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https://reachmd.com/programs/cme/updates-head-and-neck-cancer-treatment-integrating-checkpoint-inhibitor-therapy-improve-outcomes/12701/

Released: 07/30/2021
Valid until: 07/30/2022
Time needed to complete: 15 minutes

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Updates in Head and Neck Cancer Treatment: Integrating Checkpoint Inhibitor Therapy to Improve Outcomes

Announcer:
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[CHAPTER 1]

Dr. Cohen:
Welcome. Recurrent to metastatic head and neck squamous cell carcinoma, or HNSCC, represents a huge healthcare burden, due to its associated morbidity and mortality. Most patients survive less than a year after diagnosis and report a poor quality of life. But checkpoint inhibitors have been showing efficacy in different settings. In this first chapter, we’re going to take a closer look at the role of checkpoint inhibitors in the shifting treatment landscape of HNSCC and key clinical trial data.

This is CME on ReachMD, and I’m Dr. Ezra Cohen.

Dr. Burtness:
And I’m Dr. Barbara Burtness.

Dr. Cohen:
Welcome, Dr. Burtness. Let’s get started. Can you bring our audience up to speed on any recent changes to the standard of care for head and neck squamous cell carcinoma? And what was new or noteworthy at ASCO this year?

Dr. Burtness:
The recent changes to the standard of care for head and neck squamous cell carcinoma really center around the advent of immune checkpoint inhibition. Antibodies to the PD-1 receptor nivolumab and pembrolizumab were approved in 2016 for treatment of cisplatin-refractory disease. The activity of these agents, which had response rates of 14%-20% and improved overall survival, immediately raised the question of whether they should be tested in the first-line setting in recurrent metastatic disease that had not previously been treated with systemic therapy. KEYNOTE-048 was a 3-arm, phase 3 trial that compared either pembrolizumab alone or pembrolizumab with chemotherapy to the control arm, which was chemotherapy with cetuximab. Each arm was compared independently, and the analysis was undertaken both for all patients and in a biomarker-directed fashion. And what we saw was that pembrolizumab alone for any patient who was PD-L1 expressing, whether it was a low expression, reflected in a CPS [combined proportion score] of 1, or high expression, reflected in a CPS cut point of 20, was superior to chemotherapy with cetuximab in terms of overall survival. For all patients, the use of pembrolizumab compared with chemotherapy and pembrolizumab was not inferior, but if you look at the subset of patients who are PD-L1 non-expressing, pembrolizumab is not equivalent to chemotherapy there.

So the recommendation is pembrolizumab monotherapy for anybody who’s PD-L1 expressing. If you then look at the arm of

chemotherapy together with pembrolizumab, all patients and all subgroups – so PD-L1 non-expressing, CPS 1 to 19, CPS 20 and higher – were superior to the cetuximab and chemotherapy combination. So that really changed the first-line treatment of recurrent metastatic disease. Immediately raised two questions. One – what is best to do if a patient does progress on pembrolizumab-based chemotherapy? And there, we continue to see the use of chemotherapy and cetuximab, and so in that context, at ASCO this year, it was very intriguing to see the report from Julie Bouman and coauthors that the HGF-directed antibody, ficlatuzumab, when combined with cetuximab in patients who were cetuximab-refractory, conveys significant activity.

And then the other question is, how can we move this into the curative setting? And as you well know, in the JAVELIN trial, using avelumab together with chemoradiation followed by avelumab, compared with chemoradiation alone, for all comers was a negative trial. There was a very intriguing signal in patients who were PD-L1 expressing, and I think there's a lot more to learn about how to introduce immune checkpoint inhibitors into that setting. We are currently accruing to trials that do it a little differently, maybe using the immune checkpoint inhibitor after chemoradiation, as is done in the ECOG-ACRIN 3161 trial. And using it before surgery, as is done in the KEYNOTE-689 trial.

So I think other things that were pretty intriguing at ASCO was the use of this novel antibody directed to TGF-beta and PD-L1. This was called bintrafusp alfa, and it's combined with IL-12 in an antibody that targets necrotic tumor, and across multiple HPV-associated cancers, so cervical, anal, oropharyngeal. This had a remarkable, 71% response rate, including in oropharynx cancer.

Dr. Cohen:
Barbara, can you provide us with one key takeaway from this chapter?

Dr. Burtness:
To me, the key takeaway from this chapter is for patients with recurrent, metastatic head and neck squamous cell carcinoma, first-line treatment should include immune checkpoint inhibition with pembrolizumab.

Dr. Cohen:
In Chapter 2, we'll be discussing the value of biomarkers with checkpoint inhibitor therapy. Stay tuned.

[CHAPTER 2]

Dr. Cohen:
Welcome. In the first chapter, we covered the latest clinical trial data in metastatic head and neck squamous cell carcinoma, or HNSCC. In Chapter 2, we'll be discussing strategies to optimize therapy with biomarkers. I'm Dr. Ezra Cohen.

Dr. Burtness:
And I'm Dr. Barbara Burtness.

Dr. Cohen:
Dr. Burtness, what is the value of PD-L1 testing with checkpoint inhibitor therapy in recurrent, metastatic head and neck squamous cell carcinoma?

Dr. Burtness:
PD-L1 is to date the best biomarker that we have for choosing whether or not to use an immune checkpoint inhibitor, how to use an immune checkpoint inhibitor. So as we discussed a little bit in Chapter 1, in the KEYNOTE-048 trial, in which we compared pembrolizumab or pembrolizumab plus chemotherapy with a control arm of chemotherapy with cetuximab, we did the analysis in a biomarker-driven fashion. We looked at combined positive score, which looks at immune histochemical staining for the ligand PD-L1, either on tumor cells or on tumor-associated immune cells, and we first looked at those patients who expressed PD-L1 the most richly, so that was the CPS 20 group. And in this CPS 20 group, pembrolizumab alone was superior to chemotherapy with cetuximab. We then passed on to all PD-L1 expressing cancers, so that was the CPS 1 group, and there again, pembrolizumab was superior to chemotherapy with cetuximab. If we looked at all comers, which was whether or not they had PD-L1 expression, pembrolizumab alone was noninferior to chemotherapy plus cetuximab, but in a subsequent analysis that we presented at AACR in 2020, we saw that for the PD-L1 non-expressing cancers, pembrolizumab alone was not equivalent to chemotherapy with cetuximab, and so that approach is neither FDA-approved nor recommended.

Then looking at the patients who received pembrolizumab plus chemotherapy, across all of the groups, whether you looked at all comers, you looked at CPS 20 and higher, you looked at CPS 1 and higher, or you looked at the PD-L1 negative, pembrolizumab with chemotherapy was superior to cetuximab with chemotherapy. So with the exception of patients who have autoimmune disease, are on steroids, are PD-L1 not expressing, and not candidates for chemotherapy, really all patients should have a pembrolizumab-based approach in first-line management. But whether you choose to add chemotherapy to that might be influenced by their PD-L1

expression.

Dr. Cohen:
And of course there are other patient characteristics that we take into account, but PD-L1 is certainly the best predictive biomarker we have. Other patient characteristics might include the HPV status of the patient, their age, their performance status, the nutritional status, and comorbidities.

Dr. Burtness:
Dr. Cohen, what other biomarkers can be used to identify patients who will benefit from checkpoint inhibitor therapy in head and neck squamous cell carcinoma?

Dr. Cohen:
There have been other biomarkers, of course, that have been studied not only in head and neck squamous cell carcinoma, but in other cancers as well.

And suffice it to say that nothing really substitutes for PD-L1. The other biomarker that has been used in head and neck cancer and other malignancies is tumor mutational burden, or TMB. And that is somewhat orthogonal to PD-L1 or these gene expression profiles. That is to say, they could be predictive for a different set of patients; however, TMB analysis, that is the readout, is not necessarily standardized.

Well, this has been great. Before we wrap up, Barbara, can you provide us with one key takeaway from this chapter?

Dr. Burtness:
The key takeaway for me is that PD-L1 expression should be measured in patients with recurrent, metastatic head and neck squamous cell carcinoma, and that it should be reported using the combined positive scoring system. And when it is expressed, it's an indication for the use of pembrolizumab.

Dr. Cohen:
Thank you. In Chapter 3, we'll be discussing how to apply these clinical data into everyday practice.

[CHAPTER 3]

Dr. Cohen:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Ezra Cohen, and here with me today is Dr. Barbara Burtness. We're looking at the latest research in head and neck cancer treatment and are about to focus on clinical tips for sequencing checkpoint inhibitor therapy.

Welcome. In Chapter 2, we identified strategies to optimize therapy in head and neck squamous cell carcinoma using PD-L1 testing and biomarkers. Now, in Chapter 3, we'll be discussing our clinical practice. I'm Dr. Ezra Cohen.

Dr. Burtness:
And I'm Dr. Barbara Burtness.

Dr. Cohen:
Barbara, do you have any specific guidance or tips for our listeners that will help them formulate sequencing strategies to improve outcomes for their patients?

Dr. Burtness:
The question of sequencing, I think, is pretty straightforward in choosing first-line therapy for most patients. So for patients who are PD-L1 expressing and do not have contraindications to immune checkpoint inhibitors – that is to say they're not on steroids, they don't have autoimmune disease – it is quite clear from KEYNOTE-048 that those patients should receive pembrolizumab in their first-line treatment, either for PD-L1 highly expressing cancers and those who are less symptomatic, pembrolizumab monotherapy, or for patients who have lower PD-L1 expression or are more symptomatic and need a response that's more dramatic and quicker, the combination of pembrolizumab together with chemotherapy.

So what about the patient who has a contraindication to pembrolizumab in the first line? I do think that we saw from CheckMate 141 and from your study, from KEYNOTE-040, that there are a small number of patients who are not PD-L1 expressing who benefit from immune checkpoint inhibitors in the platinum-refractory setting. And so, again, as long as there is not a medical contraindication from steroid therapy or severe autoimmune disease for those patients, when they progress on platinum-based chemotherapy or platinum plus cetuximab, I would still give them a shot at an immune checkpoint inhibitor.

I think that the more complicated thing, and where we have less information, really, is what about the patient who receives pembrolizumab in the first-line setting and then progresses? And there, I think, for patients who did not receive chemotherapy before, it has been pretty common to offer them chemotherapy or chemotherapy with cetuximab. We have a new trial launching in ECOG-ACRIN, which will randomize those patients to either chemotherapy with cetuximab, chemotherapy with bevacizumab, based on the ECOG-1305 trial, or the regimen of atezolizumab and bevacizumab, which of course has shown the remarkable activity in several other cancers. There is also a trial looking at the combination of lenvatinib with pembrolizumab in patients who failed first-line immune checkpoint inhibitor therapy, and there it's randomized up against a standard of care that's an investigator's choice arm.

Dr. Cohen:
With respect to sequencing therapy, I have a patient, actually, currently in treatment, who received pembrolizumab in the first line, did well for a few months but never had a response, and unfortunately, about 6 months in she clearly had progressive disease, an oral cavity cancer, and she had a recurrence at the retromolar trigone. And you could, in fact, see that there was a bit of a cutaneous fistula beginning, unfortunately, in that area. She came to us for thoughts about subsequent therapy, and I decided to treat her with a combination of paclitaxel and cetuximab. And although she hasn't had her first scan yet, I'm happy to report that her pain is much improved, and believe it or not, the fistula has healed up. And I think a couple of points to make here was, first, we didn't wait a very long time from the end of the pembrolizumab to starting subsequent therapy, and as we've talked about, we started both a taxane and cetuximab – two agents that had not been tried in her cancer before. And although I couldn't point to which one is having this what appears to be a positive effect, I think the combination does appear to be quite effective. And that's a general paradigm that I've been using in my practice – anti-PD-1 in the first line, either alone or with chemotherapy and then, if patients progress, try to combine cytotoxic chemotherapy with cetuximab in those second-line patients.

So now that we have established anti-PD-1 therapy in recurrent metastatic head and neck cancer, Barbara, do you have any clinical tips for us about managing or even preventing adverse effects from checkpoint inhibitor therapy for patients with head and neck squamous cell carcinoma?

Dr. Burtness:
I think the main thing is that patients should be very, very well educated about what the potential signs of an immune-related adverse event might be. So we make sure that patients know to call for diarrhea, for shortness of breath, or cough. We follow their laboratory studies quite closely. We try to get a baseline cardiac echo so that if there are any suggestions of cardiac effects later, we have something for comparison. I think the early experience with very, very severe immune-related adverse events is something that we're not, you know, perhaps seeing as much now that we're able to get on top of these immune-related adverse events early with steroids.

For patients who have radiographic evidence of pneumonitis but preserved oxygenation who are feeling well, we actually continue therapy. So I think it's a matter of educating the patient and staying in close communication.

I think for the facial edema, we've done quite well with lymphedema management for many of the patients sleeping with the head elevated. On occasion, I've found myself using steroids to bring that under control. But in general, I think it responds very well to conservative measures.

Dr. Cohen:
I think for me the key takeaway is that we are doing better for patients with recurrent metastatic head and neck cancer. We have pembrolizumab and nivolumab as anti-PD-1 antibodies, and what's nice to see is that the subsequent therapy in patients who have had those as first line appears to be doing better as well, being more effective as well. So although we don't have a standard second-line therapy yet, those studies are underway, it does appear that, overall, patients with recurrent metastatic head and neck cancer are, in fact, living longer with this disease.

Dr. Burtness:
For the overall program, I think the message is that immune checkpoint inhibitors have changed the management of patients with recurrent metastatic head and neck cancer and that for almost all patients, pembrolizumab should be part of the first-line management.

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

Dr. Burtness:
Thank you.

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