr. Petrylak, can you talk about emerging neoadjuvant and adjuvant immunotherapy strategies that are coming our way?

Dr. Petrylak:
Well, I think there's some very, very interesting strategies that are now emerging in neoadjuvant and adjuvant settings. And the thought is, is to move the checkpoint therapy, as well as some of the targeted therapies, up front in the treatment of these diseases.

So there are trials that are looking at the combination of enfortumab plus pembrolizumab as neoadjuvant therapy. There are trials that are looking at chemotherapy combined with checkpoint therapy, as neoadjuvant therapy. Also, one of the problems, of course, with neoadjuvant therapy is about 30% of patients are not eligible to receive cisplatin, and these patients go on to cystectomy without receiving neoadjuvant chemotherapy. So we actually presented some data back at the ASCO GU meeting earlier this year, looking at enfortumab vedotin as a single agent in patients who are platinum-ineligible, or cisplatin ineligible. And we found that there was about a 36% complete response rate in these patients, which parallels what we see with neoadjuvant therapy with cisplatin-based regimens. So all these treatments and combinations are beginning to move up front earlier, and that of course is going to present a dilemma later on, if these patients do relapse, as to what should be done with these patients and should you repeat checkpoint therapy? Should you repeat some of the agents that you've used in neoadjuvant setting? I think that's going to lead to some very, very interesting clinical trials in the future.

So I think it's very interesting that we're moving these agents up earlier, and not only in the neoadjuvant setting, but in the adjuvant as well as the setting of maintenance therapy.

In EV-103, there was a cohort that looked at neoadjuvant therapy for those patients who are cisplatin-ineligible. And a different dosage of enfortumab was administered. It was enfortumab at 1.25 mg/kg on day 1 and day 8 of a 21-day cycle, so that's a little bit different than the approved indication for metastatic disease. But nonetheless, this was given for 3 cycles prior to cystectomy. And what we found was, is that 36% of patients had a complete response. This is comparable to what we see with cisplatin-based chemotherapy. There are trials that are now looking at the combination of enfortumab plus pembrolizumab in the neoadjuvant setting, and that's being randomized against standard of care chemotherapy.

So the question, of course, is going to be how do we manage the neuropathy? And that's why it's so important that we have a good concept of stopping early if patients have – or at least reducing dose or holding dosages – if patients do develop neuropathy, because we're looking at a long-term picture in these particular patients, which is a little bit different than those patients with metastatic disease.

There are trials that are now also looking at adding other agents to checkpoint in the maintenance setting.

One of the cooperative groups is looking at the combination of avelumab plus cabozantinib and comparing that to avelumab alone as maintenance therapy to determine, of course, if adding more treatment in this clinical situation is going to improve the overall survival. Remember, we have about a 27-month median survival with avelumab alone in this group of patients. Another trial is looking at sacituzumab govitecan combined with cisplatin as initial therapy for those patients with metastatic disease, and then giving checkpoint therapy plus sacituzumab as maintenance for those patients who respond.

So we're moving these checkpoints up earlier, as well as some of the targeted agents, and I think it's going to at least have us think about different clinical questions in the future. How do we sequence these drugs in the best fashion? Do we repeat drugs that have been used in the neoadjuvant and adjuvant setting and then if these patients relapse past a year from their treatment? So I think there are going to be a lot of interesting clinical trials about the reapplication of checkpoints, about the toxicities of these drugs given earlier, and how this will also affect the overall picture of not only muscle-invasive bladder cancer, but metastatic disease.

Dr. Parikh:
So I think what we're hearing from Dr. Petrylak is that this field is extremely dynamic and that things are changing, looking at a lot of novel combinations in the neoadjuvant setting, the maintenance setting in metastatic disease, and the adjuvant setting. So there will be a lot coming our way in the years to come.

In Chapter 4, we'll be discussing regional issues in the testing and treatment of bladder cancer. Stay tuned.

[CHAPTER 4]

Dr. Parikh:
Welcome back. After discussing adjuvant and neoadjuvant therapy for muscle-invasive bladder cancer, let's turn now to regional considerations for testing and treatment.

Dr. Petrylak, what are some regional challenges clinicians face when implementing treatment for bladder cancer, both within the US and outside of the US?

Dr. Petrylak:
So, I mean, I think there is several different factors that come into play in terms of the overall care of patients. I think the most important in the United States is a multidisciplinary team approach. So, for example, in the neoadjuvant setting it's been disappointing, the number of patients despite positive data, that have received neoadjuvant chemotherapy or perioperative chemotherapy, and in some studies it's as low as 20%. That number, I think, is increasing, and I think we need to make sure that both the urologists and oncologists are aware that neoadjuvant therapy improves survival and that this can be administered safely to our patients. The other group, of course, I think, that is important to note, is those patients who are cisplatin-ineligible. In the past, those patients have gone on directly to cystectomy, and now that we have clinical trials for these patients both with checkpoints as well as with combination therapy, it's important that the urologists know and to refer those patients to oncology. For example, in the Southwest Oncology Group, we're now looking at a trial of checkpoint therapy plus carboplatin and gemcitabine in those patients who are platinum ineligible. It's a randomized study, but it is a study that does need to be performed to help determine whether early chemotherapy in this group of patients will improve survival.

I think also one of the important factors in the United States is making sure these patients are tested for biomarkers, particularly FGF. As we know, about 10% of patients express FGF, and there are drugs that target FGF, such as erdafitinib, which are FDA-approved for those patients with metastatic urothelial carcinoma, both in the platinum-ineligible and in those patients with prior chemotherapy.

So I think that communication is the key. The team approach is the key to making sure that our patients get the best possible care. Now, one of the issues outside of the United States, of course, is drug access and drug availability. Not all of these agents are approved in different geographic regions, so what I encourage the patients in those countries is to speak to their physicians about clinical trials that may benefit the patient in this particular situation or at least give them access to some of the newer drugs.

So I think that we've come a long way in the treatment of urothelial carcinoma. Think back to 2013, where we really had no FDA-approved agents in the second line, and then around 2016, 2017, we started seeing approvals of the checkpoints, and then more recently, enfortumab vedotin, sacituzumab, and erdafitinib. So we have many more treatments available for our patients. We're seeing responses, and long-term responses, with enfortumab vedotin in visceral disease, and these are things I've never seen before. So clinical trials, communication, these are key and important to taking care of our patients.

Dr. Parikh:
Yes, it's been fascinating to watch the field evolve in the treatment of bladder cancer in the last several years. And to summarize, as you mentioned, a multidisciplinary approach is critical in treating patients, both with localized disease as well as advanced disease, and participation in clinical trials may be critical for patients, especially those outside of the United States.

Dr. Petrylak:
And let's not forget the radiation oncologists as well, because they are looking at bladder preservation techniques with radiation therapy, chemotherapy, and immune therapy. And there are national clinical trials that are underway to ask these questions as to what the proper sequencing and what the roles are of immunotherapy in these patients. So again, I think it's important that you have a good team of physicians behind you to help take care of you.

Dr. Parikh:
Absolutely. Did not mean to short shrift the radiation oncologists.

So unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Petrylak, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Petrylak:
Thank you, it's been a pleasure.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Prova Education.

To receive your free CME credit, or to download this activity, go to ReachMD.com/innovations-in-oncology/ Thank you for listening.

* [Note: atezolizumab's bladder cancer indications were recently withdrawn, although it is still currently recommended in the NCCN Guidelines for patients whose tumors express PD-L1 or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression.]