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The Future of HNSCC: Aligning Teams, Transforming Care

Dr. Uppaluri:
Hello and welcome. How can medical, surgical, and radiation oncology teams coordinate care and make evidence-based treatment decisions for patients with head and neck squamous cell carcinoma? That's what we'll explore today.

This is CE on ReachMD, and I'm Dr. Ravindra Uppaluri.

Dr. Lee:
And I'm Dr. Nancy Lee.

Dr. Uppaluri:
So first, I'd like to begin by reviewing the clinical trial data for adding immunotherapy to the management of locally advanced resectable head and neck cancer patients, including the KEYNOTE-689 and the NIVOPOSTOP trials.

So first, the phase 3 KEYNOTE-689 study evaluated the efficacy and safety of adding neoadjuvant and adjuvant pembrolizumab to standard of care in patients with resectable locally advanced head and neck cancer. Seven hundred fourteen patients with stage III and IV head and neck cancer were enrolled at 192 sites across the world, and patients were randomized 1:1 to receive either standard of care alone or standard of care plus pembrolizumab, which included 2 cycles of neoadjuvant pembrolizumab. In addition to the neoadjuvant pembrolizumab, those in the pembrolizumab plus standard-of-care arm also received pembrolizumab concurrent with adjuvant therapy followed by maintenance pembrolizumab.

All patients in both arms underwent standard-of-care surgery followed by adjuvant radiation with or without cisplatin-based chemotherapy, depending on pathologic risk factors identified from the surgical specimens.

The primary endpoint was event-free survival, which is defined as recurrence or death assessed by blinded independent central review. And the key secondary endpoints included overall survival and a major pathologic response, which is defined as tumor reduction of 90% or more in surgical specimens.

For all participants, the results showed that the pembrolizumab plus standard-of-care arm performed better than the standard-of-care arm alone. Median event-free survival was significantly different between the 2 arms, 51.8 months in the group who received pembrolizumab versus 30.4 months with standard treatment. Both these event-free survival and the major pathologic response benefits were observed more frequently in patients whose tumors expressed PD-L1.

At the first interim analysis, overall survival was not significant, but this is going to be tested at later time points as specified in the predefined statistical plan.

Importantly, blinded independent pathologic review also showed that high-risk pathologic features, which is positive margins or extranodal extension, were reduced and occurred at 32.5% in the pembrolizumab plus standard-of-care arm versus 44.4% in standard-of-care arm. And because of this finding, fewer participants in the pembrolizumab group had postoperative high-risk pathologic features and thus avoided having to receive adjuvant chemoradiotherapy.

Based on these findings, the FDA approved pembrolizumab for patients with resectable locally advanced head and neck cancer whose tumors had a combined positive score of 1 or greater as a neoadjuvant and adjuvant treatment as I described.

So moving on then to the NIVOPOSTOP trial. This was a phase 3 trial completed by the GORTEC Cooperative Group, and it also tested this idea of perioperative immunotherapy in surgically resected head and neck cancer patients. They asked whether addition of nivolumab to the adjuvant phase would improve outcomes in patients with high-risk locally advanced head and neck cancer patients.

So in contrast to KEYNOTE-689, which had all stage III and IV patients, this trial was focused specifically on adjuvant therapy and focused on high-risk head and neck cancer patients. And this is defined as patients who had surgery already but in their pathologic findings had high-risk features that included those with extranodal extension of tumor in the lymph nodes, microscopic positive margins, or multiple perineural invasion, or 4 or more cervical lymph nodes involved with metastatic tumor.

Patients were randomized to receive standard of care adjuvant chemoradiation alone, or the experimental arm with nivolumab given that was prior to chemoradiation plus chemoradiation and then maintenance also. The primary endpoint of this trial was disease-free survival, but this was by investigator assessment. A secondary assessment of blind independent central review was also performed.

The authors reported that the investigator-reported disease-free survival was improved with the addition of nivolumab in the adjuvant setting, with a hazard ratio of 0.76 and a *P* value of 0.034. The 3-year disease-free survival was 63.1% with nivolumab added to chemoradiation versus 52.5% with chemoradiation alone. A secondary endpoint of blinded independent central review showed a hazard ratio of 0.89, but after adjustment the sensitivity was 0.81.

So really the implications of this are that the findings of NIVOPOSTOP are really another encouraging addition to the concept of perioperative immunotherapy in head and neck cancer patients.

Finally, I'd like to conclude by saying that reassuringly in the KEYNOTE-689 trial, the surgical completion rates were similar in both arms of the study. This had been a key question prior because this idea with adding neoadjuvant pembrolizumab would alter patients' ability to undergo curative intense surgery.

Dr. Lee, before we dive into multidisciplinary planning, can you talk a little more about who may benefit from these treatment approaches?

Dr. Lee:
Yes, thank you, Dr. Uppaluri, for that great summary. We know that when we see a head and neck cancer patient, the importance of having the surgeon assess the patient, the medical oncologist, as well as the radiation oncologist, a team approach is very important to identify the best and most ideal patient to be treated using the KEYNOTE-689 pathway.

And in general, it is for patients who have resectable locally advanced head and neck squamous cell carcinoma. And we do want to test for PD-L1 status. It should be PD-L1 CPS greater than or equal to 1. In other words, if you have a patient with a 0 score, that person is not ideal for the 689 pathway.

And patients are selected before the surgeon takes the patient to the operating room, and this is why it's so important that the team approach, everyone sees the patient up front. You can think of anyone with your HPV-negative tumor that's stage III and IV. With the HPV-positive tumor, although it was a small proportion of patients, this is namely for the very high-risk HPV-positive tumor that you can also consider if in your center the best approach is using this neoadjuvant approach.

And the results of the trial, which in my mind that's something that's very good for our patients, is not having the need to give everyone high doses of radiation after surgery along with chemotherapy. As you know, this is very toxic if you do a concurrent chemoradiation, cisplatin, and a 66 Gy radiation. So that if we can actually mitigate that, meaning a downstaging of the tumor and patients only need to have a lower dose of radiation therapy without the addition of chemotherapy, that will improve the patient-reported outcome.

Dr. Uppaluri:
Great. Now that we've identified appropriate candidates for perioperative immunotherapy, let's talk more specifically about multidisciplinary planning and delivery of this treatment approach. Who needs to be involved and who does what, when, and how can we tighten cross-discipline coordination?

Dr. Lee:
Sure. As stated, that it's so important that when we have a head and neck cancer patient come to us that all 3 disciplines—surgery, medical oncology, and radiation oncology—will see the patient up front. One of the reasons is when 3 disciplines see together, for example, if 1 discipline does not feel the patients can tolerate pembrolizumab, it should be identified up front. So we need to align the 3 groups together.

We need to have the biomarker testing, especially prior to receiving pembrolizumab. We should test for the CPS score. And then, of course, this treatment sequencing should be done in a very coordinated fashion, as this is a multimodality therapy treatment paradigm for the patient.

And we can up front define who does what. For example, the medical oncologist is really taking the front seat in the very beginning with the patient's journey with pembrolizumab up to 2 cycles, and then that's the time when radiation oncology and surgery is really in the back seat. And then when we're about to enter into the surgical realm, the medical oncologist will then ensure and make sure that the patient sees the head and neck surgeon to make sure all the preoperative testing is done so that there's a seamless integration of these 2 approaches.

And finally, after surgery, there is the postoperative period. This is where the radiation oncologist and/or the medical oncologist can also align themselves with the surgeon so that the patient can have a very integrated sequential approach, so they're not lost having to figure out who to see next.

Communication is key here between the 3 disciplines as well as the patient to ensure there's a seamless integration. And toxicity monitoring is really something that we have to be mindful of. Sometimes we may say 1 discipline takes over certain areas of the patient, such as if it's a dental issue, the radiation oncologist wants to make sure the patient sees the dentist before starting radiation therapy. So in other words, you can divide and conquer depending on the toxicity, and you can decide up front as a team who's going to hold responsibility for that toxicity and the management. And this way, if the toxicity becomes escalated, all 3 teams will be made aware as well.

And of course after treatment there's the post-treatment assessment scheduling patients to see all 3 disciplines in the first follow-up visit. And then because the patients are still continuing with pembrolizumab, during this time the medical oncologist is probably going to take the front seat in seeing the patients, as they will assess the response, and then however the surgeon and the radiation oncologist also should be integrated at various time points so that the patients are not left alone.

Dr. Uppaluri:
Thanks, Nancy. So I think the key point you've highlighted here is multidisciplinary integration, which is really critical for both the NIVOPOSTOP and the KEYNOTE-689 regimens.

For NIVOPOSTOP, briefly, I think this is really an adjuvant-based trial. So really the role of the medical and radiation oncologist comes in, in coordinating the immunotherapy delivery after surgery. So again, I think that being aware of the pathology and if a patient's already gone through surgery, that may be an approach for the very high-risk patients.

One potential benefit of KEYNOTE-689 is that it encompasses both the neoadjuvant and adjuvant component. So it encompasses both a broader group of patients beyond which that is being focused on by NIVOPOSTOP and has the potential of a de-intensification of therapy in a subset of patients up front.

So what KEYNOTE-689 showed that stage III patients could also really benefit from this, which would be excluded in the adjuvant approach of NIVOPOSTOP.

One additional point I want to really comment on is the timing of surgical intervention and the details around the neoadjuvant component. This has been an area that has been discussed a lot, because we want to get patients to their curative-intent surgical approach, and how to coordinate the neoadjuvant piece has been a key implementation concern for many people around the country and the world.

A major issue is the CPS testing piece, and we hope ultimately that we will have a setting where there will be reflex CPS testing on all patients who are biopsied. But in the current era, this is variable across institutions. So how to get CPS testing defined up front and given the US FDA approval is a key challenge. And especially in centers that are seeing a lot of referral-based patients, patients may have had a biopsy outside and they come in to see us, and how to navigate that is a challenge for many surgeons in deciding if a patient qualifies for the KEYNOTE-689 regimen. So what we ___ have done is if the biopsy is accessible and the patient is amenable, we've re-biopsied patients to accelerate that process, and that's been a way to kind of advance the selection of patients for this.

Finally, with respect to optimal timing, it is a bit of a coordination issue after the second dose of neoadjuvant pembrolizumab in the patients who received the KEYNOTE-689 regimen. And we have been a bit flexible in our own practice where we are okay with scheduling that surgery after about a week after that second dose is delivered, and that's worked well for our surgical coordination.

Finally, I really want to really highlight the importance of the medical oncologist and radiation oncologist integrating in the neoadjuvant phase to really monitor the patient closely for any adverse events or any other concerns that arise.

So finally then moving on, let's discuss toxicity. What do we see in these patients treated with perioperative immune checkpoint

inhibitors? And how can we collaborate to manage them and educate our patients? Dr. Lee?

Dr. Lee:
Yes, Ravi, thank you. And again, as Dr. Uppaluri stated, the importance of a multidisciplinary team approach, and it's not just for treatment, it's also toxicity monitoring.

The beauty of KEYNOTE-689 is that pembrolizumab is very well tolerated, but during that time, your medical oncology should be very well versed to how to take care of any immune-related AEs. And namely what we've seen mainly is fatigue. People are a little bit more tired but otherwise quite well tolerated.

And when during the surgery and then even just perioperatively, it is really a joint shared ownership, co-management, because if you think about your patient, they want to know who to call when there is a problem. So it is important that your team decide who's the first doctor to call, and if you don't reach that doctor who's the second team to call. And this is really up to the local practice what you have shared in terms of your decision and ownership so that the patient will have a seamless treatment pathway.

Dr. Uppaluri:
So from my perspective, I think this really highlights the multidisciplinary care as we talked about. From a surgical standpoint, again just to highlight, especially in KEYNOTE-689, there were no sort of concerns with respect to getting patients to surgery in terms of adverse events in the neoadjuvant phase, another reassuring finding from these studies.

Well, thank you very much, Dr. Lee, it was great speaking with you today.

Dr. Lee:
Thank you. Similarly, I really enjoyed our conversation, and I think one of the excitements for me about this trial is the chance and the coordination to work with our colleagues. We are all very busy. We tend to exist in our own little silos, but this trial actually brings us together—the surgeon, medical oncology, radiation oncology together for the management for our patients.

Dr. Uppaluri:
That's all the time we have today. I want to thank you and the audience for listening in and for joining me and for sharing all your valuable insights.