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How Modulation of Apoptotic Pathways Can Fill Important Unmet Needs in LA SCCHN

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Dr. Schoenfeld:
This is CME on ReachMD, and I'm Dr. Jonathan Schoenfeld. Today, Dr. Robert Ferris and I will be discussing locally advanced squamous cell carcinoma of the head and neck. We'll be looking at unmet needs in treatment and describing how therapeutic modulation of the apoptotic pathway may improve patient outcomes in patients with this type of cancer. Welcome, Dr. Ferris.

Dr. Ferris:
Thank you, Dr. Schoenfeld. Glad to be here.

Dr. Schoenfeld:
Dr. Ferris, concurrent chemo radiotherapy or CRT is the first line standard of care for eligible patients with locally advanced squamous cell head and neck cancers. However, there are efficacy and tolerability issues with this approach. Could you describe these issues for us?

Dr. Ferris:
Sure. In the curative population that we call locally advanced squamous cell carcinoma of the head and neck, we have surgical and non-surgical options. And as you described, the non-surgical standard of care is CRT or concurrent chemoradiation. So the first decision that gets made is whether this is a resectable situation or not, or can we preserve the organ with concurrent chemoradiation? The clinician also has to look at whether the patient has human papillomavirus positive or negative disease, since that has implications for prognosis. And so concurrent chemoradiation is effective, is curative for locally advanced head and neck squamous cell carcinoma, but has some toxicities. These include acute ones like mucositis, altered taste, dysphasia, xerostomia. And then after months and years we often see dysphasia fibrosis. And outcomes from concurrent chemoradiation for HPV [human papillomavirus]-positive squamous cell carcinoma are in the 80 to 90% or above with this type of therapy. Despite those toxicities for HPV-negative disease, the survival hasn't really improved beyond 40 to 50% at two and three years despite concurrent chemoradiation, which is relatively toxic, and that's the rate of efficacy.

Dr. Schoenfeld:
Yeah, and just wanted to reiterate the fact that we really need further improvements for those patients with a poor prognosis to help improve outcomes for this group of patients.

Dr. Ferris:
Yeah, and so in that situation you described, particularly the high tumor burden in HPV negative group, we often adopt an add-on strategy to try to add new therapies on top of the existing standard of care of concurrent chemoradiation and ones that don't substantially add to the toxicity. Dr. Schoenfeld, there's been a substantial effort to assess the therapeutic role of immunotherapy in the management of locally advanced squamous cell carcinoma of the head and neck. Could you discuss those attempts and how successful is that approach?

Dr. Schoenfeld:
Yeah, as you well know, immunotherapy and specifically immune checkpoint inhibitors have been a huge advance for patients with squamous cell carcinoma of the head and neck in the recurrent and metastatic setting. Initially the benefit for immune checkpoint inhibitors were established in the, in the second line setting for patients with recurrent metastatic disease with important studies such as the CheckMate 141 study that demonstrated the survival advantage for the PD-1 inhibitor nivolumab compared to other systemic therapy. And more recently, the KEYNOTE-048 study established either the PD-1 inhibitor pembrolizumab or pembrolizumab combined with chemotherapy as standard first-line treatment for patients with recurrent or metastatic head and neck squamous cell carcinoma. So there was hope that these results would translate into a benefit for immune checkpoint inhibitors when added to standard therapy in patients with locally advanced squamous cell carcinoma.

But unfortunately, several randomized studies have now shown that translating the benefit in the recurrent and metastatic setting for immune checkpoint inhibitors to our locally advanced squamous cell carcinoma patients is not that straightforward. In particular, the JAVELIN head and neck 100 study randomized patients with locally advanced squamous cell head and neck cancer to chemoradiation with or without the PD-L1 inhibitor avelumab, followed by 12 additional months of avelumab. This study, of course, failed to meet its primary endpoint as there was no benefit in progression-free survival with the addition of avelumab to standard chemoradiation. And similarly, the KEYNOTE-412 study had a relatively similar design, except testing the PD-1 inhibitor pembrolizumab in combination with chemoradiation therapy. Similar to the JAVELIN study, there was no benefit overall for pembrolizumab, compared to placebo. So there's still ongoing studies looking at the addition of immune checkpoint inhibitors, for example, following chemoradiation such as the IMvoke010 study or looking at immune checkpoint inhibitors before surgery, such as the KEYNOTE-689 study or the IMSTAR head neck studies. But right now I think you'll agree that there's no conclusive, randomized evidence that immunotherapy improves outcomes in patients with locally advanced squamous cell head and neck cancers.

Dr. Ferris:
Yes, I agree. One small randomized phase two study out of our institution presented to ESMO 2023 randomized patients, about 40 per arm to concurrent chemoradiation with pembrolizumab at the same time or sequentially pembrolizumab after chemo and radiation. And we saw the sequential approach yield 10 to 12% better progression-free and overall survival, a small study. So that was a numerical but not a statistically significant difference. But at four years, there was a statistically significant rate of improved local regional control with sequential immunotherapy after concurrent chemoradiation suggesting that that is a significantly different regimen for us to apply.

Dr. Schoenfeld:
That's a good point, and hopefully we can build off of those results in the future.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Jonathan Schoenfeld, and here with me today is Dr. Robert Ferris. Our focus today is unmet needs in the treatment of locally advanced carcinoma of the head and neck. We're also breaking down how modulation of the apoptotic pathway by small molecule SMAC mimetics may improve patient outcomes.

Shifting gears, Dr. Ferris, genetic alterations in the apoptotic pathway are common and especially important in our discussion of locally advanced squamous cell cancers of the head and neck. As a prelude to our final topic, what do our learners need to know about the apoptotic pathway and how it's therapeutic manipulation might improve patient outcomes?

Dr. Ferris:
Well, we have a video that would address some of that, then focus on the apoptotic cell death pathway, which is quite potent, so we should take a listen for that.

[audible video]

Hopefully that video helped explain how the apoptotic cell death pathway was important, as well as the role of IAPs and tumor escape in reduced apoptosis and tumor cell death.

As the video described, overexpression of IAPs [inhibitor of apoptosis] and SMAC [second mitochondria-derived activator of caspase] in tumor cell escape and reduced apoptosis and tumor cell death is a complex pathway, but it is targetable. These SMACs are intended to regulate how cells die. It's obviously a very important pathway in normal cells and one that tumors may harness to retain their viability and avoid susceptibility to radiation and chemotherapy. So the potential therapeutic role of SMAC mimetics is to block these inhibitors enabling the apoptotic pathway to progress. And this may have beneficial effects for immunogenic cell death in the tumor microenvironment suggesting that it could be a great partner in locally advanced disease to interact favorably with cancer immunotherapy as well.

Dr. Schoenfeld:
Yeah, and just wanted to also highlight the data that suggests the importance of these IAP proteins in mediating resistance to

chemoradiation and chemotherapy and radiation. And so I think there are great opportunities for these IAP inhibitors or SMAC mimetics to work to overcome this resistance and sensitize to those types of treatments for our patients that we're treating.

Dr. Ferris:
So moving on, Dr. Schoenfeld, now that we have a better understanding of the apoptotic pathway and the potential of SMAC mimetics and the treatment of locally advanced head and neck cancer, could you present some recent clinical trial data on potential therapeutic SMAC mimetics xevinapant?

Dr. Schoenfeld:
Yeah, thanks for the question. So, you know, to back up, I just want to make sure all of our listeners have an understanding of what xevinapant is. So xevinapant is an oral antagonist of the inhibitor of apoptosis or IAP proteins that we were just speaking about specifically of what we think are some of the most important inhibitors of apoptosis. And those are the proteins XIAP and CIAP one and two. Additionally, xevinapant is an oral drug and importantly for head and neck patients that sometimes have significant swallowing issues as they go through treatment, xevinapant can be administered via a feeding tube if that's what's required specifically in regards to head and neck cancer. Preclinical head and neck models suggested that there was synergy between xevinapant and chemoradiation. And for this reason, it was tested in a randomized phase two study compared to placebo in 96 patients with locally advanced squamous cell head and neck cancer receiving definitive chemoradiation.

In terms of the primary endpoint, xevinapant significantly improved local regional control at 18 months, to 54% versus 33% with placebo. And this translated into a doubling of progression-free survival at three years from 36 to 72% with a hazard ratio of 0.33. And xevinapant also improved survival at three and five years with a hazard ratio of 0.47. Overall survival was almost doubled at five years from 28 to 53% with xevinapant. As a result of these exciting data, there are ongoing phase three trials, as you know, evaluating xevinapant for locally advanced head and neck squamous cell patients. Specifically, the TrilynX study randomizes 700 patients with stage three four A or four B squamous cell carcinoma of the oral pharynx, hypopharynx or larynx to chemoradiation with xevinapant versus placebo. Mirroring the design of the phase two study, although with the addition of three additional cycles of therapy after chemoradiation is completed.

The primary endpoint of this study is event-free survival and secondary endpoints are progression-free survival, overall survival, local regional control safety, and others. And then there's a very important second phase three study that addresses a different locally advanced squamous cell head and neck cancer population with a high unmet need. And those are the high-risk patients who undergo surgery but have the very highest risk factors for recurrence following surgery. And that's specifically positive margins or pathologic, extra nodal extension. These patients, of course, would often get postoperative radiation along with chemotherapy cisplatin to reduce the chance of recurrence, but many of these patients who are older or have comorbidities are not good candidates for cisplatin and so receive radiation alone. And so this study, the X-Ray Vision study randomizes these patients to radiation with xevinapant versus radiation and placebo with a primary endpoint being disease-free survival.

Dr. Ferris:
I think those are very important data. The phase two TrylynX data are quite impressive and we anxiously await results from the phase three. It's also important to note that xevinapant and SMAC mimetics may be radio sensitizers and potentially a deintensification or replacement strategy for very-good-prognosis patients or those who are not candidates as you pointed out in the X-Ray Vision trial, not candidates for cisplatin, such as those over 70 or with other contraindications to cisplatin.

Dr. Schoenfeld:
Great. Thanks. Well, well this has certainly been a fascinating conversation, but before we wrap up, Dr. Ferris, can you briefly share one important take home message with our audience?

Dr. Ferris:
Yes. Now that we have some new biological mechanisms such as the apoptotic pathway and SMAC mimetics to target, the potential for new therapies to improve survival or potentially replace some of the toxicity of the existing concurrent chemoradiation is an exciting time.

Dr. Schoenfeld:
Yeah, I really think IAP inhibitors and SMAC mimetics have the potential to really help unlock better outcomes for our patients receiving radiation or chemoradiation or maybe other therapies as well.

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

Dr. Ferris:
Thank you Dr. Schoenfeld, and I really enjoyed it.

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