Clinical Considerations in Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck

Announcer:
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Dr. A. Castro:
Squamous cell carcinoma of head and neck cancer is one of the most common cancers worldwide with over 500,000 new cases and 380,000 deaths annually. In this regard, the poor outcomes associated with recurrent metastatic squamous cell carcinoma of head and neck represent significant unmet medical need. For these patients, first-line pharmacologic therapy includes chemotherapy, target therapies and immunotherapy, often in combination. Nonetheless, treatment selection is widely recognized as difficult due to complex patient and disease factors.

This is CME on ReachMD, and I am Dr. Anna Castro. Joining me to discuss these issues are Dr. Gilberto Castro and Dr. Ricard Mesia. To get us started, Dr. Gilberto Castro, what are the typical presentations of patients with squamous cell carcinoma of head and neck? Can you tell us about the general prognosis and severity of burden of their disease?

Dr. R. Castro:
We need to consider that most of the patients that have been already diagnosed with head and neck squamous cell carcinoma—typically they have a heavy history of smoking and alcohol habits, and around 70–80% of them are usually diagnosed with locally advanced disease. In front of this, we need also to consider they are usually very symptomatic, usually with swallowing problems, breathing problems, bleeding, pain, weight loss and infections, and most importantly, most of them are usually presenting with comorbidities like COPD, anemia, hepatitis. And in terms of burden of this disease, we need to consider that some of them need to be treated as soon as possible in order to have a symptomatic relief. And taking all of this into account, unfortunately the median overall survival of these patients is around 15 to 20 months.

Dr. A. Castro:
Dr. Ricard, with this as background, what patient and disease characteristics go into determining the selection of first-line pharmacological treatments for patients with recurring metastatic squamous cell carcinoma of the head and neck?

Dr. Mesia:
First of all, I would like to remind you that up to now, just before the immune checkpoint inhibitors appearance, other lines of the recurrent metastatic disease treatment decided the treatment according to the patient's ECOG PS. Performance status probably is the main factor to select the treatment, to choose this treatment. Only patients with PS 0, 1 or 2 were treated. And in these patients with PS 0–2, we choose treatment according to the other important factors, such as comorbidities.

Previous chemotherapy treatments: The burden of cisplatin received in time from last dose of the cisplatin condition our selection of treatment. Age: We usually use (inaudible) scales in order to know whether this old patient is fit, unfit, or just in the middle, and we need to up the treatment according to these scales. Other factors that could influence in the election is nutritional status or patients' preferences.

We have incorporated 3 other main factors. First, it's time from the last dose of cisplatin. Second, PD-L1 CPS from the results of the KEYNOTE-048 study which have changed just now the first line of treatment. And third, symptom burden.

Dr. A. Castro:
So let's dig a little deeper. More specifically, could you describe patient outcomes associated with the use of first-line immunotherapy both with or without chemotherapy as compared to EXTREME regimen? Essentially, what are we learning from the data emerging from KEYNOTE-048. Gilberto?

Dr. R. Castro:
In fact, based on some patient factors, tumor factors and the available resources, nowadays we have at least 3 options for treating these patients with recurrent or metastatic head and neck squamous cell carcinoma. Namely, we have today—first one—the EXTREME regimen, or in other words, the combination of platinum, 5-FU and cetuximab. Secondly, we have the TPEx regimen, the combination of a taxane plus platinum plus cetuximab, that in order to be administered we need a hematopoietic growth factors. And finally, based on the KEYNOTE-048 trial, we have the possibility of treating these patients with pembrolizumab alone or pembrolizumab plus platinum plus 5-FU.

The KEYNOTE-048 trial is a phase 2 trial that has been already published, and in this trial these patients with recurrent or metastatic squamous cell carcinoma, they were randomized between the EXTREME regimen, pembrolizumab alone, or the pembrolizumab plus 5-FU plus platinum. The combination of pembrolizumab plus platinum plus 5-FU was superior to the EXTREME regimen in terms of overall survival, and pembrolizumab alone was not inferior to the EXTREME regimen in terms of overall survival. In terms of how to select the best patients for the best treatment, we need to consider, as I have already mentioned, some patient factors like tumor burden, like comorbidities, like the presence or not of autoimmune disease, renal function, hepatic function, and we need also to consider as tumor-related factors, we need to check the expression of PD-L1 using the CPS score.

Dr. A. Castro:
Thank you, Dr. Gilberto. Dr. Ricard, could you compare and contrast the toxicities associated with immunotherapy with and without chemotherapy, the EXTREME regimen and TPEx regimen?

Dr. Mesia:
Immune checkpoint inhibitors could produce an inflammation in any body organ. They are immune-related adverse events, and they occur in about 60% of the treated patients, although only 15% are grade 3/4, and therefore, they are forced to stop the treatment and probably are in the majority of cases completely. With immunotherapy, we have changed the typical adverse events of chemotherapy for immune-related adverse events, but when we combine immune checkpoint inhibitors with chemotherapy, we will have added twice the adverse events of both and lead to discontinuation in about 20% also.

Comparing EXTREME and TPEx, it is important to note that toxicity was lower in the TPEx arm. Hematological toxicity and
electrolyte disorders were inferior with TPEx. Neutropenia of greater than 2 in EXTREME was 49% versus 23% in those patients treated with TPEx, and unique level disorders of grade 3 or 4 were more frequent in the EXTREME arm than in the TPEx arm statistically.

Another thing I think is important now is the CD4 lymphocyte clone. In those patients who have CD4 lymphocyte clone of less than 200 per mL or (inaudible) of HIV is an absolute contraindication for chemotherapy or immune checkpoint inhibitors. And also, patients' untreated chronic hepatitis B or C is an absolute contraindication for both types of treatments.

Dr. A. Castro:
Unfortunately, we are near the end of today's discussion. In the time remaining, perhaps each of you can describe what you think the most important takeaways are for your colleagues. Dr. Gilberto, let's hear your takeaways first, please.

Dr. R. Castro:
I think in terms of takeaway messages, one thing that I would like to stress is that in front of these options, the correct, the adequate patient selection is absolutely critical. As Dr. Ricard Mesia has just pointed out, performance status, comorbidities and, for example, disease burden I think is also an important thing to consider, proliferation rate, and nowadays we need to check the PD-L1 expression.

Dr. A. Castro:
Dr. Ricard, anything to add to that?

Dr. Mesia:
Yes, from now we are going to decide the treatment in recurrent metastatic disease according to platinum sensitive or refractory, patient characteristics, mainly ECOG PS and comorbidities, tumor characteristics, and here I include tumor burden and tumor (inaudible), and also PD-L1 by CPS measurement. In those patients, platinum refractory, nivolumab or pembrolizumab is indicated in the majority of them except for those patients who progress fast, those patients who have a high symptomatic burden where we will prefer a combination of chemo, probably a combination of chemo plus cetuximab, maybe taxol and cetuximab. In platinum-sensitive patients, the treatment will depend on CPS. Where CPS is greater than 20, we will prefer pembrolizumab alone and keep on EXTREME or TPEx in second line. For those patients with a high tumor burden, we will prefer a combination of chemo plus pembrolizumab. In CPS between 1–19, we prefer the combo, the combination of chemotheraphy plus pembrolizumab in all the cases except probably those with only metastatic disease where we can start with pembrolizumab alone. For all these patients with CPS less than 1, standard treatment is still EXTREME or TPEx.

Dr. A. Castro:
Well, with those comments in mind, I want to thank my guests, Dr. Gilberto Castro and Dr. Ricard Mesia, for helping us to better understand how to select first-line treatment therapies for patients with recurring metastatic squamous cell cancer of head and neck.

Dr. Li:
Hi, everyone. This is Dr. Li from NYU. I'm a medical oncologist specializing in head and neck cancer. You just heard this nice presentation about treatment for recurrent and metastatic head and neck cancer. Treatment of head and neck cancer has multiple challenges. Many people have a recurrent or metastatic head and neck cancer. Usually, these patients have a very high tumor burden and also have a lot of symptoms—pain and dysphagia and are highly symptomatic. Especially in Asia and in China, the head and neck actually has higher incidence, and the treatment has not been uniform.

As you know, there are a lot of challenges in the treatment for recurrent and metastatic head and neck cancer. In the past 20 years, recurrent and metastatic head and neck cancer have been treated with EXTREME regimen in the first line, basically cisplatin plus fluorouracil plus cetuximab, which is available in China. It has had not much progression in the past 20 years until recently with the introduction of immunotherapy.

Recently reported KEYNOTE-048 introducing of immunotherapy to first-line treatment for metastatic and the recurrent head and neck
cancer.

Announcer:
KEYNOTE-048 was a phase 3 study comparing pembrolizumab alone or plus chemotherapy versus cetuximab plus chemotherapy for the management of recurrent or metastatic squamous cell carcinoma of the head and neck. Participants were assessed for PD-L1 status as well as other eligibility criteria, and randomly allocated 1:1:1 to pembrolizumab alone, pembrolizumab plus a platinum and 5-fluorouracil, or cetuximab plus a platinum and 5-fluorouracil, also known as the EXTREME regimen.

When comparing patient outcomes for overall survival in KEYOTE-048, pembrolizumab plus chemotherapy was superior to EXTREME whether the combined positive score results, or CPS for PD-L1 status, was ≥20 or ≥1; this outcome also extended to the overall population regardless of PD-L1 status.

Findings were mostly similar when comparing pembrolizumab monotherapy with EXTREME for patient cohorts who were CPS ≥20 or ≥1; however, in the overall population pembrolizumab monotherapy was not inferior to EXTREME. However, KEYNOTE-048 did not specifically address patients who were CPS <1 nor breakout populations within the CPS range of 1 to <20, which remains an area of interest.

Pembrolizumab monotherapy and/or in combination with chemotherapy is indicated in the US and European Union for the management of recurrent or metastatic squamous cell carcinoma of the head and neck. However, pembrolizumab, while available in China, is not currently approved for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck.

Dr. Li:
I will emphasize the treatment of head/neck cancer should be data-driven, and I know they are not necessarily uniform because China has large geographical locations, which really make a difference.

Thank you for listening to the presentation.

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