



Three-weekly cisplatin or weekly cisplatin chemoradiotherapy for locally advanced head and neck squamous cell carcinoma—the jury is still out

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Epidemiology of head and neck cancer (HNC)

According to cancer statistics for 2012 (GLOBOCAN), the global incidence of HNC in that year stood at around 680,000, with 390,000 of these cases occurring in Asian countries. Around 240,000 Asian people died from HNC, accounting for 5.5% of cancer deaths (1). Traditionally, patients with head and neck squamous cell carcinoma (HNSCC) have a significant smoking and drinking history, and around 60% present with advanced disease (Stage III and IV), for which prognosis remains poor. Meanwhile, the worldwide incidence of human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma continues to increase worldwide. For example, the annual rate of increase in the United States and Finland is 5% and 6%, respectively (2). A second important causative agent is Epstein-Barr virus (EBV), present in most cases of nasopharyngeal cancer (NPC), a condition which is particularly common in southern China and Southeast Asia (3). These virally related types of HNC tend to respond to radiation therapy and chemotherapy, resulting in a better prognosis than the traditional type of HNSCC (2,3).

Standard chemoradiotherapy (CRT) for HNC

Surgical treatment is one of the mainstays for locally advanced HNSCC. However, for post-operative patients with high-risk factors for recurrence, such as microscopic margin positivity and extra-nodular extension, surgery alone

and/or adjuvant radiation therapy (RT) are insufficient. The addition of cisplatin to RT was developed to improve the post-operative prognosis in these patients. This addition showed a survival benefit over RT alone in two pivotal randomized trials, EORTC22931 and RTOG95-01, with a hazard ratio (HR) of death of 0.702 and absolute 5-year survival benefit of around 10% (4-6). Both trials used cisplatin 100 mg/m² every 3 weeks (three-weekly cisplatin) concurrent with RT. This regimen is accordingly considered the standard regimen for post-operative high-risk HNSCC. However, in their randomized study in 83 HNSCC patients with high-risk factors for recurrence, Bachaud *et al.* used a weekly cisplatin schedule at a flat dose of 50 mg/body concurrent with RT. Results showed a survival benefit over RT alone, albeit that sample size was small (7).

Another treatment option for locally advanced HNSCC in patients hoping for organ preservation or unresectable disease is definitive CRT. For organ preservation, RTOG91-11 is a pivotal randomized trial. Patients with locally advanced laryngeal cancer and hope of laryngeal preservation were randomized to one of three treatments: induction cisplatin plus fluorouracil followed by RT, three-weekly cisplatin concurrent with RT (three-weekly cisplatin + RT), or RT alone. At two years, the primary end point of laryngeal preservation rate was significantly better with three-weekly cisplatin + RT than induction chemotherapy followed by RT or RT alone (8). For patients with unresectable disease, Intergroup 0126 (INT0126)

is a pivotal trial. In that trial, patients with unresectable locally advanced HNSCC were randomized to one of three treatments: RT alone, three-weekly cisplatin + RT, or a split course of RT and three cycles of concurrent infusional fluorouracil and bolus cisplatin chemotherapy. The primary endpoint of overall survival (OS) was significantly better in the three-weekly cisplatin + RT arm than the other two arms (9). A meta-analysis of individual patient data from 93 randomized trials and 17,346 patients with head and neck cancer (MACH-NC) found that the addition of chemotherapy, especially platinum-based chemotherapy, concurrent with RT showed a greater benefit (HR of death 0.81, 5-year absolute benefit 6.5%, $P < 0.0001$) than induction or adjuvant chemotherapy (10,11).

Evidence of weekly cisplatin + RT

Among the various treatment schedules of cisplatin, the most accepted standard treatment for locally advanced HNSCC is three-weekly cisplatin + RT (4,5,8-11). However, previous reports in Europe and the U.S. demonstrated that only around 60% of patients completed 3 cycles of three-weekly cisplatin and complied with the criteria for dose reduction (4,5,9,12). In addition to this poor compliance, high rates of severe acute and late adverse reactions remain matters of concern, including renal impairment, myelosuppression and hearing disturbance. These findings revealed an unmet need for a more feasible and less toxic CRT for locally advanced HNSCC, and one of the candidates is weekly cisplatin + RT. The expected theoretical rationale for low-dose cisplatin given weekly is that it: (I) increases treatment compliance while maintaining dose intensity and avoids unscheduled interruptions of RT; (II) reduces chemotherapy-related acute and late side effects without jeopardizing treatment outcomes; (III) enhances radiosensitization of the tumor; and (IV) demonstrates a similar survival benefit over RT alone in HNSCC as that seen in NPC treated with weekly cisplatin + RT (13-15). Moreover, with regard to the relationship between therapeutic effect and cisplatin dose, cisplatin has shown a certain additive effect to radiotherapy at a cumulative dose of 200 mg/m² or more in concurrent CRT regardless of the type of administration (bolus or fractionated) (16-19). In addition, from the meta-analysis of prospective trials of three-weekly cisplatin + RT and weekly cisplatin + RT, which nevertheless included only a few randomized trials of weekly cisplatin + RT (7,20), both treatment approaches might be equal in efficacy but differ in some toxicity

profiles, such as myelosuppression, nausea/vomiting and nephrotoxicity (21). As outlined above, weekly cisplatin + RT has gradually gained clinical acceptance without any support from a large randomized trial (20,21).

Recent report from Tata Memorial Hospital (Noronha *et al.* J Clin Oncol 2018;36:1064-72)

Data for weekly cisplatin + RT were limited until Noronha *et al.* from Tata Memorial Hospital (TMH) reported their paper, 'Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial,' published in the *Journal of Clinical Oncology* in 2018 (22). Eligible patients had locally advanced HNSCC of the oral cavity, oropharynx, hypopharynx, larynx or metastatic cervical lymphadenopathy of unknown primary. Patients with locally advanced HNSCC who had unresectable disease or hoped for organ preservation received definitive CRT. However, in contrast to these patients, those who were disease-free but at high risk of recurrence received post-operative CRT. Primary endpoint was locoregional control (LRC). Secondary endpoints were progression-free survival (PFS), OS, toxicity, compliance, response rate and quality of life. The aim of the study was to test the non-inferiority of weekly cisplatin + RT compared with the standard treatment of three-weekly cisplatin + RT in terms of LRC. The authors assumed a 2-year LRC of three-weekly cisplatin + RT of 60%, set a non-inferiority margin of 15% and tested non-inferiority with a two-sided α of 0.05 and power of 80%. Considering an attrition rate of 5%, the planned sample size was 300 patients. Between 2013 and 2017, 300 patients were randomized, with 150 in each arm. Among them, the majority of patients had oral cavity cancers (87%) and received post-operative CRT for high-risk recurrence (93%). Only 7% of all patients received definitive CRT for unresectable disease or organ preservation. With a median follow-up of 22 months, the primary endpoint of 2-year LRC with weekly cisplatin + RT was 58.5%, which was significantly worse than that with three-weekly cisplatin + RT of 73.1% (HR 1.76; 95% CI, 1.11–2.79, $P = 0.014$). Among secondary endpoints, median PFS with weekly cisplatin + RT was 17.7 months versus 28.6 months with three-weekly cisplatin + RT (HR 1.24; 95% CI, 0.89–1.73, $P = 0.21$). Median OS with weekly cisplatin + RT was 39.5 months, but OS was not reached with three-weekly cisplatin + RT (HR 1.14; 95% CI, 0.79–1.65, $P = 0.48$). With regard to toxicity, grade 3 or

higher acute toxicities, particularly including leucopenia, neutropenia, infection, hyponatremia and hearing impairment, were significantly higher with three-weekly cisplatin + RT than weekly cisplatin + RT (84.6% vs. 71.6%, $P=0.006$). Thus, the authors concluded that three-weekly cisplatin + RT at dose of 100 mg/m^2 resulted in superior LRC, albeit with more toxicity, than weekly cisplatin at a dose of 30 mg/m^2 and should remain the preferred CRT regimen for post-operative high-risk HNSCC.

As the authors pointed out, this was the first randomized trial with sufficient sample size to compare the standard three-weekly cisplatin + RT with weekly cisplatin + RT. Nevertheless, a number of caveats exist.

First, the trial included two different treatment strategies: definitive CRT for unresectable disease and organ preservation and post-operative CRT for those patients at high risk for recurrence. Although these two treatment strategies are completely different, the authors assumed a sample size based on the same 2-year LRC rate and non-inferiority margin. This is the most critical point of this trial, although most of the enrolled patients had post-operative high-risk features.

Second, the weekly cisplatin dose of 30 mg/m^2 may be suboptimal. Indeed, this dose has only been established for early stage NPC (15). In locally advanced NPC and locally advanced cervical cancer, weekly cisplatin at a dose of 40 mg/m^2 is recognized as optimal (13,23). Moreover, in randomized trials, especially non-inferiority trials, the comparability of the treatment arms is critical. Accordingly, the planned cumulative dose of cisplatin in the weekly cisplatin + RT arm was 210 mg/m^2 ($30 \text{ mg/m}^2 \times 7$ times) versus 300 mg/m^2 with three-weekly cisplatin + RT. The reason for the inferiority of weekly cisplatin + RT in the TMH trial was therefore mainly attributable to the under-dosing of weekly cisplatin rather than to the weekly strategy itself. For these reasons, comparison with the standard three-weekly cisplatin dose of 100 mg/m^2 requires a weekly dose of 40 mg/m^2 . To this end, the JCOG Head and Neck Cancer Study Group (JCOG-HNCSG) has initiated the JCOG1008 trial with weekly cisplatin (40 mg/m^2) + RT in comparison with the standard three-weekly cisplatin (100 mg/m^2) + RT. Enrollment of post-operative high-risk HNSCC patients will be completed in late 2018 (24).

Third, trial results from single institution studies should always be interpreted with care. In fact, most patients in the TMH study had oral cavity cancer (87.3%), likely reflecting the local habit such as betel nut chewing. This prejudiced patient background affects the generalizability

of the trial results. In addition, quality assurance of RT was not performed. The compliance and quality of RT planning deeply affect treatment outcomes in clinical trials of HNSCC (25). For these reasons, a conclusive decision will require a multi-center randomized trial with a reliable data center and quality assurance center.

In conclusion, notwithstanding the report of Noronha et al, weekly cisplatin + RT should not be used outside clinical trials for locally advanced HNSCC. In particular, weekly cisplatin (30 mg/m^2) + RT may worsen treatment outcomes. Until the results of ongoing trials are available, three-weekly cisplatin (100 mg/m^2) + RT remains the standard treatment for locally advanced HNSCC (21,24).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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