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Global Perspectives on Perioperative Immunotherapy in LA HNSCC

Announcer:
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Dr. Harrington:
Perioperative immune checkpoint inhibitors have demonstrated efficacy in resectable head and neck squamous cell carcinoma, reducing the risk of recurrence and disease progression in earlier stages of disease. Join us as we examine implementing perioperative immunotherapy across different regions.

This is CE on ReachMD, and I'm Dr. Kevin Harrington.

Dr. Le Tourneau:
And I'm Dr. Christophe Le Tourneau.

Dr. Harrington:
So Christophe, can you start our discussion, please, by reviewing unmet needs in resectable, locally advanced head and neck squamous cell carcinoma.

Dr. Le Tourneau:
First of all, patients can undergo surgery if they’re fit for surgery and if consequences are expected to be acceptable for these patients. Then these patients undergo radiation or chemoradiation, depending on pathological features. But despite this, nearly 50% of patients will eventually relapse, usually within 2 years, and these patients have a very poor prognosis, with a median of overall survival around a year.

So it is critical to increase the cure rates of these patients, and immunotherapy is one of these strategies. It has been shown to produce efficacy in the recurrence of metastatic setting, and evaluating immunotherapy in earlier stages of the disease is an appealing strategy.

Dr. Harrington:
That's excellent. Christophe, many thanks for that.

As we know, there have been really very significant attempts to combine immunotherapy with radiation or chemoradiation to try to accentuate the immunological impact of radiation within the tumor microenvironment. I think at the moment, it's fair to say that a great deal of that effort, looking for that synergistic interaction between radiation-inducing immunogenic cell death, priming immune responses, and then increasing those by co-administration of immune checkpoint inhibitors concomitantly as part of curative intent treatment with radiation, have as yet, sadly, largely failed.

And I think it's worth picking up on this notion that there has been a strong desire to translate those benefits that we've seen in relapsed metastatic disease with immunotherapy and bring them further forwards into the curative setting. There have been attempts to do that with concomitant chemoradiation, but more recently, we've begun to see significant movement now with the neoadjuvant and adjuvant setting around the perioperative period, and that is something that we're going to discuss further.

So, Christophe, I would like to invite you now to review the clinical data supporting the use of perioperative immune checkpoint inhibitors in this context of locally advanced head and neck squamous cell carcinoma.

Dr. Le Tourneau:
Yeah, sure. So the main trial that evaluated immunotherapy in the perioperative setting was the KEYNOTE-689 trial that evaluated the addition of pembrolizumab to standard of care in patients with resectable, locally advanced head and neck squamous cell carcinoma.

So in the experimental arm, patients received immunotherapy, namely pembrolizumab, before surgery, during radiotherapy or chemoradiation, and then in the adjuvant setting. So some patients received concomitant cisplatin through radiotherapy, depending on the pathological features.

So that trial was positive in terms of event-free survival in all-comers, with a hazard ratio of 0.73 and a median EFS of 52 months versus 30 months. That trial was also positive in patients with a CPS of 1 or more, with a hazard ratio of 0.70 and a median EFS of 60 months versus 30 months in the standard of care arm. And obviously the trial was even more positive in the CPS 10 or more patient population, with a hazard ratio of 0.66 and a median EFS of 60 months versus 27 months.

Interestingly, the major pathological response in all-comers was almost 10%, and that rate was even higher in patients with CPS more than 1 or more than 10, with a major pathological response rate of almost 14%.

So pembrolizumab, given these results, was approved by the FDA this year in patients with a CPS of 1 or more.

Importantly, pembrolizumab was not the only drug to be evaluated in this setting. Nivolumab was also evaluated in patients with resectable, locally advanced head and neck squamous cell carcinoma in the NIVOPOSTOP trial.

This trial was a little bit different since eligible patients had to have undergone surgery and had to have high-risk pathological features, including either invaded margins, extracapsular extension, 4 or more invaded lymph nodes, or perineural invasions.

In that study, patients started nivolumab after surgery and not before, like in the KEYNOTE trial, and then received nivolumab during chemoradiation and in the adjuvant setting as well. And this trial was also positive in terms of disease-free survival in all-comers, with a hazard ratio of 0.76.

So these are the 2 main trials in this setting.

Dr. Harrington:
Thanks for those excellent perspectives, Christophe. I think it is really extremely exciting that we sit at, I think, a flexion point in the practice of oncology for patients with locally advanced head and neck cancer.

These 2 positive clinical trials with really quite interestingly different outcomes. So for instance, in the KEYNOTE-689 study, we see the benefit appears to accrue in terms of protection against metastatic failure of disease, whereas in the NIVOPOSTOP study, we see that that benefit appears to be in terms of locoregional control, albeit we haven't yet seen the definitive peer-reviewed publication in that space to be able to really pick apart those data for the NIVOPOSTOP study.

So I think there's a great deal more to learn in this space, but really a very exciting opportunity for our patients, and also an opportunity for us as a community to change the way we may practice together.For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Kevin Harrington, and here with me today is Dr. Christophe Le Tourneau. We're discussing global perspectives on perioperative immunotherapy in locally advanced head and neck squamous cell carcinoma.

Dr. Le Tourneau:
Using pembrolizumab in the neoadjuvant setting is really a paradigm change, since it's being used before surgery. And effective communication and collaboration among specialists will be crucial to ensure the timely consideration of perioperative immunotherapy as well as the management of adverse events.

So, Kevin, can you share your perspective on multidisciplinary coordination and management of locally advanced head and neck squamous cell carcinoma in this setting?

Dr. Harrington:
I think it's going to be really essential that we focus on working together as a multidisciplinary team across the various specialties

responsible for taking care of patients with locally advanced squamous carcinoma of the head and neck. We are not going to be able to continue in a process whereby perhaps the surgeon makes the initial decisions and then radiation oncologists and medical oncologists contribute to the discussion after an initial decision to operate has been taken place. So the workflow will change.

In light of the KEYNOTE-689 study, we will need to have early testing for PD-L1 CPS in order to guide treatment in line with the approval for treatment with neoadjuvant and adjuvant pembrolizumab for patients with a PD-L1 CPS of greater than or equal to 1. We're going to have to put in place mechanisms whereby patients receiving these early immunotherapy interventions before surgery who develop immune-related adverse events—we're going to have to put in place mechanisms for managing those.

We're going to have to bring the surgical community with us to make sure they're comfortable and confident that what we are doing in terms of initial neoadjuvant treatment is not going to impair or in any way negatively impact their ability to deliver their important surgical treatment for the patient.

Now, when we assess the pathology, our pathology colleagues in the MDT are now going to have to learn to, I guess, look at tumors where there is significant reduction in viable tumor material within the specimens. And those assessments of major pathological response, determination of resection margins, and presence or absence of extracapsular spread are going to be critical in guiding risk-adapted adjuvant treatment.

And for the radiation oncologists, of course, it's going to be really important to start to think about how do we integrate radiation into this postsurgical management decision, especially when we see in KEYNOTE-689 fewer patients require concomitant cisplatin—possibly an opportunity to reduce radiation volumes and perhaps even radiation doses.

I think we're in a phase where we're going to be reimagining and redefining the way we deliver treatment in the adjuvant setting in light of these really important practice-changing works in 689.

Dr. Le Tourneau:
Yeah, and I think we have been used to discuss all of our patients during tumor boards. And this is something that is broadly done. I think it will be important in some cases to re-discuss our patient, as you mentioned Kevin, after 1 injection or 2 injections of immunotherapy before surgery. Because some patients might have adverse events or not respond enough to treatment, and these patients will have to be discussed again during tumor board. So the collaboration will have to be even closer than before, I would say, with this paradigm change.

So now let's turn our focus to differences between the US and European practices when it comes to perioperative immunotherapy use. So, Kevin, do you see regional variations in approvals, guidelines, and access to immunotherapy?

Dr. Harrington:
Absolutely Christophe. We work in a global community, but of course, we have to respect the fact that across different areas within the globe, different decisions will be taken based around local and regional needs, and so we shouldn't expect that what is true in one jurisdiction will necessarily hold in another.

We also have to recognize, of course, that the nature of head and neck cancer is not exactly the same across the globe. So the disease that you and I might treat in Western Europe and perhaps with colleagues in the United States doesn't necessarily mirror exactly the disease elsewhere.

So for instance, a large number of the patients in KEYNOTE-689 and in NIVOPOSTOP had oral cavity cancers. But those oral cavity cancers that you and I are used to treating may differ very significantly from those, for instance, that are seen in patients in India or, indeed, in patients in Latin America, for instance.

So we're going to have to adjust to and respect those differences and take account of locoregional differences in how drugs are approved and how they are delivered.

Now, in addition, we have to take account of the fact across the globe that different clinical disciplines have different roles in how they manage patients. And so in many places, we will see distinct clinical teams with surgeons, medical oncologists, radiation oncologists, delivering very specific components of the care. Elsewhere in the world, we have to acknowledge the fact that there will be places where, for instance, surgeons may be responsible for delivering systemic therapies. In other areas, my own included in the UK, for instance, clinical oncologists will deliver both the radiation and the drug treatment. So we have to adjust to those, and we have to be aware of the fact that the multidisciplinary decision-making process may vary.

And then finally, we have to respect the fact that within different parts of the world there are different strengths. In the northern parts of Europe compared with the more eastern parts of Europe, there may be differences in how patients are treated, either with

chemoradiation or with more surgical approaches, with a greater use of surgery, perhaps, in more easterly areas within Europe, and that will vary across the world.

Perhaps, Christophe, how can we improve this multidisciplinary coordination? How can we take account of referral systems to make sure that our patients are able to access and benefit from perioperative immune checkpoint inhibitors when they're diagnosed with locally advanced head and neck cancer?

Dr. Le Tourneau:
So pembrolizumab has been approved by the FDA in June this year, and hopefully the European approval will come very soon. Pembrolizumab in the perioperative setting does not belong to the guidelines right now because it's so close to the FDA approval, but that will certainly come very soon, and especially in the NCCN Guidelines and in the ESMO guidelines in October.

I think discussing patients in tumor boards, as we mentioned already, will be key. And this is something that is broadly done in big centers, I would say, around the globe.

But now there's a proportion of patients who get surgery for this kind of locally advanced head and neck squamous cell carcinoma in smaller centers or in private institutions where sometimes tumor boards are less effective, if I can say. So I think it will be critical to really organize a way to discuss these patients in a tumor board with the radiation oncologist, the medical oncologist, or the clinician oncologist and the surgeons so that none of the patients misses the opportunity to give immunotherapy if they are eligible for immunotherapy.

So what we want at the end is that patients get the best treatment. And for that, the coordination is key, and we probably need to improve that, especially in countries where some of the patients get surgery in smaller centers without the discussion in tumor boards.

Dr. Harrington:
Well, that's all we have time for today. So I want to thank our audience for listening. And I want to thank you, Dr. Le Tourneau, for joining me and sharing all of your valuable insights.

Dr. Le Tourneau:
Thanks, Dr. Harrington, for this very nice discussion.

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