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Revolutionary Approaches to Improving Outcomes in Unresected LA SCCHN

Announcer:
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Dr. Cohen:
This is CME on ReachMD, and I'm Ezra Cohen. Today, Dr. Kevin Harrington, Dr. Deborah Wong, and I will be discussing locally advanced squamous cell carcinoma of the head and neck, or LA SCCHN. We'll look at the challenges, current treatment landscape, and some exciting new data for a novel approach to treatment using inhibitor of apoptosis [IAP] protein antagonists. Welcome.

Dr. Harrington:
Thank you, Dr. Cohen. I'm glad to be here.

Dr. Wong:
Thank you. It's good to be here with both of you.

Dr. Cohen:
Great. Our first question today and topic focuses on the current landscape in locally advanced squamous cell carcinoma of the head and neck, and I'll turn to you, Dr. Wong. First and foremost, what are the unmet needs associated with managing locally advanced squamous cell carcinoma? And what are some of the more interesting data from recent clinical trials?

Dr. Wong:
Yeah, thank you so much, Dr. Cohen. I think the challenge for locally advanced squamous cell carcinoma of the head and neck is that outcomes for patients are – we certainly can do better for them. About two-thirds of patients with head and neck squamous cell cancers will present with locally advanced disease, that's stages III to IVB, and despite aggressive therapy, the median overall survival is 20 months.

Certainly, we know that the survival rate is dependent on disease biology, wherein patients with HPV-negative head and neck cancers have a poorer survival rate with a 5-year survival rate of less than 25% for stages for IVA to IVB, whereas those who have HPV-positive locally advanced stage III disease have a 50% 5-year survival rate. Even in the setting of a better prognosis of squamous cell carcinoma of the head and neck, up to 50% of patients will relapse. And this is despite a multimodal therapy.

There are some exciting data that we are awaiting, incorporating the addition of immune checkpoint inhibitors into definitive local treatment. And here are some studies that we're awaiting. So first, atezolizumab, which is a PD-L1 antibody, is being evaluated in a phase 3 study as adjuvant monotherapy. In the IMvoke010 study, patients with high-risk locally advanced squamous cell carcinoma of the head and neck are randomized 1:1 after completing definitive local therapy to atezolizumab or placebo for a year with the coprimary endpoints of event-free survival and overall survival. Interestingly, patients on this study could have received surgery or nonsurgical definitive local treatment followed by definitive radiation with or without chemotherapy.

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A second study that is very exciting is KEYNOTE-689, for which we are also awaiting the data for. In this study, which is a phase 3, randomized, open-label study, patients with resectable head and neck cancer are randomized to pembrolizumab or no neoadjuvant pembrolizumab and, following surgery, will receive adjuvant therapy comprised of standard of care chemoradiation or radiation as dictated by their pathology, and pembrolizumab or placebo.

And finally, a third study is the IMSTAR-HN study evaluating neoadjuvant nivolumab followed by adjuvant nivolumab with or without ipilimumab for locally advanced resectable squamous cell cancers of the head and neck.

So I think that these 3 studies incorporating immunotherapy into definitive local treatment are studies to watch out for.

Dr. Cohen:
Thanks, Dr. Wong, for that excellent review. I think looking at the possibility of immunotherapy as a peri-operative or peri-radiation treatment certainly seems promising based on the data we've seen so far using either neoadjuvant, adjuvant, or the combination of neoadjuvant and adjuvant, and we're certainly awaiting the data from the trials you mentioned quite eagerly.

Dr. Harrington:
Dr. Cohen, now that we have a clearer picture of the burden faced by our patients, what can you tell us about the emerging evidence?

Dr. Cohen:
Well, as you've heard, there really is an unmet need in locally advanced head and neck cancer, and we've tried to meet that need, really, for decades, employing different agents and different mechanisms. Most recently, we've begun to incorporate immunotherapy into the context of cisplatin radiation, especially for high-risk locally advanced patients, and these can be either HPV negative or HPV positive.

For instance, the JAVELIN HN 100 study administered PD-L1 antibody called avelumab starting 1 week prior to definitive chemotherapy radiation with cisplatin and single daily fractionated radiation, and then followed by avelumab maintenance for up to 1 year.

By the same token, the KEYNOTE-412 study had a very similar design, of course using a different agent, this time pembrolizumab. Again pembrolizumab given concurrently with chemotherapy and radiation, and then as maintenance therapy for up to a year.

What we know now from both of those studies is that neither one met its primary endpoint. JAVELIN had progression-free survival, and KEYNOTE-412 had event-free survival as primary endpoints, very similarly defined. Interestingly, the KEYNOTE-412 did seem to begin to trend towards a benefit to the addition of pembrolizumab, but did not reach the prespecified level of statistical significance. And so, so far, those 2 and some other trials have shown us that the concurrent administration of a PD-1 or PD-L1 antibody to either radiation therapy alone or chemotherapy radiation does not seem to improve survival.

Contrast that with a randomized phase 2 study looking at an agent called xevinapant, which is, of course, a SMAC [second mitochondrial-derived activator of caspases] mimetic or an IAP antagonist. In that trial, the agent, xevinapant, was added, again, to standard cisplatin radiation and compared to placebo in a, I would say, a quite high-risk population of locally advanced squamous cell carcinoma of the head and neck consisting mostly of HPV-negative heavy smokers and heavy drinkers. And what that study showed was a dramatic benefit, in my opinion, to the addition of xevinapant on all the endpoints reported, including locoregional control, which was the primary endpoint, progression-free survival, and as the data matured, eventually a benefit to overall survival. And almost a doubling, by the way, of overall survival at 5 years, again, in this high-risk patient population.

And so, although the trials with immunotherapy thus far have been disappointing, we do have emerging data using a different mechanism targeting, this time, apoptosis that may take us to a new standard, hopefully in the near term.

Dr. Harrington:
I think those are fascinating insights. And for me, the takeaway message is that in combining immunotherapy in induction, concomitant, and adjuvant phases alongside curative intent, radiation, or chemoradiation, we have been unsuccessful. But we actually now have an alternative approach based around modulation of cell death mechanisms, and that's going to be fascinating to test in clinical studies.

Dr. Cohen:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Ezra Cohen, and here with me today are Drs. Kevin Harrington and Deborah Wong. Our focus is on the exciting data for IAP antagonists and improving survival outcomes in our patients with locally advanced squamous cell carcinoma of the head and neck.

Dr. Wong:
Dr. Harrington, I couldn't agree with you more. Now that Dr. Cohen has kind of introduced this xevinapant to us, what can you tell us about the apoptotic pathway as it relates to locally advanced squamous cell head and neck cancer?

Dr. Harrington:

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To get to terms with some of the terminology around apoptosis and cell death mechanisms, we now have an animation that will walk us through some of those details.

[VIDEO PLAYS.]

Announcer:
Anticancer cellular stress in the intrinsic apoptotic tumor pathway leads to the release of various proteins from mitochondria. These proteins form a regulatory apoptosome that activates caspase-9, leading to the activation of caspases-3, 7, and subsequent tumor apoptosis. The extrinsic apoptotic pathway also drives apoptosis, but this happens through the activation of caspase-8, then 3, 7, and subsequent tumor apoptosis. Both apoptotic pathways are downregulated by IAPs, or "inhibitor of apoptosis proteins." SMAC* is also released from mitochondria during cellular stress. This protein antagonizes IAPs and frees caspases from IAP downregulation. Exogenous small molecule SMAC mimetics are now being assessed in cancer therapy. Like endogenous SMAC, these agents antagonize IAPs, resulting in an increased apoptotic signal. SMAC mimetics may also support heightened inflammatory antitumor responses from immune cells in the tumor microenvironment. This occurs by activating noncanonical NF-KB** signaling, with release of IAP inhibition downstream of the TNF receptor.

Dr. Harrington:
As we've seen from the video, apoptosis is mediated through 2 main processes. Intrinsic apoptosis is triggered by genotoxic stress, which acts at the level of the mitochondrion to release components that form the apoptosome within the cytoplasm of the cell, activating caspase-9 and, ultimately, the executioner caspase, caspase-3. In addition, the extrinsic pathway, which receives signals from ligands binding to receptors on the cell surface, activates caspase-8, and ultimately, again, caspase-3 to mediate cell death.

As part of the control of apoptosis, cancer cells will frequently upregulate proteins that are capable of inhibiting signaling. These are the inhibitor of apoptosis proteins. And these can be one mechanism whereby cancers can avoid treatment-induced cell death in response to either radiation or chemotherapy or the combination. By developing drugs that can inhibit these inhibitors of apoptosis proteins, or IAP inhibitors, otherwise known as SMAC mimetics, we have the potential to develop new therapeutic approaches. One such drug is xevinapant, which is already in randomized phase 2 and now randomized phase 3 clinical trial evaluation.

Dr. Wong:
Thank you, Dr. Harrington, for walking us through the mechanism of action for xevinapant. I think this is a really exciting molecule. It's a novel agent with a unique mechanism of action. I think the phase 2 data evaluating xevinapant with chemoradiation are really exciting, including demonstrating an improved median overall survival. And I'm really looking forward to seeing the results of the phase 3 study.

Dr. Harrington:
Dr. Cohen, can you tell us the significance of clinical endpoints in clinical trials for locally advanced squamous carcinoma of the head and neck?

Dr. Cohen:
Certainly. We, of course, rely on clinical endpoints to define new standards of care and assess the efficacy of different agents and different modalities and regimens. And we've traditionally used overall survival as the endpoint for, certainly, approvals and registration, but also to define new standards of care. The problem, of course, with overall survival is that it takes a long time or a longer time to realize, and the trials then require a larger number of patients. The good thing about overall survival is that it is a definitive; it's either yes or no. And of course, it's an endpoint that is critically important to both patients and providers.

However, we are always looking for other endpoints that may help us to speed the research process and the time to new approvals and therefore change the unmet needs and the standards in these patients. And an endpoint that has emerged is either event-free survival or disease-free survival. These are 2 that are quite closely – they're very similar to each other. They're closely defined. And what they encompass, really, are not only that question of survival, that is, alive or not alive, but also, and quite critically for patients with locally advanced head and neck cancer, the recurrence of the cancer. That is to say, either locally, regionally, or metastatically, and those events would then count in the either event-free survival or disease-free survival endpoint.

And we realized a couple of things about these as potential surrogate endpoints. First, they actually track very well with overall survival in prior meta-analyses looking at patients who are treated with either radiation therapy alone or chemotherapy radiation. It appears that there's a very high correlation in the range of 98% of these endpoints with overall survival. And of course, those endpoints read out sooner with smaller sample sizes. But also, if we think about patients with head and neck cancer, the recurrence of their disease is, without a doubt, a significant clinical event. Not only can it produce symptoms, it certainly can lead to mortality and, hence, the close correlation with overall survival, or it often requires a subsequent intervention, and that intervention could be morbid itself: surgery, re-irradiation, or systemic therapy.

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So we're beginning to realize more and more, and regulatory authorities are beginning to accept, that event-free or disease-free survival may be adequate surrogates for overall survival in our patients with locally advanced squamous cell carcinoma of the head and neck, and hopefully this will be widely accepted in the near term.

Well, that's all the time we have today, so I want to thank our audience for listening in and thank you, Drs. Kevin Harrington and Deborah Wong, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Harrington:
And with my thanks to you, Dr. Cohen, and to Dr. Wong for what has been an excellent exchange.

Dr. Wong:
Yes, thank you all for joining us. And thank you, Dr. Cohen and Dr. Harrington, for this really interesting discussion.

Announcer:
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