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

Xiuning Le[1], Ehab Y. Hanna[2]

[1]Department of Thoracic and Head and Neck Medical Oncology, Division of Cancer Medicine, [2]Department of Head and Neck Surgery, Division of Surgery, University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Correspondence to: Ehab Y. Hanna, MD, FACS. Department of Head and Neck Surgery, Division of Surgery, University of Texas, MD Anderson Cancer Center, Houston, TX 77030, USA. Email: eyhanna@mdanderson.org.

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).

Comment on: Noronha V, Joshi A, Patil VM, *et al.* Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial. J Clin Oncol 2018;36:1064-72.

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/m^2 every 3-week.

Since the publication of those two studies (20,21), cisplatin at 100 mg/m^2 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/m^2 confers a survival benefit.

Dosing schedule optimizations have looked at weekly cisplatin dosing ranging from 30 to 40 mg/m^2 or daily administration from 5 to 7 mg/m^2. Weekly dosing has gained popularity compared to the traditional dose of 100 mg/m^2 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/m^2 once a week

compared with cisplatin once every 3 weeks at 100 mg/m^2, 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/m^2 resulted in superior LRC, albeit with more toxicity, than did once-a-week cisplatin at 30 mg/m^2 and should remain the preferred chemoradiotherapy regimen for locally advanced HNSCC in the adjuvant setting*" (30).

Cisplatin 40 mg/m^2 weekly

While the Noronha study offered solid evidence that 100 mg/m^2 every 3 weeks is superior to 30 mg/m^2 weekly for adjuvant concurrent chemoradiotherapy in oral cavity cancers, it is unclear whether higher weekly doses (such as 40 mg/m^2) may show non-inferiority in efficacy. In the Noronha study, for every 3 weeks group, the median cumulative cisplatin dose was 300 mg/m^2 (range, 200–300 mg/m^2) with dose intensity estimated at was 42 mg/m^2/wk (range, 33.3–47.7 mg/m^2/wk), whereas in the weekly dose group the median cumulative cisplatin dose was 210 mg/m^2 (range, 180–210 mg/m^2) with dose intensity at 30.7 mg/m^2/wk (range, 28.8–33.4 mg/m^2/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/m^2 weekly is not the commonly used weekly dose in the United States and many European countries. Instead, cisplatin 40 mg/m^2 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/m^2 weekly. In the only published randomized study, Tsan *et al.* attempted to compare cisplatin at 100 mg/m^2 every 3 weeks versus cisplatin at 40 mg/m^2 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/m^2 weekly versus 100 mg/m^2 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/m^2 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/m^2 every

3 weeks resulted in superior local-reginal control, with more toxicity, than cisplatin at 30 mg/m^2 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/m^2 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/m^2 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.

References

1. Ghantous Y, Abu Elnaaj I. Global Incidence and Risk Factors of Oral Cancer. Harefuah 2017;156:645-9.
2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014. SEER Cancer Statistics Review 2017.
3. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst 2000;92:709-20.
4. Agrawal N, Frederick MJ, Pickering CR, et al. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. Science 2011;333:1154-7.
5. Stransky N, Egloff AM, Tward AD, et al. The mutational landscape of head and neck squamous cell carcinoma. Science 2011;333:1157-60.
6. Gillison ML, Chaturvedi AK, Anderson WF, et al. Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. J Clin Oncol 2015;33:3235-42.
7. Demers GW, Foster SA, Halbert CL, et al. Growth arrest by induction of p53 in DNA damaged keratinocytes is bypassed by human papillomavirus 16 E7. Proc Natl Acad Sci U S A 1994;91:4382-6.
8. Khan MA, Tolleson WH, Gangemi JD, et al. Inhibition of growth, transformation, and expression of human papillomavirus type 16 E7 in human keratinocytes by alpha interferons. J Virol 1993;67:3396-403.
9. Schwarz E, Freese UK, Gissmann L, et al. Structure and transcription of human papillomavirus sequences in cervical carcinoma cells. Nature 1985;314:111-4.
10. Storey A, Thomas M, Kalita A, et al. Role of a p53 polymorphism in the development of human papillomavirus-associated cancer. Nature 1998;393:229-34.
11. Carlander AF, Gronhoj Larsen C, Jensen DH, et al. Continuing rise in oropharyngeal cancer in a high HPV prevalence area: A Danish population-based study from 2011 to 2014. Eur J Cancer 2017;70:75-82.
12. Louie KS, Mehanna H, Sasieni P. Trends in head and neck cancers in England from 1995 to 2011 and projections up to 2025. Oral Oncol 2015;51:341-8.
13. Nguyen-Tan PF, Zhang Q, Ang KK, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. J Clin Oncol 2014;32:3858-66.
14. O'Sullivan B, Huang SH, Su J, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. Lancet Oncol 2016;17:440-51.
15. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:122-37.
16. Adelstein D, Gillison ML, Pfister DG, et al. NCCN Guidelines Insights: Head and Neck Cancers, Version 2.2017. J Natl Compr Canc Netw 2017;15:761-70.
17. Denis F, Garaud P, Bardet E, et al. Final results of the 94-

01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004;22:69-76.
18. Department of Veterans Affairs Laryngeal Cancer Study Group, Wolf GT, Fisher SG, et al. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 1991;324:1685-90.
19. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091-8.
20. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945-52.
21. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937-44.
22. Cooper JS, Zhang Q, Pajak TF, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2012;84:1198-205.
23. Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355:949-55.
24. Pignon JP, le Maitre A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14.
25. Strojan P, Vermorken JB, Beitler JJ, et al. Cumulative cisplatin dose in concurrent chemoradiotherapy for head and neck cancer: A systematic review. Head Neck 2016;38 Suppl 1:E2151-8.
26. Bachaud JM, Albin N, Gay C, et al. [Concomitant association of radiotherapy and chemotherapy (CDDP 4-6 mg/m2/daily in continuous i.v. administration) in locally advanced ORL tumors]. Bull Cancer 1994;81:212-8.
27. Bachaud JM, Chatelut E, Canal P, et al. Radiotherapy with concomitant continuous cisplatin infusion for unresectable tumors of the upper aerodigestive tract: results of a phase I study. Am J Clin Oncol 1997;20:1-5.
28. Jeremic B, Shibamoto Y, Stanisavljevic B, et al. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. Radiother Oncol 1997;43:29-37.
29. Marcu L, Bezak E, Olver I. Scheduling cisplatin and radiotherapy in the treatment of squamous cell carcinomas of the head and neck: a modelling approach. Phys Med Biol 2006;51:3625-37.
30. Noronha V, Joshi A, Patil VM, et al. Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial. J Clin Oncol 2018;36:1064-72.
31. Tsan DL, Lin CY, Kang CJ, et al. The comparison between weekly and three-weekly cisplatin delivered concurrently with radiotherapy for patients with postoperative high-risk squamous cell carcinoma of the oral cavity. Radiat Oncol 2012;7:215.
32. Geeta SN, Padmanabhan TK, Samuel J, et al. Comparison of acute toxicities of two chemotherapy schedules for head and neck cancers. J Cancer Res Ther 2006;2:100-4.
33. Espeli V, Zucca E, Ghielmini M, et al. Weekly and 3-weekly cisplatin concurrent with intensity-modulated radiotherapy in locally advanced head and neck squamous cell cancer. Oral Oncol 2012;48:266-71.
34. Uygun K, Bilici A, Karagol H, et al. The comparison of weekly and three-weekly cisplatin chemotherapy concurrent with radiotherapy in patients with previously untreated inoperable non-metastatic squamous cell carcinoma of the head and neck. Cancer Chemother Pharmacol 2009;64:601-5.

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

