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Systemic Therapy in Patients with LA-SCCHN: Future Directions

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Hello, my name is Denis Souliéres. I'm a medical oncologist at the Centre Hospitalier de I'Université de Montréal. And we are going to discuss briefly systemic therapy for locally advanced squamous cell carcinoma of the head and neck, what is the current state, and basically, what are future directions and what have we learned from recent trials.

These are my disclosures. Most research grants are given to my institution. And I participate in ad boards and speaker bureau from different companies. So the learning objectives of this capsule is to first recognize the needs for novel therapies for locally advanced head and neck cancer and to summarize the main findings from recent major trials in locally advanced head and neck cancer.

And we're also going to identify phase III trials that are ongoing for which the results are expected and might change the field in terms of how we treat patients with locally advanced head and neck cancer. There is clearly a need for novel therapies in the context of locally advanced head and neck cancer. We do know that it is the mainstream of how people are presenting with this disease.

So most people with head and neck cancer will present with locally advanced disease. About 66% of those who have localized disease will have locally advanced disease when they-- in the advent of their first presentation. We know that most of these patients, a great majority of them, will have either locoregional recurrences or distant relapse at some time after the initial treatment for locally advanced disease.

So there is a need for improvement so that we have better local control and better distant metastasis control as well. We also are in a need of treatment options that are better in the context of head and neck cancer. But we have had some quite good news over the last 10 years for recurrent disease with the advent of immunotherapy and especially with anti-PD-1 agents that have proven to not only increase the response rate but also increase survival, and possibly for some patients, give them very long-term survival, as was proven in the context of KEYNOTE-40 and KEYNOTE-48.

We know that there's a lot of chemoresistance in patients with head and neck cancer and also partly due to the fact that these are patients that we are heavily treating with a platinum agent. And we do know that at some point, not only is there resistance, but there is also intolerance to these types of agents. So therefore, there is a need to try to see if incorporating agents that have not only been used for locally advanced, recurrent and metastatic setting can be used earlier. And we are also looking at whether or not there are possibilities of getting rid of the chemotherapy with platinum backbone, which is the cause of so much toxicity.

We know that these are patients that are at high risk for a poor prognosis. So a lot of patients with head and neck cancer in the local advanced setting will have a smoking history, a history of alcohol consumption, and also chewing tobacco products as well that are being used. And indeed, for example, it's mainly the battle fruit that is the object of so many oral cavity cancer.

So these are clearly prognostic elements. These are also causal elements in the context of head and neck cancer. But clearly, they are prognostic. So patients that are still smoking, still drinking at the time of their treatment will have a poorer prognosis than those who don't. We know that there is a possibility that there is chronic oral trauma or leukoplakia that might also play a role in not only the occurrence of cancer, but also in the poor prognosis after a treatment for locally advanced disease.

HPV-negative is now the minority of patients that we see with oropharynx cancer. But these are patients who have much poorer prognosis. But we also know that patients who are HPV-positive, if that is combined with tobacco use or alcohol use, these will have a worse prognosis than those who are just HPV-positive without those risk factors. So there is clearly elements that we need to look at in terms of identifying patients who are at poorer prognosis and who might require a different type of therapy.

There are some major trials that have been reported for locally advanced head and neck cancer over the last couple of years. The first one I'm going to mention is KEYNOTE-412. KEYNOTE-412 was looking at the addition of pembrolizumab to a backbone of chemoradiation therapy, chemotherapy being with a platinum agent, and also with the use of pembrolizumab after the use of the chemoradiation therapy.

Unfortunately, this trial did not prove to have a positive endpoint. It is a negative trial in terms of the overall population. But what we've learned, at least from a bit of this trial, is if this had been specifically targeting those with expression of PD-L1, it might have been a positive trial. But this is not something we can say. The intent-to-treat analysis on the overall population was negative, even though there seems to be a trend for the patients who have a tumour that is positive for PD-L1.

The JAVELIN Head and Neck 100 trial is one that has been reported, but for which we know that the use of avelumab-- so in this context, not an anti-PD-1, like pembro, but an anti-PD-L1. So in this context, again, looking at avelumab plus chemoradiation therapy, followed by avelumab maintenance compared to chemoradiation therapy alone. And in this context, the progression-free survival was not attained.

And if anything, in terms of looking even at the overall survival with time, it seems to have been a bit worse with those who were treated with avelumab compared to chemoradiation therapy alone. So a bit of a lesson learned here that, again, an anti-PD-L1 agent doesn't seem to do the trick in terms of improving results for locally advanced setting compared to chemoradiation therapy.

The NRG-HN004 trial is one that was looking at the use of radiation plus durvalumab, so another type of anti-PD-L1 agent, versus radiation plus cetuximab for patients who had previous untreated head and neck cancer and for patients, who in this context, were at a contraindication to a platinum agent because of renal failure, because of hearing problems, because of other comorbidities. So this is a very specific group of patients for which we want to de-escalate treatment by using less toxic agents, like durvalumab or cetuximab.

In this context, the use of radiation therapy plus durvalumab did not show a signal towards an improved progression-free survival. And in fact, if anything, it probably led to worse outcome in

terms of the locoregional failure rate compared to cetuximab plus radiation therapy. So in this context, we can say that even an anti-PD-L1 agent combined with radiation therapy, even in a category of patients who are platinum-ineligible, did not show an improvement compared to the standard therapy of radiation therapy or radiation plus cetuximab.

In France and in some parts of Europe, the GORTEC, a group has led a research called REACH. And this REACH trial, they were looking at two categories of patients, so patients who were fit to receive a platinum agent and patients who were unfit to receive a platinum agent. And in this context, patients were to receive, if they were platinum-fit, radiation therapy with IMRT with a platinum agent compared to IMRT plus a combination of cetuximab and nivolumab, followed by a maintenance with avelumab for a period of up to a year. We'll come back to this specifically in terms of the results.

Cohort 2 was addressing those were unfit to receive a platinum agent. So patients were to receive either IMRT plus cetuximab or the same combination of IMRT, cetuximab, and avelumab, followed by the avelumab maintenance. For the platinum-unfit patients, so the cohort 2, there was a small effect in terms of adding avelumab to cetuximab plus radiation therapy in terms of the progression-free survival, but did not reach the level of statistical significance.

So the primary endpoint was not met. And therefore, we cannot say that this is an adequate therapy for those who are platinum-ineligible. For the cohort 1 of a platinum-fit patients, actually, this trial was stopped early on because of a futility assay that proved that patients were not deriving any type of benefit from avelumab, cetuximab, plus radiation therapy compared to a platinum agent.

And therefore, that part of the trial was completed early and ended because of the possible deleterious effect of this new combination compared to chemotherapy plus radiation therapy.

There was a trial that was very interesting over the last couple of years using docetaxel. So it's a randomized phase II that led to a phase III investigating radiation therapy plus docetaxel versus radiation therapy alone for patients who had head and neck cancer, who were ineligible to receive a platinum agent. And in this context, even a small dose of docetaxel 50 milligrams per metre square given every week in the course of the radiation therapy did lead to an improvement in disease-free survival as well as overall survival in this group of patients who were platinum-ineligible.

And that has clearly probably defined a population of patients for which we do have a possible new therapy that we were not using before. The only element out of that trial is that it did not compare to cetuximab radiation therapy and compared to radiation therapy.

Even though there is no proof that cetuximab plus radiation therapy is better for the platinum-ineligible patient, it did end up being a standard that a lot of people were using. So here, we have at least a level 1 evidence of a combination that seems to work better for those who are platinum-ineligible.

In terms of phase II trials, there is also a trial that looked at the use of pembrolizumab plus radiation therapy versus cetuximab plus radiation therapy for those with locally advanced disease. And this was, again, for a group of patients who were considered to be platinum-ineligible or who could not receive a platinum agent for some reason.

Here, in this trial, this randomized phase II, it did not improve the tumour control rate of pembro plus radiation therapy compared to cetuximab plus radiation therapy and therefore did not lead to further studies, even though the combination of pembro plus radiation therapy appeared to be less toxic for that category of patients.

Now we're going to look at ongoing trials for locally advanced head and neck cancer, things that are going to be probably reported over the next year or over the next couple of years. TrilynX is the first one to be on that list. It's a phase III trial. That was the-- that is supposed to be the confirmatory trial of a randomized phase II that used an agent called Xevinapant in combination with a platinum agent plus radiation therapy compared to chemoradiation therapy for locally advanced disease.

In this trial, the randomized phase II, even though it did not reach level of statistical significance that were high enough to lead to direct approval, it did show that Xevinapant was better in terms of the progression-free survival as well as the overall survival when they were receiving Xevinapant in addition to chemoradiation therapy.

Now, in the context of the phase III, so a much larger number of patients, we're looking at exactly the same design, except that there is also the use of Xevinapant for three months after the initial treatment of chemoradiation therapy. So hopefully, the results out of this trial will be available over the next year and could lead if it leads to a confirmation of the phase III trial-- of the phase II trial could lead to a very new standard for locally advanced disease.

And using the same agent, there is a phase III trial that is looking at the use of Xevinapant plus radiation therapy compared to radiation therapy for patients who have had surgery. So it's a context here of an adjuvant setting compared to a primary treatment with chemoradiation therapy. Here, we have adjuvant after the use of the first treatment, which is surgery.

And again, here, we want to show that Xevinapant, in addition to radiation therapy, leads to an improvement in disease-free survival as well as overall survival for those who have undergone surgery. Hopefully, this, again, will lead to a change in the paradigm of what we're doing for those patients who are mainly directed to radiation therapy.

For some of those, they are not led to only radiation therapy. They're led to chemoradiation therapy. But this is based on the stratification based on a number of risk factors of recurrence. So this is addressing the category of patients who are not receiving a platinum agent post-surgery.

KEYNOTE-689 is a trial looking at the use of pembrolizumab given prior to surgery for patients who have locally advanced disease. So there are a lot of phase II trials that have proven that the use of immunotherapy in the context of neoadjuvant therapy leads to significant response rates. And here, we're looking at whether or not the use of pembrolizumab, so an anti-PD-1 agent, before

surgery and after the surgery, before the initiation of a treatment with platinum plus radiation therapy or platinum-- or radiation therapy alone leads to an improvement in different parameters.

The primary endpoint, we will be looking at event-free survival. But there also is the possibility of looking at the reduction of need for a platinum agent after surgery for patients who have received neoadjuvant pembrolizumab. So there are different endpoints that could lead to a modification of practise for patients for which it is decided to go for surgery for locally advanced disease.

And here, we're mainly looking, obviously, at oral cavity as well as larynx cancer, much more than for oropharynx, even though these are not excluded from this trial. We do not for that-- know that for oropharynx, m we will favour, most of the time, chemoradiation therapy. But the advance of robotic surgery has led to a significant number of patients who are not treated with surgery for oropharyngeal cancer as well.

IHN01 is another trial looking at a new agent, nimotuzumab. Nimotuzumab is an EGFR inhibitor, which has a different affinity compared to cetuximab. And what has been reported, first, the response rate seems to be higher for head and neck cancer with this type of agent. But it also leads to fewer side effects that are related to the EGFR with nimotuzumab compared to what we've seen with either cetuximab or panitumumab.

So here, we're going to be looking at the adjuvant setting for patients who have had a surgery for locally advanced disease and who require radiation therapy and who will receive nimotuzumab at the same time as radiation therapy.

The RTOG9320 trial is also looking at a setting of patients who have undergone surgery for locally advanced disease. And in this context, it's relooking at the question of radiation therapy compared to radiation plus cetuximab. Even though I mentioned to you before that in a large number of settings, it is considered to be like the standard to use, cetuximab plus radiation therapy, it has not been proven up to date out of a randomized phase III trial. And this RTOG trial is trying to do just that, so the use of radiation therapy or radiation plus cetuximab.

A bit of the same design compared to the trial that I just presented before, the IHN01, but with an agent that has been reported to have much more side effects compared to nimotuzumab, at least from the randomized phase II that we have or the overall trials that we know out of cetuximab and nimotuzumab. So this would be interesting because this is looking not just at DFS but also at overall survival as the primary endpoint.

And the last trial in terms of ongoing major trials for locally advanced trials or locally advanced disease is the use of NBTXRT-- R3, sorry, in combination with radiation therapy plus or minus cetuximab versus radiation plus or minus cetuximab. So again, here, we're looking at patients who have locally advanced disease, who are platinum-eligible because of comorbidities or because of their age.

And this is an interesting agent. So a hafnium oxide in the form of a nanoparticle, which is injected in the tumour, doesn't have to be injected in all sites of disease, but only in sites of disease that are more important, that are reported to be more than 3 centimetres. And the object would be that it

is a sensitizer to radiation therapy. And by using this agents in large, bulky parts of the disease, it will lead to a better control of the disease, and therefore will lead to a better progression-free survival.

So this trial is ongoing. We don't know exactly when all patients are going to be randomized up to now. But it is certainly a setting that is interesting, looking at modifying the effect of radiation therapy by a nanoparticle that leads to radiosensitization.

So the key learning points of what I've just presented is that we do know about the complex nature of locally advanced disease for head and neck cancer. In some settings, especially for locally advanced settings for oropharynx, we're mainly led up to now to a combination of chemoradiation therapy. And the results that we get out of regular practise now are better because we have much more patients who are HPV-positive.

Nonetheless, there are quite a few patients who are oropharynx HPV-positive, who will lead to have recurrence, either locally or distally, and for which we are trying to find new ways or better ways to control the disease so that we don't have those recurrences for locally-- from locally advanced disease after a primary treatment with chemoradiation therapy.

Some of the elements that I've presented to you are not showing that we have much more options for the cisplatinum-ineligible, maybe in terms of the use of docetaxel in combination with radiation therapy. So that's probably the most interesting group right now for the locally advanced disease that we're treating primarily.

For those who are treated adjuvantly, we have a large number of different settings that we are looking at. So those were our platinum-ineligible, those who don't require a platinum agent based on the results that we have before from adjuvant disease-- adjuvant treatment for locally advanced disease that has gone through surgery. But hopefully, we're going to be able to find new combinations, possibly with radiosensitizer, like Xevinapant, which might play a role in that category of patients.

So we certainly have promise from different trials that are ongoing. I just mentioned Xevinapant. This is probably one of the most interesting agents because of the knowledge that we have of the randomized phase II that led to significant positive results, we do hope that it will be confirmatory in the context of the phase III trial for locally advanced disease that is treated primarily.

But we also are looking at new agents, like I mentioned, the nanoparticle in terms of a hafnium oxide that will lead to radiosensitization as well. So these are interesting elements that will lead us to look very specifically at those types of results over the next couple of years. And with this, I will end this presentation. Thank you.