Optimal regimen of cisplatin in squamous cell carcinoma of head and neck yet to be determined

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Provenance: This is a Guest Editorial commissioned by Section Editor Jing-Ru Jiang, MD (Department of Neurology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China).


Submitted Apr 03, 2018. Accepted for publication May 04, 2018.
doi: 10.21037/atm.2018.05.10
View this article at: http://dx.doi.org/10.21037/atm.2018.05.10

Squamous cell carcinoma of the head and neck (SCCHN)

Head and neck cancers account for more than 550,000 cases and 380,000 deaths annually worldwide and are the 6th most common cancer type (1). Head and neck cancers can arise in the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid, and salivary glands and include a variety of histopathologic tumors. Squamous cell cancer (SCC) is the most common pathological type of head and neck cancer (2).

SCCHN can be largely divided to two distinct groups based on their oncogenesis pathways: tobacco and alcohol-related and human papilloma virus (HPV)-associated (3). Tobacco and alcohol-related SCCs are usually associated with an altered p53 gene, frequently in conjunction with chromosome 7 aneuploidy, and have an increased proliferative index as measured by Ki-67 (4,5). Most of the oral cavity cancers, larynx and hypopharynx cancers are tobacco and alcohol-related. Human papillomavirus (HPV) infection (especially high-risk HPV subtypes) is responsible for most of the SCCs arising in the oropharynx (represented by the lymphoid-rich areas of the base of tongue and tonsil) (3,6). After infection of the squamous mucosa in the area, HPV is integrated into the host genome, inactivates the retinoblastoma gene (Rb), and stops its negative feedback on viral E6 and E7 proteins, which results in overexpression of tumor suppressor protein p16 (7-10). Those genetic changes lead to cancer cell proliferation. A majority of the oropharynx cancers are HPV-associated.

In both the United States and Europe, the incidence of HPV-associated SCCHN has been rising, whereas the tobacco and alcohol-related SCCHN has been decreasing (6,11). In England, epidemiology studies projected that by 2025 oropharynx cancer could compose 35% of all SCCHN (12). In Asian countries, the tobacco and alcohol-related SCCHN still remains dominant.

HPV-associated SCCHN has better prognosis than the stage-matched HPV-negative cancers (13,14). To acknowledge the difference, the tumor, node, metastasis (TNM) staging system of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) separated staging systems for HPV positive and HPV negative oropharyngeal carcinomas in the eighth edition [2017] (15,16). In the HPV-associated SCCHN cancers, de-intensification of the therapies is being investigated in clinical trials.

Concurrent chemoradiotherapy for locally advanced SCCHN

In general, early-stage SCCHNs are treated with single modality local-regional approaches, surgery or radiotherapy. Most of the locally advanced squamous cell head and neck cancer (stages III–IV) still has high curative potential, therefore, definitive local therapy, such as surgery and/or
radiation therapy, is still the key component of the initial treatment of locally advanced SCCHN. The choice of definitive treatment differs according to primary site of the disease. For oral cavity cancers, surgery is a common first choice. For cancers from oropharynx and nasopharynx, definitive radiation with or without concurrent chemotherapy is usually the treatment of choice (17). And for larynx and hypopharynx cancers, a combined modality therapy for organ preservation is usually preferred (18,19).

Chemotherapy has been introduced into multimodality management of SCCHN in an effort to improve cure rates and functional outcomes. Cisplatin has been the most extensively investigated concurrent chemotherapy agent for more than 50 years, due to its radio-sensitizing role. In a randomized phase III study in patients who had high-risk features, Bernier et al. showed that concurrent postoperative administration of cisplatin and radiotherapy significantly improve the rate of local and regional control (hazard ratio 0.61, P<0.01), without impacting cumulative incidence of metastases (20). Similarly, Cooper et al. showed combining cisplatin with radiotherapy improved local-regional control and progression-free survival (PFS) (21). Both studies chose the regimen of cisplatin at 100 mg/m² every 3-week.

Since the publication of those two studies (20,21), cisplatin at 100 mg/m² every 3-week has been the standard-of-care as concurrent adjuvant chemoradiotherapy for high risk patients. While the benefit was established in the studies, toxicity was also observed in both studies. Bernier et al. reported higher incidences in severe (grade 3 or higher) adverse effects in functional mucosal, muscular fibrosis, as well as cytopenia and nausea/vomiting in the combined group (20). Cooper et al. found that the addition of chemotherapy to radiotherapy increased the incidence of severe adverse effects (grade 3 and higher) from 34% to 77% (P<0.001) (21,22).

In oropharyngeal cancers, Denis et al. showed that concomitant radiochemotherapy as definitive treatment confers lower local and regional failure rate compared with radiotherapy alone (GORTEC 94-01) (17). In this study, carboplatin with fluorouracil was given every 3 weeks was the chemotherapy regimen. Again, toxicity was higher in the concomitant group, including more frequent need for a feeding tube (17).

Further consolidating the role of concurrent chemotherapy to radiation therapy, MACH-NC was reported by Pignon et al. after performing a meta-analysis of chemotherapy in head and neck cancers. In this study, 16,485 randomized patients aggregated from 87 phase III clinical trials from 1965 and 2000 was analyzed. Pignon et al. reported an overall survival (OS) benefit of 4.5% at 5 years when chemotherapy was added to radiation therapy versus radiotherapy alone (hazard ratio 0.88) (23,24).

**Dose and schedule of concurrent cisplatin**

Now that the local-regional control benefit of addition of cisplatin to radiation has been established in adjuvant setting as well as in definitive setting, investigations started to focus on understanding the optimal dosing and schedule of cisplatin.

To determine the optimal cumulative dosing, Strojan et al. performed meta-analysis from 11 prospective randomized trials, and 7 non-randomized trials. Although the benefit signal was noisy, when the analysis was limited to the 6 studies with chemoradiotherapy as a definitive treatment, a significant improvement in OS was identified with increasing cumulative cisplatin doses. A 2.2% OS benefit between the chemoradiotherapy group and the radiotherapy alone group was observed for every 10 mg increase in the cumulative cisplatin dose (25). Because the frequent omission of the third dose of cisplatin due to toxicity, it is generally accepted that cumulative dose of cisplatin greater or equal to 200 mg/m² confers a survival benefit.

Dosing schedule optimizations have looked at weekly cisplatin dosing ranging from 30 to 40 mg/m² or daily administration from 5 to 7 mg/m². Weekly dosing has gained popularity compared to the traditional dose of 100 mg/m² every 3 weeks (26-28). There are two inter-related goals behind this move: one is to decrease toxicity, and two is to improve treatment compliance in order to achieve a higher cumulative cisplatin dose and, in turn, the efficacy of concurrent chemoradiotherapy. Interestingly, a modeling study by Marcu et al. demonstrated that daily administration dosing of cisplatin with radiotherapy is more efficient than weekly cisplatin, which can increase tumor control efficacy from 6% to 35% (29). This work did not compare every 3 weeks to weekly dosing.

**Weekly versus every 3-week cisplatin in Noronha et al. study**

To understand whether weekly cisplatin is an acceptable alternative to the standard every 3 weeks schedule, Noronha et al. conducted a phase III randomized trial to evaluate for non-inferiority of cisplatin 30 mg/m² once a week...
compared with cisplatin once every 3 weeks at 100 mg/m², while both groups receiving concurrent radiotherapy with a curative intent (30). Between 2013 and 2017, 300 patients were randomized, with 150 on each arm. Among them, majority of the patients were males (89%) with oral cavity cancers (87%). In this trial, concurrent chemoradiotherapy was mostly used as an adjuvant therapy for high-risk features after surgery (93%) and was only used as definitive treatment in 7% of the cases.

The primary objective of the study was to determine whether weekly cisplatin concurrent with radiotherapy was non-inferior to once every 3 weeks cisplatin in prolonging loco-regional control (LRC) in locally advanced HNSCC. The study had a median follow-up of 22 months. Noronha et al. reported the estimated cumulative 2-year loco-regional control rate to be 58.5% in the weekly cisplatin arm and 73.1% in the once every 3 weeks arm, hence a difference of control rate of 14.6% (95% CI, 5.7% to 23.5%; P=0.014; hazard ratio 1.76; 95% CI, 1.11 to 2.79). The secondary end points included other efficacy measures, such as PFS, OS. In this study, estimated median PFS in the weekly arm was 17.7 months (95% CI, 0.42 to 35.05 months) and in the once every 3 weeks arm was 28.6 months (95% CI, 15.90 to 41.30 months), with HR 1.24 (95% CI, 0.89 to 1.73; P=0.21). In this study, the estimated OS was 39.5 months in the weekly group, whereas the OS was not reached (NR) in the once every 3 weeks group (HR, 1.14; 95% CI, 0.79 to 1.65; P = 0.48). The other set of secondary end points were toxicity, both for acute and chronic, compliance, response rate, and quality of life. The grade 3 or higher acute toxicity was observed in 71.6% of patients in the weekly group and in 84.6% of patients in the once every 3 weeks group (P=0.006). Therefore, the authors suggested that “once-every-3-weeks cisplatin at 100 mg/m² resulted in superior LRC, albeit with more toxicity, than did once-a-week cisplatin at 30 mg/m² and should remain the preferred chemoradiotherapy regimen for locally advanced HNSCC in the adjuvant setting” (30).

Cisplatin 40 mg/m² weekly

While the Noronha study offered solid evidence that 100 mg/m² every 3 weeks is superior to 30 mg/m² weekly for adjuvant concurrent chemoradiotherapy in oral cavity cancers, it is unclear whether higher weekly doses (such as 40 mg/m²) may show non-inferiority in efficacy. In the Noronha study, for every 3 weeks group, the median cumulative cisplatin dose was 300 mg/m² (range, 200–300 mg/m²) with dose intensity estimated at was 42 mg/m²/wk (range, 33.3–47.7 mg/m²/wk), whereas in the weekly dose group the median cumulative cisplatin dose was 210 mg/m² (range, 180–210 mg/m²) with dose intensity at 30.7 mg/m²/wk (range, 28.8–33.4 mg/m²/wk). The difference in cumulative dose might be sufficient to explain the difference in LRC rate. Therefore, one may hypothesize that a higher weekly dose resulting in comparable cumulative dose might be able to eliminate the difference in LRC rate.

In fact, although chosen in the Noronha study, cisplatin at 30 mg/m² weekly is not the commonly used weekly dose in the United States and many European countries. Instead, cisplatin 40 mg/m² weekly has been accepted widely, including in multiple clinical trials, such as trials in adjuvant settings, ECOG 3311 (NCT01898494) and ECOG 3132 (NCT02734537). Evidence from prospective randomized trials is limited for cisplatin 40 mg/m² weekly. In the only published randomized study, Tsan et al. attempted to compare cisplatin at 100 mg/m² every 3 weeks versus cisplatin at 40 mg/m² weekly with concurrent radiotherapy. Because of slow recruitment, the study ended after only 55 patients had been recruited. After a median follow-up of 12 months, there was no advantage observed in terms of locoregional control or overall survival between the two arms. All of the grade 4 toxicities occurred in the every 3-week group, and the overall toxicity was significantly greater in this group (P=0.020), as expected (31).

In a few retrospective cohorts of studies reviewing cisplatin at 40 mg/m² weekly versus 100 mg/m² every 3 weeks with concurrent radiotherapy, the patients who received weekly dosing were generally older, with less robust kidney functions and/or performance status (32-34). For example, Uygun et al. reviewed 50 patients with previously untreated inoperable SCCHN who received concurrent cisplatin with radiotherapy. They found similar objective response rate in two groups (90% vs. 92%). The grade 3–4 toxic events were seen in 53% of every 3-week group and 40% of weekly group, which was not statistically significant (P>0.05) (34). Those data collected from retrospective cohorts showed that cisplatin 40 mg/m² weekly is a promising regimen with potential comparable efficacy to 100 mg every 3 weeks. Further prospective randomized control trial validation is required.

Summary

Noronha et al. showed that cisplatin at 100 mg/m² every
3 weeks resulted in superior local-regional control, with more toxicity, than cisplatin at 30 mg/m² weekly as adjuvant chemoradiotherapy in oral cavity cancers. There are still questions in cisplatin dosing schedule as concurrent chemoradiotherapy to be answered. One question is whether higher weekly dose with comparable cumulative dose as every 3 weeks will lead to comparable efficacy, as there was not sufficient data to conclude whether cisplatin at 40 mg/m² weekly is adequate for efficacy in SCCHN. The other area of focus is the HPV-associated oropharyngeal cancers, where patients have good prognosis and therapy de-intensification is the primary need. It has not been explored whether concurrent cisplatin 30 mg/m² weekly will be sufficient in this subtype of SCCHN as definitive or adjuvant therapy. In summary, while the optimal dosing schedule of concurrent cisplatin remains to be determined for various subtypes of SCCHN in different settings (adjuvant versus definitive), it is reasonable for oncologists who care for patients with SCCHN to choose cisplatin dosing schedule based on each patient's tolerability and preference.

Acknowledgements

We thank Dr. Mehmet Altan for careful review of the manuscript.

Footnote

Conflicts of Interest: Xiuning Le is supported by Conquer Cancer Foundation (American Society of Clinical Oncology), and received a consultant fee from Eli Lilly and Company. Ehab Y. Hanna has no conflicts of interest to declare.

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Cite this article as: Le X, Hanna EY. Optimal regimen of cisplatin in squamous cell carcinoma of head and neck yet to be determined. Ann Transl Med 2018;6(11):229. doi: 10.21037/atm.2018.05.10