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Accelerating Evidence-Based Care in LA SCCHN

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Dr. Cohen:
This is CME on ReachMD, and I'm Dr. Ezra Cohen. Today, Dr. Susan Yom and I will be discussing locally advanced squamous cell carcinoma of the head and neck, or LA SCCHN. We'll be evaluating the emerging importance of incorporating early endpoints into our treatment landscape for these patients. More specifically, we'll focus on why early endpoints may provide therapeutic advantages when compared with overall survival, which is our current gold standard.

Welcome, Sue.

Dr. Yom:
Thank you, Ezra. So glad to be here with you.

Dr. Cohen:
Let's get right into our discussion on endpoints in clinical trials. And let me ask you, Sue, what are some of the early endpoints that are being considered for use in clinical trials?

Dr. Yom:
Well, I think as you said, overall survival really is considered the gold standard and is very familiar to people, and some of the reasons are that it's really easily defined and assessed by people who don't have to be trained. It's a hard endpoint. It doesn't entail bias. It doesn't require special expertise to assess. And for these reasons, it can be very translatable to large-scale studies across many heterogeneous and different types of centers.

But we also know that there are problems with overall survival. As we've gained sophistication, we've realized that people often with head and neck cancer may die from other causes. And so these competing risks can confound survival. And secondly, there can be intervening therapies, and at the time a trial is designed, you can't always anticipate all these other therapies, secondary or tertiary level, that may be offered later which could change the survival of the patients in that trial. Finally, I'll just say that whether survival is the only meaningful endpoint, especially in head and neck cancer where local-regional control is so important, as we know, for function and quality of life, it's really a pressing question whether living longer with poor quality of life is acceptable and meaningful to patients.

I will also just mention briefly that there are logistical issues with overall survival, and these could be considered by some quarters as delay to progress because you need longer follow-up to properly assess overall survival since you have to follow the patients all the way through. And also as a result of that, you often need a relatively larger sample size because progression does not always result in death, so you have to add more patients to show those survival differences.

For these reasons, other earlier endpoints, as you alluded to, become more popular. Some of these include things like progression-free survival [PFS], time to progression, time to treatment. These are kind of restrictive because they are really based on disease progressions and other types of events that indicate failure of therapy might not get counted.

So that leads us to the last category of endpoints that have found increasing favor. One of these is event-free survival, or EFS. It has

become increasingly of interest, especially with the rise of neoadjuvant therapies prior to surgery or radiation.

EFS can encompass a number of important therapy-related aspects all in one endpoint. And for EFS, it's important to understand that the events will be defined in advance based on the specific trial protocol. So this would include disease progression, of course, just like PFS, but also death as a result of therapy. And EFS for this reason is a very flexible and somewhat broader-use type of endpoint.

Disease-free survival [DFS], another one, is considered a version of PFS that's expanded to indicate the time the patient lives, but its weakness is that it can typically only be used in a patient who has some point at which they're clearly free of disease.

And then, finally, local-regional control is an endpoint that has always been popular and remains popular. Its virtues are that it's very singular in its focus, and as we stated earlier, local-regional control is very meaningful to patients and clinicians.

I'll just list a couple examples of some of the recent head and neck cancer trials that have used these endpoints, such as IMvoke010, which used event-free survival by independent review as its primary endpoint. KEYNOTE-689, which likewise used event-free survival as one of its primary endpoints. IMSTAR-HN, which used a primary endpoint of DFS with a secondary endpoint of local-regional control, as well as overall survival. And JAVELIN 100, which used a primary endpoint of progression-free survival by investigator assessment that had secondary endpoints of overall survival, response, and duration of response.

Dr. Cohen:
Thanks, Sue.

Dr. Yom:
So, Ezra, now that we have a basic understanding of the range of these endpoints and some of their pros and cons, what can you tell us about the emerging evidence that supports the use of these endpoints in locally advanced squamous cell carcinoma of the head and neck?

Dr. Cohen:
Of course, we have to consider that these endpoints are defined differently, and as mentioned, they have their own advantages and disadvantages. We have to also keep in mind that locally advanced squamous cell carcinoma of the head and neck is truly a local-regional disease, and unfortunately, many patients recur with that.

The symptoms produced from head and neck cancer are also often due to local-regional disease. And then, when we look at endpoints, local-regional control does become relevant because of what I just said. However, of course, local-regional control only focuses on those aspects of the disease and doesn't take into account other clearly important events, such as distant relapse or even death. And that's why event-free survival and disease-free survival are gaining greater and greater traction in these types of randomized phase 3 studies.

Beyond that, we do have some data that we can look at. In fact, there was a meta-analysis performed in 2009 by Michiels et al. that demonstrated a very tight correlation between overall survival and event-free survival in both radiation therapy alone, and chemotherapy radiation trials in locally advanced head and neck cancer. Now, this meta-analysis was performed prior to HPV having such an impact on our disease and also clearly before immunotherapy entered the treatment armamentarium. However, more recent data from Black et al. actually validated the use of event-free survival or disease-free survival, both similarly defined, and really extended the potential use of these as surrogate endpoints for overall survival in locally advanced head and neck cancer.

Dr. Yom:
Well, we certainly want to accelerate progress. We have so many choices to investigate. And I'll just say that I think these endpoints, even if they aren't used for formal approval, could be really useful in screening these competing regimens. At the same time, we all want to get advances to patients sooner, and so it's really important that we keep thinking about which endpoints could be reliable or valid for approval.

Dr. Cohen:
Great point, Sue.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Ezra Cohen, and here with me today is Dr. Susan Yom. Our focus is on the incorporation of early endpoints into treatment for our patients with locally advanced squamous cell carcinoma of the head and neck.

Let's now drill a little bit deeper into some novel agents, especially ones that are affecting apoptosis. And so before we provide examples of how early endpoints can be incorporated into clinical trials for locally advanced squamous cell carcinoma of the head and neck, could you give us some background on inhibitors of apoptosis and their role in cancer pathophysiology?

Dr. Yom:

Well, certainly this class of agents is very exciting right now and has received quite a bit of attention. So exposure to DNA-damaging agents, like chemotherapy or radiation, works by causing release of what's called SMAC, second mitochondria-derived activator of caspases, from the mitochondria into the cytosol where it inhibits these inhibitors of apoptosis proteins, or IAPs. And this blockade then results in downstream apoptosis and production of inflammatory cytokines. And these are important mechanisms in how radiation and chemotherapy work. But there are also mechanisms that enable cancer cells to suppress apoptosis, and one of these is overexpression of those IAPs. And by overexpressing the IAPs, the cancer cells can suppress apoptosis by preventing the activation of caspases and bocking NF-kappa B activity. Then you don't get the release of inflammatory cytokines, such as TNF-alpha, for example. So overexpression of IAPs has been reported in many cell-types including head and neck cancer, and overexpression has been shown in laboratory models, as well as animal models, to prevent the induction of apoptosis specifically related to chemotherapy cisplatin and radiotherapy.

The reason why these have become so exciting for people is that xevinapant has emerged as probably the most advanced agent in this class in testing. It acts as a SMAC mimetic that inhibits IAPs and thus releases the blockade on caspase activity and promotes NF-kappa B signaling. And by restoring the sensitivity to apoptosis, it's hoped that xevinapant can reduce resistance to chemotherapy and radiotherapy.

I'll just mention that while this agent is the furthest along, now in phase 3 testing with chemoradiation, there are other IAP inhibitors, such as tolinapant, which has a broader range of activity against more IAPs and has been associated with caspase-independent necroptosis. And birinapant, dasminapant, and some that don't even have names like, LCL161, just to be fair. And all of these represent a very exciting new class of drugs that takes us back to the fundamentals of DNA damage.

Dr. Cohen:
It's certainly an exciting time to be exploring these agents in the context of locally advanced head and neck cancer, especially when we consider the potential use of early surrogate endpoints.

Dr. Yom:
I agree. And so, Ezra, what are some examples of upcoming clinical trials in LA SCCHN that you know of which will be using some of these early endpoints?

Dr. Cohen:
I think we can focus on the data using xevinapant and go back to the phase 2 study that now has quite nicely matured. This was a trial that simply compared the addition of xevinapant to standard chemotherapy radiation in the form of cisplatin and single daily fractionated radiation in a group of patients that were clearly high risk for recurrence. The trial's endpoint was local-regional control at 18 months, and at first report, that endpoint was clearly both statistically and clinically significant difference in favor of the experimental arm including xevinapant. As the trial matured, interestingly enough, the results continued to get better with respect to lower hazard ratios, and then we saw positivity for progression-free survival at 3 years.

Most recently, as, again, the data had matured, we were able to see the 5-year data, which demonstrated now a difference in overall survival. In fact, a doubling of overall survival in the experimental arm employing xevinapant. And so here's a great example of how surrogate endpoints, when applied in the appropriate context, can give you a meaningful early readout for overall survival.

To review, local-regional control was the first to read out; it was positive. A little bit later than that, we saw a difference in progression-free survival. And then finally, as the data matured, in fact, we did see a dramatic difference in overall survival. And that of course leads us into the, now, phase 3 studies of xevinapant in locally advanced head and neck cancer that are employing similar strategies with respect to endpoints. The TrilynX study replicates the phase 2 data closely, but not exactly, in that it adds xevinapant to standard cisplatin radiation. And here, though, the primary endpoint is event-free survival with important secondary endpoints of progression-free survival, local-regional control, and overall survival. This study has actually completed accrual, and so now we are waiting for that first analysis to read out.

In a similar fashion, we have the XRay Vision trial, which is a postoperative study using early endpoints in locally advanced head and neck cancer. Here, disease-free survival as a potential surrogate for overall survival, time to treatment failure, and quality-of-life measures. Now both of these are registrational trials, and the expectation is that these early surrogates will validate in overall survival.

And of course, these are discussions that were had with regulatory agencies prior to undertaking the studies. In fact, when we look at the possible incorporation of these earlier endpoints, we do know that the FDA has conducted 2 workshops examining surrogate endpoints in locally advanced head and neck cancer. And although no formal conclusion was made from those workshops, the general feeling was that endpoints like event-free survival or disease-free survival would, in fact, be suitable. And the FDA is continuing to discuss this.

Dr. Yom:
That is so exciting to see that some of these early endpoints are actually producing trials that could result in overall survival differences.

Dr. Cohen:
Well, Sue, this has certainly been a fascinating conversation. Before we wrap up, can you briefly share one take-home message with our audience?

Dr. Yom:
Well, I think what's important is what's meaningful for our patients. And we can talk about endpoints, but what's really important is how are we using these endpoints to get to what we want, which is really getting these advances to our patients who need them and who are facing really life-threatening conditions.

Dr. Cohen:
I couldn't agree more, and I'll also say that it's certainly exciting to have novel agents that, at least in early studies, seem to be quite effective. So hopefully, as the phase 3 data emerge for xevinapant and other agents, we will see progress in locally advanced head and neck cancer for our patients.

Dr. Yom:
That would be amazing.

Dr. Cohen:
That's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. Susan Yom, for joining me and for sharing all your valuable insights. It was great speaking with you today.

Dr. Yom:
It's always great to speak with you, Ezra, and really enjoyed this topic.

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