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Systemic Therapy in Patients with LA-SCCHN: Current State and Unmet Needs

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Hello, everyone. My name is Anna Spreafico. I'm a medical oncologist and clinician investigator at the Princess Margaret Cancer Centre in Toronto. Both my practise and research are focused on head and neck malignancy and early phase clinical trials. Today, I will provide a brief overview of the current systemic therapy strategies in patients with locally advanced head and neck squamous cell carcinoma and the future directions.

Here's my disclosures. So head and neck is the sixth most common cancer in Canada, and these diseases include tumours located in different area of the head and neck, including oropharyngeal space, oral cavity, larynx, and hypopharynx. Tobacco consumption and the human papillomavirus infection, particularly for the oropharyngeal cancer in this case, are the major risk factors.

The overall incidence of the human papillomavirus positive oropharyngeal cancer is increasing in North America, while the incidence of human papillomavirus negative disease primarily related to tobacco and alcohol consumption is decreasing. Today, we will discuss the current treatment option for locally advanced squamous cell carcinoma of the head and neck, recognize the unmet needs of this patient population, describe the alternative treatment option, and the emerging therapies for these patients.

So randomized trials and large meta analysis have demonstrated a significantly improved overall survival, disease-free survival, and locoregional control when chemotherapy is delivered in combination with radiation treatment as compared to radiation treatment alone for patients with locally advanced head and neck cancer.

When chemotherapy is delivered with radiation, cisplatin is the preferred radiosensitizer agent. High-dose cisplatin, also defined bolus cisplatin, is delivered at 100 milligrams per metre square once every three weeks generally given on day 1, 22, and 43 during the course of radiation treatment. Radiation is typically used at conventional fractionation at two grey over on a daily basis, five days a week, for a total of 70 grey in seven weeks.

Due to some concern about toxicity, so side effects, a weekly regiment of cisplatin also define low-dose cisplatin at 40 milligram per metre square on a weekly basis can be used. In addition, carboplatin has been used to substitute cisplatin for patients with specific comorbidities in case cisplatin cannot be delivered in a safely manner.

In the absence of a definitive prospective comparison trials, it is nevertheless unclear whether weekly cisplatin and more importantly carboplatin are less toxic or equally efficacious as the high-dose cisplatin. Currently, there is a larger randomized trials ongoing from a cooperative group, the NRG-HN009 study, which is an ongoing phase II, phase III trial comparing low dose to high-dose cisplatin.

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As mentioned, concurrent chemoradiotherapy with cisplatin is the mainstay in the organ preservation management for patients with locally advanced head and neck cancer squamous cell carcinoma high dose cisplatin plus radiation has shown to improve locoregional control and survival. The efficacy of cisplatin-based chemotherapy radiation appears to correlate with the cumulative total dose of cisplatin during the seven weeks of radiation.

However, as I mentioned, cisplatin is associated with some side effects, both considered acute as well as potentially long-term side effects, which can impact the quality of life of patients. In addition to the acute side effects that can be nausea, vomiting, risk of severe infection amongst others, the main long-term side effects of cisplatin may include nephrotoxicity, so kidney dysfunction.

Auto toxicity, so hearing damage. And neurotoxicity. Mainly, peripheral neuropathy. Due to this cisplatin safety profile, several patients are unable to receive the full three doses of the high-dose cisplatin. And therefore, treatment adherence protocol can be suboptimal. And weekly cisplatin has been widely used as a possible alternative.

This regiment has not been evaluated in a large randomized studies versus concurrent high-dose cisplatin chemoradiotherapy or radiotherapy alone. And the NRG trial that I've mentioned is the trial ongoing that hopefully will be able to answer this question. Therefore, the use of weekly cisplatin is not supported thus far by level 1A evidence in the international guidelines.

Finally, weekly cisplatin doses that are less than 40 milligrams per metre squared have failed to show superiority or even non-inferiority to radiotherapy alone or to high-dose cisplatin in terms of efficacy and treatment compliance in multiple clinical trials. So overall, cisplatin is used very widely for patients with locally advanced head and neck squamous cell carcinoma undergoing organ preservation curative intent treatment.

However, not all the patients are eligible to receive cisplatin. So the cisplatin eligibility can be broadly separated into two main categories. Some patients may be ineligible for cisplatin because of what we call secondary resistance. So for example, patients who have received platinum-based treatment and have had a recurrence or development of static disease with a very short disease-free interval between the prior platinum-based regimen.

Or patients who have an absolute or relative contraindication to cisplatin because of high risk of adverse events or other factors. So for example, contraindication to cisplatin either upfront or during treatment can be in case of kidney dysfunction, as I mentioned, baseline hearing dysfunction, baseline peripheral neuropathy, pregnancy or lactation, or HIV positivity with abnormal CD4 counts or intractable nausea, vomiting, dysphagia, and as I mentioned, other toxicity while on therapy.

While nausea and vomiting are, to a certain degree, self-limiting, they reversible. And there are a lot of medications that can be given to properly address these symptoms. Some other adverse events or side effects can be more challenging to manage. Relative contraindication to cisplatin also include the age. So patient over the age of 70, high consideration has to be given to that.

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Equal performance status of equal or greater than two. Substantial weight loss or more than 10% of baseline body weight within a short period of time and a low BMI or a low body weight. In patients who are ineligible for cisplatin, carboplatin has been empirically used. And I would say empirically used.

Carboplatin is associated with an increased risk of myelotoxicity. So side effects to the bone marrow as compared to cisplatin, but it's certainly less neurotoxic and less nephrotoxic. However, carboplatin is not as effective as cisplatin for its direct anti-tumour effect. It is not clear, and there's no data to show that carboplatin is effective at least as cisplatin as a radiosensitizer.

There been several studies that have compared carboplatin alone and cisplatin alone for the chemoradiation of the head and neck cancer. Some examples include a randomized study in patients with locally advanced nasopharyngeal cancer where concurrent chemoradiation using carboplatin demonstrated comparable efficacy and better tolerability when compared to chemoradiation with cisplatin.

However, I want to point out that this patient population was patients with nasopharyngeal cancer, which are a different disease than head and neck cancer. There was also a randomized phase II study that included about 119 patients with head and neck squamous cell carcinoma in which weekly carboplatin resulted in significantly increased five-year local recurrence but did not impact overall survival.

And there was no statistically significant difference in this term when compared to daily low-dose cisplatin. And then a randomized phase III trial that compared radiation therapy alone to chemoradiation with 100 milligrams of metre squared of cisplatin. So the high-dose cisplatin, and chemoradiation with carboplatin with an AUC of seven given on day on days 2, 22, and 42.

And in this trial, carboplatin-based chemoradiotherapy was superior to radiation alone but inferior to cisplatin-based treatment with respect to the time to progression and median overall survival. So certainly not a lot of positive data for carboplatin. So beyond chemotherapy, epidermal growth factor receptor overexpression is common in squamous cell carcinoma of the head and neck and is associated with the poor overall survival.

These data have led to the development of inhibitors of this pathway, such as the EGFR monoclonal antibody cetuximab. The pivotal study of cetuximab was a phase III trial reported by Bonner and colleagues who randomly assigned about 424 patients with locally advanced stage III and IV squamous cell carcinoma of the hypopharynx, oral pharynx, and larynx to receive radiation with or without cetuximab.

Locoregional control and median overall survival were significantly improved in patients treated with radiation therapy and cetuximab as compared to radiation alone. So based on these studies, cetuximab became the first targeted therapy approved by the Food and Drug Administration in locally advanced squamous cell carcinoma back in 2006.

More recently, in 2021, after scan three, an open-label randomized controlled phase III trial reported the results of patients with stage III and IV head and neck squamous cell carcinoma, which

were staged according to the seven edition randomized to receive either intravenous cetuximab with loading dose one week before the start of the radiation treatment, followed by a weekly cetuximab during the radiation.

Versus a weekly intravenous cisplatin 40 milligram per metre squared, so the low dose, during the radiation. Radiation was the conventional fractionation. The primary endpoint of this study was overall survival, and the study was closed earlier after an unplanned interim analysis when 298 patients had been randomized.

At three years, the overall survival was 88% and 78% in the cisplatin and cetuximab group respectively. However, importantly, the cumulative incidence of locoregional failure at three years was 23% in the cetuximab arm as compared to the 9% in the cisplatin arm. So overall, cetuximab was inferior to cisplatin regarding locoregional control for concomitant treatment with radiation in patients with locally advanced head and neck squamous cell carcinoma.

Overall, novel strategies are certainly needed to attempt to improve the outcome of patients with locally advanced squamous cell carcinoma of the head and neck, or at the very least, to preserve the good outcome while sparing acute and long-term toxicity of chemotherapy. While immunotherapy has shifted the paradigm of the cancer treatment over the past decade and is certainly commonly used and is the first line choice for patients with recurrent metastatic squamous cell carcinoma head and neck, the use of immunotherapy in the locally advanced setting remains limited to clinical trials.

And we'll hear about immunotherapy more. Beyond the immune checkpoint inhibitors, the inhibitors of apoptosis have emerged as an attractive area of investigation. Treatment resistance is one of the key factors in local or distant failure. And so evasion of apoptosis plays a major role in this as cancer cells are unable to resist the cell's death induced by anticancer treatments.

Inhibitors of apoptosis protein have generated interest given that the resistance to anti-cancer agents is becoming more prominent. Xevinapant is a first in class oral small molecule of inhibitors of apoptosis protein that has been shown to restore cancer cell sensitivity to apoptosis, and therefore, enhance the effect of anti-cancer treatments, such as chemotherapy and radiotherapy.

Particularly, this agent has shown clinical proof of concept when combined with chemoradiation. In a double blind randomized trials of chemoradiation plus Xevinapant versus chemoradiation plus placebo in patients with locally advanced squamous cell carcinoma of the neck, Xevinapant demonstrated superior efficacy as a significantly improved locoregional control at 12 months after the end of chemoradiation, which was the primary endpoint.

And the three-year progression free survival versus placebo plus chemoradiation without increasing toxicity. So overall, the treatment option for patients with locally advanced head and neck carcinoma, as I've shown you, have really not changed much in the last 20 plus years. However, there's a lot of efforts that have been placed to identify new treatment strategies.

But we have not quite achieved this goal. Lots of clinical trials ongoing, and hopefully, some data will be available in the near future. Targeted therapy has been used as an alternative option in

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patients who are ineligible for cisplatin, but several studies are ongoing to evaluate the role of novel and alternative therapies in patients with locally advanced squamous cell carcinoma of the head and neck. And hopefully, in the near future, we will be able to improve patient selection strategies in order to achieve a better cure. Thank you.