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A Randomized Controlled Trial Comparing Two Different Schedules for Cisplatin Treatment in Patients with Locoregionally Advanced Nasopharyngeal Cancer

Wei-Xiong Xia[1,2], Xing Lv[1,2], Hu Liang[1,2], Guo-Ying Liu[1,2,3], Rui Sun[1,2], Qi Zeng[4], Si-Wei Li[5], Hao-Yuan Mo[1,2], Fei Han[1,2], Dong-Hua Luo[1,2], Qing Liu[6], Meng-Yun Shi[3], Yan-Fang Ye[3], Jing Yang[7], Liang-Ru Ke[1,2], Meng-Yun Qiang[1,2], Wen-Ze Qiu[1,2], Ya-Hui Yu[1,2], Kui-Yuan Liu[1,2], Xin-Jun Huang[1,2], Wang-Zhong Li[1,2], Shu-Hui Lv[1,2], Zhuo-Chen Cai[1,2], Jing-Jing Miao[1,2], Ling Guo[1,2], Ming-Yuan Chen[1,2], Ka-Jia Cao[1,2], Lin Wang[1,2], Chong Zhao[1,2], Pei-Yu Huang[1,2], Qiu-Yan Chen[1,2], Yi-Jun Hua[1,2], Lin-Quan Tang[1,2], Chao-Nan Qian[1,2], Hai-Qiang Mai[1,2], Xiang Guo[1,2], and Yan-Qun Xiang[1,2]

ABSTRACT

Purpose: Previous studies suggest that a cumulative cisplatin dose of 200 mg/m^2 might be adequate in the intensity-modulated radiation therapy (IMRT) era for locoregionally advanced nasopharyngeal carcinoma (LANPC). However, two cycles of once-every-3-weeks cisplatin at 100 mg/m^2 has never been prospectively compared with standard once-a-week cisplatin regimen.

Patients and Methods: This trial was conducted at three hospitals from 2011 to 2016. Patients who met the eligibility criteria were recruited (ChiCTR-TRC-12001979) and randomly assigned (1:1) via a computer-generated sequence to receive once-every-3-weeks cisplatin at 100 mg/m^2 for two cycles or once-a-week cisplatin at 40 mg/m^2 for six cycles concurrently with IMRT. Primary endpoint was failure-free survival and between-group absolute difference of 10% as the noninferiority margin.

Results: A total of 510 patients were enrolled. Median follow-up time was 58.3 months with 85.4% of 3-year failure-free survival in the once-every-3-weeks group and 85.6% in the once-a-week group. An absolute difference of −0.2% (95% confidence interval, −6.3 to 5.9; $P_{\text{noninferiority}} = 0.0016$). Acute toxicities of grade 3 or higher occurred in 55.8% in the once-every-3-weeks group and 66.3% in the once-a-week group ($P = 0.015$). The most common acute toxicities were hematologic abnormalities, including leukopenia (16% vs. 27%; $P = 0.0022$) and thrombocytopenia (1% vs. 5%; $P = 0.015$). The late grade 3–4 auditory loss rate was significantly lower in the once-every-3-weeks group than the once-a-week group (6% vs. 13%; $P = 0.0039$).

Conclusions: Once-every-3-weeks cisplatin as concurrent chemoradiotherapy is noninferior to once-a-week cisplatin in the treatment efficacy in the LANPC. Although both regimens are well tolerated, severe acute toxicities and late-onset auditory loss are higher in the once-a-week group.

Introduction

Nasopharyngeal carcinoma (NPC) is the most common type of malignancy originating in the nasopharynx. NPC is prevalent in southern China and southeastern Asia, resulting in about 130,000 new cases worldwide each year. Radiotherapy is the cornerstone of initial treatment for nondisseminated NPC due to its deep-seated location and radiosensitivity. The landmark Intergroup 0099 (INT-0099) trial and several meta-analyses showed that the addition of three cycles of cisplatin-based concurrent chemotherapy (CCRT) with or without adjuvant chemotherapy to radiotherapy significantly improved survival in patients with locoregionally advanced NPC (1–4). According to the National Comprehensive Cancer Network (NCCN) guidelines, cisplatin remains the most commonly used and effective platinum agent in the chemotherapy of NPC since 1980s (3, 5).

Questions remain, however, about the optimal schedule and dosing of concurrent cisplatin (4, 5). On the basis of the duration of IMRT that is conducted within 6–7 weeks, concurrent once-a-week cisplatin for 6–7 cycles or once-every-3-weeks cisplatin for three cycles are widely used and accepted in practice. There were studies suggested that a

[1]State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, P.R. China. [2]State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Sun Yat-sen University Cancer Center, Guangzhou, P.R. China. [3]Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, P.R. China. [4]Department of Radiation Oncology, the Fifth Affiliated Hospital, Sun Yat-Sen University, Zhuhai, P.R. China. [5]Department of Radiation Oncology, the Affiliated Hospital of Guilin Medical University, Guilin, P.R. China. [6]Department of Medical Statistics and Epidemiology, Sun Yat-Sen University Cancer Center, Guangzhou, P.R. China. [7]Department of Radiation Oncology, Shanghai Proton and Heavy Ion Center, Shanghai, P.R. China.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

W.-X. Xia, X. Lv, H. Liang, and G.-Y. Liu contributed equally to this article.

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Corresponding Authors: Yan-Qun Xiang, Department of Nasopharyngeal Carcinoma, Sun Yat-Sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, P.R. China. Phone: 86208734-3392; Fax: 8620-87343359; E-mail: xiangyq@sysucc.org.cn; Xiang Guo, guoxiang@sysucc.org.cn; and Hai-Qiang Mai, maihq@sysucc.org.cn

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Translational Relevance

Cisplatin-based concomitant chemoradiotherapy is the standard treatment modality for patients with locoregionally advanced nasopharyngeal carcinoma (NPC), though current schedule and dose of cisplatin are not optimal. Mounting retrospective evidence indicates that a cumulative dose of cisplatin with 200 mg/m^2 could obtain acceptable survival benefit. However, there is no prospective study to provide high-level evidence and clarify the efficacy of this therapeutic strategy so far. Our study is the first phase III clinical trial to head-to-head assess the efficacy and acute and late toxicity profiles of once-every-3-weeks versus once-a-week cisplatin regimens in patients with locoregionally advanced NPC. Our findings suggest that two cycles of cisplatin at 100 mg/m^2 once-every-3-weeks concurrently with intensity-modulated radiotherapy is the promising chemoradiotherapy regimen for locoregionally advanced NPC, with less acute and late-onset toxicities.

lower dose cisplatin given on a weekly basis may offer a promising efficacy and lower toxicity (6). Later, Chan and colleagues conducted a randomized phase III clinical trial and confirmed that weekly cisplatin 40 mg/m^2 concurrently with radiotherapy conferred a survival advantage compared with radiation alone (7, 8). However, in their study, the tolerance of the weekly cisplatin regimen was still unsatisfactory because of toxicities, with only 60% patients completing five or more cycles. At the same time, three cycles cisplatin at 100 mg/m^2 once-every-3-weeks was initially recommended on the basis of the INT-0099 study, but there was observed unsatisfactory compliance due to significant acute toxicities resulting in dose-limiting delivery (1). Recently, Lee and colleagues (9) conducted the combined analysis of the NPC-9901 and the NPC-9902 trials, and the results showed that no significant survival difference was observed between patients who received two or three cycles of once-every-3-weeks cisplatin at 100 mg/m^2. Emerging studies did imply that two cycles of once-every-3-weeks cisplatin at 100 mg/m^2 is reasonable for CCRT (10). Also, with the decreasing one cycle of cisplatin, the toxicities might be decreased consequently. Yet there were few trials to head-to-head directly compare two cycles of once-every-3-weeks cisplatin with six cycles of once-a-week cisplatin for the concurrent treatment of locoregionally advanced NPC (LANPC; refs. 1, 7, 11–17).

Therefore, the hypothesis of this study was that two cycles of once-every-3-weeks cisplatin at 100 mg/m^2 would be noninferior to once-a-week cisplatin at 40 mg/m^2 in the efficacy among patients with LANPC and deceased toxicity.

Patients and Methods

Study design and participants

This is a randomized, open-label, noninferiority phase III trial at three institutions in an endemic area of NPC in southern China. The trial protocol is available in Supplementary Data S1. Eligible participants were randomly assigned (1:1) to receive either six cycles of once-a-week (once-a-week group) or two cycles once-every-3-weeks cisplatin (once-every-3-weeks group) using block randomization with a block size of six (only known to the statistician). Randomization was performed centrally via a computer-generated randomization sequence and was stratified according to hospital and disease stage (T1–4N2, T1–4N3, T3N0–1, and T4N0–1). Details of the randomized allocations were contained in sequentially numbered, opaque, sealed envelopes prepared by the statistician. Treatment allocation was unmasked. After participants signed informed consent, investigators of each center opened the envelopes and assigned participants to the corresponding interventions. The study was approved by Institutional Review Board of each site and was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonization.

Eligible participants were ages 18–65 years with nonmetastatic, histologically proven non-keratinizing stage III or IVa–b NPC [according to the American Joint Committee on Cancer (AJCC) 7th edition stage system]. All participants had Karnofsky scores of at least 70 and adequate bone marrow, liver, and renal function.

The main exclusion criteria included previous chemotherapy, radiotherapy, or definitive surgery of the primary tumor or lymph node; previous invasive malignancies except excised basal-cell skin carcinoma, cervical carcinoma *in situ*, superficial bladder tumors (Ta, Tis, and T1); who were pregnant or lactating, and who had any mental disorder or somatic comorbidities of clinical concern. Details of pretreatment evaluation are shown in the eMethods in Supplementary Data S2.

Procedures

Patients assigned to the once-a-week cisplatin group received intravenous cisplatin 40 mg/m^2 for 2 hours every week concurrently with IMRT for a maximum of six cycles. Patients assigned to the once-every-3-weeks cisplatin group received intravenous cisplatin 100 mg/m^2 for 2 hours every 3 weeks for two cycles concurrently with IMRT.

In the once-every-3-weeks group, patients were given 4 days of hydration (on days 0–3) and diuretics (mannitol 50 g intravenously over 30 minutes and furosemide 20 mg intravenously over 10 minutes) on the day of cisplatin administration to prevent nephrotoxicity. No hydration and diuresis were administered in the once-a-week group. Antiemetic drugs, such as 5-hydroxytryptamine-3 receptor antagonists (ondansetron 8 mg or granisetron 3 mg, intravenously) and dexamethasone (10 mg intramuscularly) plus metoclopramide (20 mg intramuscularly), were given to prevent chemotherapy-induced nausea and vomiting. Prophylactic G-CSF were not allowed. Chemotherapy dose modifications and radiotherapy treatment are described in the eMethods in Supplementary Data S2.

Three months after radiotherapy, treatment responses were assessed with physical examination, head and neck MRI or CT, and flexible nasopharyngoscopy, according to the RECIST (version 1.1; ref. 18). Details of follow-up are shown in the eMethods in Supplementary Data S2.

Efficacy and safety analyses

The primary endpoint was failure-free survival (FFS), which was defined as the time from randomization to documented local or regional relapse, distant metastasis, or death from any cause, whichever came first. Secondary endpoints included overall survival (OS), distant metastasis-free survival (DMFS), locoregional FFS (LRFS), response rates after treatment, and toxic effects. The detailed description of endpoint definition is shown in the eMethods in Supplementary Data S2. Toxicities were scored according to Common Terminology Criteria for Adverse Events (version 4.03). Late-onset radiation toxicities were assessed using the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme (19).

Statistical analysis

In this study, we assumed that once-a-week cisplatin concurrent with IMRT was the standard arm because of perceived lower toxicity

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and convenience (7, 20). On the basis of the literatures, we hypothesized that FFS was 80% at 3 years for LANPC receiving standard concurrent chemoradiation with IMRT (21–24). Because previous evidence showed that cisplatin-based concurrent chemoradiotherapy results in a benefit in FFS of approximately 19%–45% at 3 years compared with radiotherapy alone (1, 25), the 10% FFS rate difference at 3 years was considered acceptable as the noninferiority margin in this trial. Clinical noninferiority was defined as not more than the allowable 10% difference in survival rates between once-every-3-weeks and once-a-week treatment groups (1, 25). If the 95% confidence interval (CI) lower boundary of the difference between the FFS of the two groups (once-every-3-weeks group minus once-a-week group) did not cross −10% then this trial would be positive in proving noninferiority. With an 80% power and a one-sided type I error 0.025, we calculated an enrollment of 246 patients per arm (total 492), assuming 5% early dropout rates or lost to follow-up.

The primary efficacy analysis was done in the intention-to-treat population, and the per-protocol population (see the Supplementary Appendix), which included all patients who received two cycles of concurrent cisplatin in the once-every-3-weeks group and at least five cycles of concurrent cisplatin in the once-a-week group. Only patients who received at least one cycle of concurrent cisplatin and radiotherapy treatment were included in the safety analysis of adverse events. We further performed an interaction analysis to explore whether the effect of the experimental treatment varied in the subgroups defined according to sex, age, tumor category, node category, and tumor–node–metastasis (TNM) stage (see the Supplementary Appendix). The interaction analysis was conducted by means of a test of treatment-by-covariate interaction on the basis of the Cox proportional hazards model. The results were compared by Student t tests or χ^2 tests. Time-to-event data were described with Kaplan–Meier curves and compared with the log-rank test. The statistical test for the primary endpoint was one sided, and $P < 0.025$ was considered significant; all other statistical tests were two sided, and P values of less than 0.05 were deemed to be significant. Analyses were done with SPSS 22.0 and R, version 3.3.1 (R Foundation for Statistical Computing).

Data sharing statement

Considering patients' privacy and related regulations in China, we chose not to make the database public to everyone. However, our raw database will be deposited on the Research Data Deposit public platform (www.researchdata.org.cn, RDDA2021001943). If a researcher wants to use our raw data for scientific research purposes, he or she could apply for use with our corresponding author and database administrator

Results

Patient characteristics

A total of 510 eligible patients (357 men and 153 women; median age, 44 years; range, 19–65 years) were randomly assigned to receive once-every-3-weeks ($n = 260$) or once-a-week ($n = 250$) cisplatin concurrently with IMRT (**Fig. 1**) between August 30, 2011, and November 10, 2016. The follow-up ended on December 31, 2019. The two treatment groups were well balanced in terms of baseline demographic and clinical characteristics (**Table 1**). Pretreatment imaging methods used to determine disease stage are presented in eTable 2 in Supplementary Data S2 and did not differ between groups.

Compliance and chemoradiotherapy delivery

Overall, 260 (100%) of 260 patients in the once-every-3-weeks group and 249 (99.6%) of 250 patients in the once-a-week group completed the scheduled total radiation dose. The dose and time intervals of radiation were well balanced between the treatment groups (eTable 3 in Supplementary Data S2).

The compliance of both cisplatin chemotherapy regimens is presented in **Table 2**. In the once-every-3-weeks group, 259 (99.6%) of 260 patients completed the protocol-defined two cycles of CCRT and were therefore included in the per-protocol population, and 1 (0.4%) patient received one cycle. The chemotherapy dose was reduced in 26 patients (10%). The median cumulative cisplatin dose was 200 mg/m^2 [interquartile range (IQR), 200–200 mg/m^2]. In the once-a-week group, 134 (53.6%) of 250 patients received all six cycles of CCRT, 226 (90.4%) patients completed protocol-defined five or more cycles and were regarded as the per-protocol population, 19 (7.6%) patients received four cycles, 5 (2.0%) patients received three or less cycles. The chemotherapy dose was reduced in 124 patients (49.6%). The median cumulative cisplatin dose was 220 mg/m^2 (IQR, 198–240 mg/m^2).

Efficacy

The intention-to-treat analyses of overall response 3 months after completion of radiotherapy did not differ between two groups, with 258 of 260 (99.2%) patients in the once-every-3-weeks group versus 249 of 250 (99.6%) patients in the once-a-week group achieving response, respectively (**Table 3**).

At the last follow-up on December 31, 2019, the patients had been followed up for a median of 58.3 months (IQR, 47.8–79.9), with the follow-up time of the last enrolled patient reaching 3 years. Overall, 87 (17.1%) of 510 patients had treatment failure or died [44 (16.9%) of 260 patients in the every-3-weeks group and 43 (17.2%) of 250 patients in the once-a-week group], including 23 local recurrences [14/260 (5.4%) vs. 9/250 (3.6%)], 20 nodal recurrences [6/260 (2.3%) vs. 14/250 (5.6%)], 50 distant failures [26/260 (10.0%) vs. 24/250 (9.6%)], and 36 deaths [21/260 (8.1%) vs. 15/250 (6.0%); **Table 3**]. One patient died for radiation-induced nasopharyngeal necrosis and hemorrhage and 1 patient died for accident in the once-every-3-weeks group, compared with 2 patients died for noncancer-related cardiopulmonary failure in the once-a-week group. No patients died during treatment.

In the intention-to-treat analysis, the FFS at 3 years was 85.4% (95% CI, 81.1–89.7) in the once-every-3-weeks group and 85.6% (95% CI, 81.3–89.9) in the once-a-week group with an HR of 1.00 (95% CI, 0.66–1.52; $P > 0.99$). The absolute difference in survival between the two groups was −0.20% (95% CI, −6.30 to 5.90; $P_{\text{noninferiority}} = 0.0016$; **Fig. 2A**), which was lower than the prespecified noninferiority margin of 10%, indicating that the once-every-3-weeks cisplatin regimen was noninferior to once-a-week cisplatin regimen. There were no differences in secondary endpoints between the two treatment groups including OS, DMFS, or LRFS analyzed by intention-to-treat analysis (**Fig. 2B–D**).

The prespecified stage-specific survival analysis by intention-to-treat showed no difference for FFS between treatment groups (eTable 4 in Supplementary Data S2). Clinical stage was an independent prognostic factor for FFS, OS, and DMFS, but not LRFS by multivariate analysis. However, treatment group was not a significant predictive factor for FFS, OS, DMFS, or LRFS (eTable 5 in Supplementary Data S2).

Safety

The safety assessment included 260 patients in the once-every-3-weeks group and 249 patients in the once-a-week group, who received at least one cycle of concurrent cisplatin and radiotherapy treatment (**Table 4**). There was no incidence of treatment-related mortality. During treatment, 145 of 260 (55.8%) patients in the

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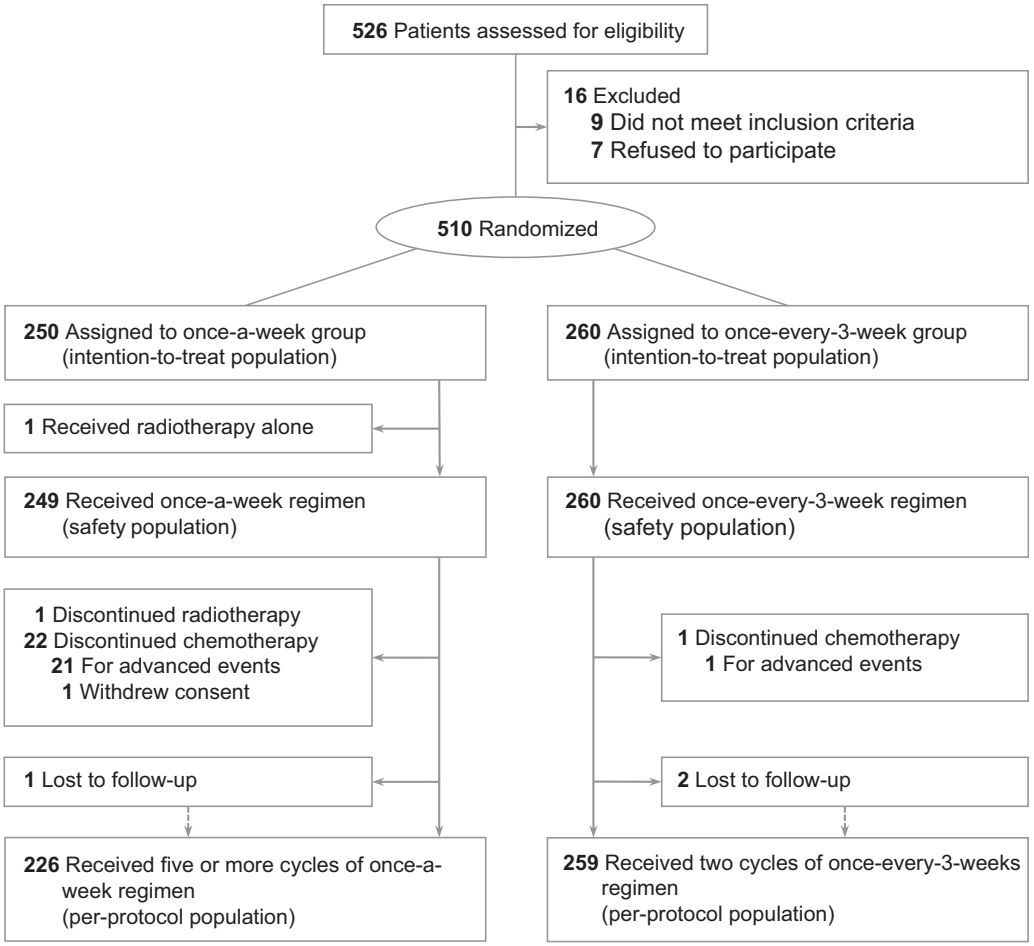

Figure 1.
CONSORT flow diagram.

once-every-3-weeks group and 165 of 249 (66.2%) patients in the once-a-week group experienced grade 3–4 acute toxic effects with significantly higher rates in the once-a-week group ($P = 0.015$). Grade 3–4 leucopenia [42/260 (16.2%) in once-every-3-weeks group vs. 68/249 (27.3%) in once-a-week group; $P = 0.002$] and thrombocytopenia [3/260 (1.2%) vs. 12/249 (4.8%), $P = 0.015$] were significantly lower in the once-every-3-weeks group compared with the once-a-week group. The other grade 3 or 4 adverse events did not differ between the treatment groups.

For late-onset adverse events, 57 (22.9%) patients in the once-a-week group and 51 (19.6%) patients in the once-every-3-weeks group experienced one or more grade 3 or 4 late-onset toxicity ($P = 0.37$). Notably, the grade 3–4 ototoxicity was significantly higher in the once-a-week group compared with once-every-3-weeks group [41/249 (16.5%) vs. 25/260 (9.6%); $P = 0.021$].

Discussion

In this randomized, phase III noninferiority trial, our results show that two cycles of once-every-3-weeks cisplatin concurrently with IMRT is noninferior to once-a-week cisplatin in terms of 3-year FFS for patients with LANPC. Furthermore, significantly less events of acute hematologic toxicities and late-onset ototoxicity were seen in the once-every-3-weeks cisplatin group compared to the once-a-week cisplatin group. To our best knowledge, this study is the first phase III randomized noninferiority clinical trial to compare the effect of two cycles of once-every-3-weeks and once-a-week cisplatin regimens head-to-head in patients with LANPC in the IMRT era.

Chemotherapy combined with radiotherapy is a crucial development for treating LANPC (4). A number of trials have demonstrated the survival benefit of concurrent chemoradiotherapy with adjuvant chemotherapy versus radiotherapy alone in LANPC (25, 26). A meta-analysis reported that the most significant benefits of chemotherapy on OS of LANPC were derived from either concurrent plus adjuvant chemotherapy or CCRT, whereas no significant benefit was seen following treatment with induction or adjuvant chemotherapy alone (3). Recently, several randomized trials have demonstrated that the addition of induction chemotherapy to concurrent chemoradiotherapy significantly improved outcomes (14, 27). On the basis of these results, concurrent chemoradiotherapy with induction or adjuvant chemotherapy is preferred recommended by the NCCN Guidelines (level 2A evidence) for stage II–IVB NPC, and concurrent chemoradiotherapy with cisplatin alone is also recommended as one of the treatment options by current NCCN guidelines (level 2B) (28). However, it is undeniable that concurrent chemoradiotherapy with cisplatin still constitutes a cornerstone in these treatment modalities.

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Table 1. Baseline characteristics of the intention-to-treat population.

Characteristics	Once-a-week group ($N = 250$)	Once-every-3-weeks group ($N = 260$)
Sex		
Male	180 (72.0%)	177 (68.1%)
Female	70 (28.0%)	83 (31.9%)
Median age, range (years)	43 (21–65)	44.5 (19–65)
Karnofsky scale		
90–100	219 (87.6%)	222 (85.4%)
70–80	31 (12.4%)	38 (14.6%)
Histopathology		
WHO II	4 (1.6%)	4 (1.5%)
WHO III	246 (98.4%)	256 (98.5%)
T classification		
T1	2 (0.8%)	1 (0.4%)
T2	9 (3.6%)	8 (3.1%)
T3	210 (84.0%)	213 (81.9%)
T4	29 (11.6%)	38 (14.6%)
N classification		
N0	29 (11.6%)	35 (13.5%)
N1	112 (44.8%)	112 (43.1%)
N2	81 (32.4%)	84 (32.3%)
N3	28 (11.2%)	29 (11.1%)
Staging		
III	197 (78.8%)	199 (76.5%)
IVA	25 (10.0%)	32 (12.3%)
IVB	28 (11.2%)	29 (11.2%)
Pretreatment Epstein–Barr virus DNA test*		
Negative	95 (38.0%)	90 (34.6%)
~4,000 copies per mL	97 (38.8%)	99 (38.1%)
>4,000 copies per mL	54 (21.6%)	69 (26.5%)
Missing	4 (1.6%)	2 (0.8%)
DNA (copies per mL), median (IQR)	287 (0–3068)	349 (0–4463)

Note: Data are *n* (%) or median (range), unless otherwise stated. *The plasma Epstein–Barr virus DNA test was optional in this trial and was not done for all enrolled patients.

Table 2. Adherence to the scheduled chemotherapy.

	Once-a-week group ($N = 250$)	Once-every-3-weeks group ($N = 260$)
No. of patients randomized	250	260
Patients starting CCRT, no. (%)	250 (100.0%)	260 (100.0%)
Total no. of cycles given, *n* (%)		
Zero cycle	1 (0.4%)	0
One cycle	1 (0.4%)	1 (0.4%)
Two cycles	2 (0.8%)	259 (99.6%)
Three cycles	1 (0.4%)	-
Four cycles	19 (7.6%)	-
Five cycles	92 (36.8%)	-
Six cycles	134 (53.6%)	-
Patients receiving reduced dose	124 (49.6%)	26 (10.0%)
Total cisplatin dose given, mg/m^2		
<100	4 (1.6%)	0
≥100 and <200	30 (12.0%)	26 (10.0%)
≥200	216 (86.4%)	234 (90.0%)
Median dose (IQR)	220 (198–240)	200 (200–200)

Abbreviations: CCRT, concurrent chemoradiotherapy; IQR, interquartile range.

In terms of the concurrent cisplatin dosing schedules, either 40 mg/m^2 once a week or 100 mg/m^2 every 3 weeks, is widely accepted practice but without high-level comparative evidence (29). The results of our trial offer evidence that two cycles of once-every-3-weeks cisplatin regimen should be a preferred concurrent cisplatin regimen in patients with LANPC, which could aid complete assessment of the different dosing schedules. Although the efficacy of the combination of induction chemotherapy was superior to that achieved with CCRT alone, the toxicity of combined induction chemotherapy was increased. In the most recent study conducted by Zhang and colleagues (27), 75.7% of patients experienced grade 3 or 4 adverse events and over 60% of patients did not complete three cycles of concurrent cisplatin in the induction and CCRT group. In this study, the results showed that two cycles of once-every-3-weeks concurrent cisplatin are less toxic than once-a-week concurrent cisplatin while maintaining efficacy. It implies that, although these results may not be directly applicable in the majority of patients with LANPC who receive three cycles of TPF or GP induction chemotherapy, two cycles of once-every-3-weeks cisplatin at 100 mg/m^2 could be the regimen with fewer toxicities for LANPC when patients have already received induction chemotherapy prior to radiotherapy. Further clinical trials are warranted to explore the optimal dose and schedule of concurrent cisplatin after induction chemotherapy.

Two clinical trials have attempted to compare once-every-3-weeks cisplatin with once-a-week cisplatin for treatment of head and neck squamous cell carcinoma (HNSCC; refs. 15, 17). The first one is a phase II trial from Korea (15), 109 patients with LANPC were randomly assigned to once-a-week cisplatin or once-every-3-weeks cisplatin concurrently with radiotherapy followed by adjuvant chemotherapy in patients with stage II–IVB NPC (AJCC 5th edition). The 3-year progression-free survival was not different between the two regimens. The other one is a phase III noninferiority trial, in this study, Noronha and colleagues reported that once-every-3-weeks cisplatin at 100 mg/m^2 was associated with improved locoregional control

Table 3. Pattern of failure and disease status at last assessment and response to treatment.

Status	Once-a-week group ($N = 250$)	Once-every-3-weeks group ($N = 260$)	All ($N = 510$)
Failure events	43 (17.2%)	44 (16.9%)	87 (17.1%)
Distant failure	24 (9.6%)	26 (10.0%)	50 (9.8%)
Locoregional failure			
Local	9 (3.6%)	14 (5.4%)	23 (4.5%)
Nodal	14 (5.6%)	6 (2.3%)	20 (3.9%)
Outcome at last assessment			
Alive, *n* (%)	235 (94.0%)	239 (91.9%)	474 (92.9%)
Died, *n* (%)	15 (6.0%)	21 (8.1%)	36 (7.1%)
Disease progression	15 (6.0%)	20 (7.7%)	35 (6.7%)
Radiotherapy-related toxicity	0 (0)	1 (0.4%)	1 (0.2%)
Response to treatment (3 months after the end of radiation)			
Overall response	249 (99.6%)	258 (99.2%)	507 (99.4%)
Complete response	243 (97.2%)	255 (98.1%)	498 (97.6%)
Partial response	6 (2.4%)	3 (1.2%)	9 (1.8%)

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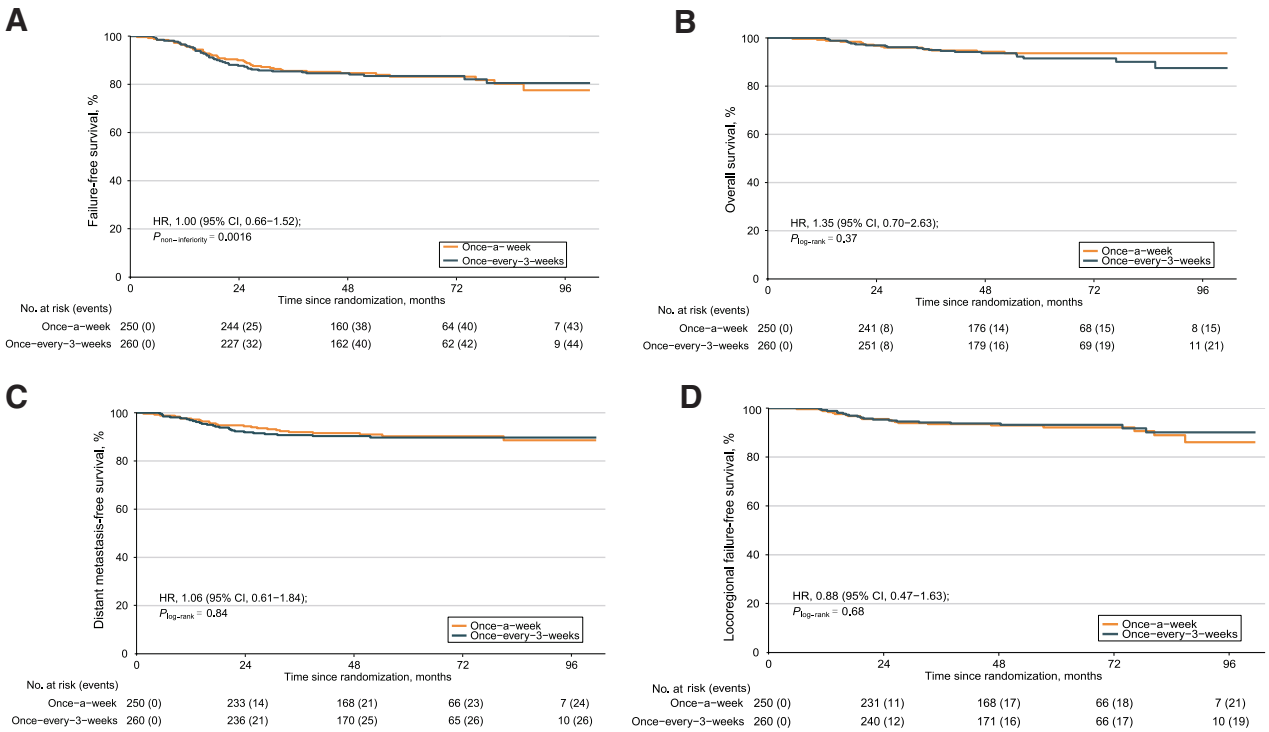

Figure 2.
Kaplan–Meier curves. FFS (**A**), OS (**B**), DMFS (**C**), and LRFS (**D**) in the intention-to-treat populations.

compared with once-a-week cisplatin at 30 mg/m^2 for definitive and adjuvant chemoradiotherapy for stage III and IV HNSCC (17). These trials have numerous important differences from our study that limit their application to clinical practice for LANPC. First, no definitive conclusions were made in the phase II study from Korea as a small sample size of patients were enrolled, resulting in low statistical power. Next, nearly 90% of patients enrolled in the latter phase III trial had oral cavity cancer and greater than 90% of enrolled patients were receiving adjuvant chemoradiotherapy. Compared with other forms of epithelial HNSCC, NPC is more sensitive to chemotherapy and radiotherapy. The application of these data to patients with LANPC treated with curative-intent chemoradiotherapy is questionable. Third, only 1 patient in the latter study received IMRT, which may have a great impact on the local control of disease. Last but foremost, in the India phase III trial, although the median cumulative cisplatin dose in the once-a-week group was 210 mg/m^2, the study chose 30 mg/m^2 as weekly cisplatin dose, which is lower than the dose listed in official guidelines for NPC. It leaves open the possibility that higher doses of weekly cisplatin may be more efficacious.

In this study, 3-year FFS in the once-every-3-weeks cisplatin group was about 85.4% (95% CI, 81.1–89.7) and 85.6% (95% CI, 81.3–89.9) in the once-a-week group, which is higher than that reported in the cisplatin-based concurrent chemoradiotherapy group in a trial conducted by Zhang and colleagues (ref. 27; 3-year recurrence-free survival, 76.5%; 95% CI, 70.4–81.5), even comparable with the 3-year recurrence-free survival (85.3%; 95% CI, 80.0–89.3) of the induction chemotherapy group. We propose two possible contributory factors. First, this could be partly explained by the fact that in our trial 11.6% of patients in the once-every-3-weeks cisplatin group and 13.5% of patients in the once-a-week group had stage T3–4N0 tumors, whereas such patients were excluded from Zhang's study. Second, in our trial 78.8% of patients in once-every-3-weeks cisplatin group and 76.5% of patients in once-a-week had stage III disease, whereas 45.9% of patients in induction chemotherapy group and 50.4% of patients in concurrent chemoradiotherapy group had stage III disease in Zhang's study. Recently, a prospective phase III trial reported by Tang and colleagues (30) included a group using three cycles of once-every-3-weeks concurrent cisplatin chemoradiotherapy, which enrolled patients with NPC with similar stages as current study, showed similar 2-year FFS (89.9% in Tang's study vs. 87.7%–90.0% in current study).

Because the lack of level 1 evidence, questions remain about the optimal schedule and dose of cisplatin. The regimen of once-a-week cisplatin at 40 mg/m^2 was usually thought well tolerated with less adverse effects and excellent outcomes (11, 31, 32). Also, three cycles of once-every-3-weeks cisplatin regimen has been well accepted in clinical practice based on the results from several phase III trials (1, 12, 24, 26). However, the completion rate of this regimen is relatively low, with 33%–88% of patients finishing the planned three cycles (1, 14, 15, 24, 30). Lee and colleagues (9) conducted the combined analysis of the NPC-9901 and the NPC-9902 trials to show that no significant survival difference was observed between patients who received two or three cycles of once-every-3-weeks cisplatin at 100 mg/m^2, implying that a cumulative cisplatin dose of 200 mg/m^2 might be adequate in the IMRT era. With the decreasing of cumulative cisplatin dose to 200 mg/m^2 may decrease the toxicity and increase the compliance to this regimen. Meanwhile, having considered the fact that the reduced duration of radiotherapy to 6–7 weeks in the IMRT era (14, 30), it is reasonable to deliver six cycles of concurrent cisplatin for once-a-week group or two cycles of concurrent cisplatin for once-

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Table 4. Adverse events.

Adverse event	OAW ($N = 249$)		OETW ($N = 260$)		P
	Grade 3	Grade 4	Grade 3	Grade 4	
Acute toxicity					
Hematologic					
Anemia	8 (3.2%)	2 (0.8%)	4 (1.5%)	1 (0.4%)	0.16
Thrombocytopenia	11 (4.4%)	1 (0.4%)	2 (0.8%)	1 (0.4%)	0.015
Neutropenia	27 (10.8%)	1 (0.4%)	23 (8.8%)	0	0.37
Leucopenia	60 (24.1%)	8 (3.2%)	41 (15.8%)	1 (0.4%)	0.002
Non-hematologic					
Stomatitis/mucositis	89 (35.7%)	0	85 (32.7%)	1 (0.4%)	0.53
Vomiting	28 (11.2%)	0	33 (12.7%)	0	0.62
Nausea	27 (10.8%)	0	30 (11.5%)	0	0.80
Hiccups	10 (4.0%)	0	15 (5.8%)	0	0.36
Constipation	4 (1.6%)	0	4 (1.5%)	0	>0.99[a]
Diarrhea	4 (1.6%)	0	9 (3.5%)	0	0.18
Dysphagia or odynophagia	7 (2.8%)	0	6 (2.3%)	0	0.72
Dermatitis	15 (6.0%)	0	22 (8.5%)	0	0.29
Xerostomia	16 (6.4%)	—	19 (7.3%)	—	0.69
Weight loss	8 (3.2%)	0	5 (1.9%)	0	0.36
Fever	2 (0.8%)	0	1 (0.4%)	0	0.97[a]
Ototoxicity	2 (0.8%)	0	3 (1.2%)	0	>0.99[a]
Neurotoxicity	0	0	1 (0.4%)	0	>0.99[b]
Atrial fibrillation	1 (0.4%)	0	0	0	0.49[b]
Stroke	0	0	0	1 (0.4%)	>0.99[b]
Renal dysfunction	1 (0.4%)	0	0	0	0.49[b]
Transaminase elevation	6 (2.4%)	0	4 (1.5%)	0	0.70[a]
Hypokalemia	11 (4.4%)	0	12 (4.6%)	1 (0.4%)	0.76
Hyponatremia	10 (4.0%)	2 (0.8%)	20 (7.7%)	2 (0.8%)	0.10
Hypocalcemia	2 (0.8%)	0	0	0	0.24[b]
Hypomagnesemia	6 (2.4%)	2 (0.8%)	3 (1.2%)	0	0.11
Any events grade ≥ 3	150 (60.2%)	15 (6%)	138 (53.1%)	7 (2.7%)	0.015
Late toxicity					
Otitis	4 (1.6%)	0	2 (0.8%)	0	0.64[a]
Ototoxicity	34 (13.7%)	7 (2.8%)	20 (7.7%)	5 (1.9%)	0.021
Tinnitus	3 (1.2%)	0	2 (0.8%)	0	0.96[a]
Eye damage	3 (1.2%)	0	4 (1.5%)	1 (0.4%)	0.77[a]
Vertigo	3 (1.2%)	0	2 (0.8%)	0	0.96[a]
Memory impairment	3 (1.2%)	0	4 (1.5%)	0	>0.99[a]
Cranial neuropathy	8 (3.2%)	1 (0.4%)	7 (2.7%)	2 (0.8%)	0.93
Myelitis	0	1 (0.4%)	0	0	0.49[b]
Peripheral neuropathy	2 (0.8%)	0	0	0	0.24[b]
Symptomatic temporal-lobe necrosis	3 (1.2%)	0	2 (0.8%)	0	0.96[a]
Bone necrosis	0	1 (0.4%)	0	0	0.49[b]
Soft-tissue damage	4 (1.6%)	0	4 (1.5%)	0	>0.99[a]
Trismus	3 (1.2%)	2 (0.8%)	2 (0.8%)	0	0.41[a]
Xerostomia	6 (2.4%)	0	5 (2.0%)	0	0.71
Dysphagia	4 (1.6%)	0	2 (0.8%)	0	0.64[a]
Dysosmia	3 (1.2%)	—	6 (2.3%)	—	0.54[a]
Any events grade ≥ 3	49 (19.7%)	8 (3.2%)	44 (16.9%)	7 (2.7%)	0.37

Note: Data are *n* (%). No grade 5 adverse events occurred during treatment. As prespecified by protocol, differences in adverse events were analyzed using χ^2 test. For adverse events that did not meet the requirement for χ^2 analysis (absolute count was <1), Fisher exact test was used.
Abbreviations: OAW, once-a-week group; OETW, once-every-3-weeks group.
[a]Adjusted χ^2 test.
[b]Fisher exact test.

every-3-weeks group patients. Therefore, we decided on two cycles of once-every-3-weeks concurrent cisplatin at 100 mg/m^2 as the comparative arm and six cycles of weekly concurrent cisplatin at 40 mg/m^2 as the standard arm in this noninferiority trial.

The tolerability profile of both concurrent chemoradiotherapy regimens were consistent with results from other studies in the same period using once-every-3-weeks and once-a-week cisplatin (14, 27, 30). It is reported that there were 61% patients in once-a-week group (median cumulative dose, 240 mg/m^2) verse 54% patients in once-every-3-weeks group (median cumulative dose, 200 mg/m^2) experienced severe acute toxic effects from two pivotal phase III trials, suggesting that weekly concurrent cisplatin with radiotherapy caused higher and more severe acute adverse effects compared with the once-every-3-weeks regimen (14, 16). In our study, consistently, we

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noted that a higher overall severe incidence of acute adverse events among patients treated with once-a-week cisplatin concurrent chemoradiotherapy (66.2%) than among those treated with once-every-3-weeks cisplatin concurrent chemoradiotherapy (55.8%); in particular, the incidence of severe leucopenia and thrombocytopenia was higher in once-a-week cisplatin group. Higher severe toxicities result in decreased compliance and delay in treatment. With a cut-off point of the cumulative dose of 200 mg/m^2 cisplatin, completion rates of five cycles of 40 mg/m^2 cisplatin in the once-a-week group were significantly lower than that of two cycles of 100 mg/m^2 cisplatin in the once-every-3-weeks group (60%–91% vs. 86%–100%, respectively; refs. 1, 11, 14, 16, 24, 27, 30, 31). Similarly, in our study, the completion rate of five cycles is 90.4% in once-a-week group and completion rate of two cycles is 99.6% in once-every-3-weeks group. Moreover, 49.6% patients in once-a-week arm required cisplatin dose reduction compared with 10.0% patients in once-every-3-weeks arm. Intriguingly, we also observed significantly higher grade 3–4 late-onset ototoxicity in the once-a-week group as well (16.5% vs. 9.6%). One of the most important contributors may be attributed to the relatively higher cumulative cisplatin dose in the once-a-week group patients than once-every-3-weeks group patients (median cumulative dose, 220 mg/m^2 vs. 200 mg/m^2). Similar result was observed in another trial focusing on locally advanced head and neck cancer (18). There is higher serious late ototoxicity (15.9% vs. 4.3%) in the cohort receiving higher cumulative cisplatin dose of 300 mg/m^2, compared with 210 mg/m^2.

Recently, one large, population-based, real-world study, focusing on patients with non-nasopharyngeal HNSCC, showed that cisplatin every 3 weeks and weekly regimens had comparable prognostic effects, but cisplatin every 3 weeks regimen was associated with statistically significantly more toxicities than weekly regimen (33). As for toxicities, it appears inconsistent with our study. Not surprisingly, in their study, nearly half of patients receiving every-3-weeks regimen reached cumulative dose of 200 mg/m^2, while only a quarter of patients receiving weekly regimen met this dose intensity. We hypothesized that both of the mode of drug administration and the cumulative dose of cisplatin would be important in terms of toxicities. Because the median cumulative dose of cisplatin was not equal between the two cisplatin regimens, the question of the relative importance of the cumulative cisplatin dose versus cisplatin schedule remains unresolved. A future study which compares two cycles of cisplatin at 100 mg/m^2 with five cycles of weekly cisplatin at 40 mg/m^2 is warranted to confirm the safety and efficacy.

Although chemoradiotherapy is also suggested for stage II NPC, a recent meta-analysis showed that concurrent chemoradiotherapy lead to increased toxicity without a survival benefit in those patients (34). For patients with stage II NPC, clinical trial enrollment is preferred to investigate whether CCRT is needed in the IMRT era. The ongoing NCT02610010 trial is designed to investigate IMRT with or without CCRT for patients with stage II NPC.

Limitations

This study has several limitations. First, this study used the TNM staging system to select eligible participants, which did not include effective prognostic biomarkers such as pretreatment plasma Epstein–Barr virus (EBV) DNA load (35, 36). However, because the problem of quantitative plasma EBV DNA assay standardization in different clinical laboratories remained unsolved before this trial started, pretreatment plasma EBV DNA load was not included as a prognostic factor in this study. Second, this trial excluded children, adolescents, and patients ages 65 years or older in consideration of their safety. Therefore, the results do not have generalizability to these patients; these patients should be considered to enroll on future studies. Finally, whether the results can be applied to non-Asian or non-endemic patient populations needs to be further assessed.

Conclusions

In conclusion, this study establishes the noninferiority of two cycles of once-every-3-weeks cisplatin at 100 mg/m^2 compared with six cycles of once-a-week cisplatin at 40 mg/m^2 in combination with concurrent IMRT in LANPC. Because of decreased acute and late-onset toxicities, two cycles of once-every-3-weeks cisplatin should be considered the preferred concurrent treatment regimen for these patients. This study was not intended to show that a high rate of survival can be achieved with concurrent chemoradiotherapy alone in LANPC, but rather it is intended to test for noninferiority between two schedules of CCRT. The standards of care for LANPC to date are concurrent chemoradiotherapy with induction or adjuvant chemotherapy and the optimal scheduling of the concurrent phase of chemotherapy remains to be investigated with the more intensive treatment regimens.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

W.-X. Xia: Resources, funding acquisition, writing–original draft. **X. Lv:** Data curation, funding acquisition, writing–original draft. **H. Liang:** Data curation, writing–original draft. **G.-Y. Liu:** Data curation, writing–original draft. **R. Sun:** Resources. **Q. Zeng:** Resources. **S.-W. Li:** Resources. **H.-Y. Mo:** Resources. **F. Han:** Resources. **D.-H. Luo:** Resources. **Q. Liu:** Data curation, methodology. **M.-Y. Shi:** Resources. **Y.-F. Ye:** Methodology. **J. Yang:** Resources. **L.-R. Ke:** Resources. **M.-Y. Qiang:** Resources. **W.-Z. Qiu:** Resources. **Y.-H. Yu:** Resources. **K.-Y. Liu:** Resources. **X.-J. Huang:** Resources. **W.-Z. Li:** Resources. **S.-H. Lv:** Resources. **Z.-C. Cai:** Resources. **J.-J. Miao:** Resources. **L. Guo:** Resources. **M.-Y. Chen:** Resources. **K.-J. Cao:** Resources. **L. Wang:** Resources. **C. Zhao:** Resources. **P.-Y. Huang:** Resources. **Q.-Y. Chen:** Resources. **Y.-J. Hua:** Resources. **L.-Q. Tang:** Data curation. **C.-N. Qian:** Visualization. **H.-Q. Mai:** Writing–review and editing. **X. Guo:** Funding acquisition, writing–review and editing. **Y.-Q. Xiang:** Conceptualization, funding acquisition, writing–review and editing.

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References

1. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 1998;16:1310–7.
2. Baujat B, Audry H, Bourhis J, Chan AT, Onat H, Chua DT, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. Int J Radiat Oncol Biol Phys 2006;64:47–56.
3. Blanchard P, Lee A, Marguet S, Leclercq J, Ng WT, Ma J, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. Lancet Oncol 2015;16:645–55.
4. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. Lancet 2019;394:64–80.
5. Chua ML, Wee JT, Hui EP, Chan AT. Nasopharyngeal carcinoma. Lancet 2016;387:1012–24.
6. Bachaud JM, Cohen-Jonathan E, Alzieu C, David JM, Serrano E, Daly-Schveitzer N. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. Int J Radiat Oncol Biol Phys 1996;36:999–1004.
7. Chan A, Leung S, Ngan R, Teo P, Lau W, Kwan W, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst 2005;97:536–9.
8. Chan A, Teo P, Ngan R, Leung T, Lau W, Zee B, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. J Clin Oncol 2002;20:2038–44.
9. Lee AW, Tung SY, Ngan RK, Chappell R, Chua DT, Lu TX, et al. Factors contributing to the efficacy of concurrent-adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: combined analyses of NPC-9901 and NPC-9902 trials. Eur J Cancer 2011;47:656–66.
10. Peng H, Chen L, Zhang Y, Li WF, Mao YP, Zhang F, et al. Prognostic value of the cumulative cisplatin dose during concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: a secondary analysis of a prospective phase III clinical trial. Oncologist 2016;21:1369–76.
11. Chan AT, Teo PM, Ngan RK, Leung TW, Lau WH, Zee B, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. J Clin Oncol 2002;20:2038–44.
12. Lee AW, Lau WH, Tung SY, Chua DT, Chappell R, Xu L, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. J Clin Oncol 2005;23:6966–75.
13. Chen QY, Wen YF, Guo L, Liu H, Huang PY, Mo HY, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. J Natl Cancer Inst 2011;103:1761–70.
14. Sun Y, Li W-F, Chen N-Y, Zhang N, Hu G-Q, Xie F-Y, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. Lancet Oncol 2016;17:1509–20.
15. Lee J, Sun J, Oh D, Lim S, Goo J, Lee S, et al. Comparison of weekly versus triweekly cisplatin delivered concurrently with radiation therapy in patients with locally advanced nasopharyngeal cancer: a multicenter randomized phase II trial (KCSG-HN10–02). Radiother Oncol 2016;118:244–50.
16. Chen L, Hu C, Chen X, Hu G, Cheng Z, Sun Y, et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. Lancet Oncol 2012;13:163–71.
17. Noronha V, Joshi A, Patil V, Agarwal J, Ghosh-Laskar S, Budrukkar A, 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.
18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
19. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the european organization for research and treatment of cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.
20. National Comprehensive Cancer Network: NCCN Guidelines: Head and neck cancer version 1; 2010. Available from:https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.
21. Kam MK, Teo PM, Chau RM, Cheung KY, Choi PH, Kwan WH, et al. Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: the Hong Kong experience. Int J Radiat Oncol Biol Phys 2004;60:1440–50.
22. Lin S, Pan J, Han L, Zhang X, Liao X, Lu JJ. Nasopharyngeal carcinoma treated with reduced-volume intensity-modulated radiation therapy: report on the 3-year outcome of a prospective series. Int J Radiat Oncol Biol Phys 2009;75:1071–8.
23. Tham IW, Hee SW, Yeo RM, Salleh PB, Lee J, Tan TW, et al. Treatment of nasopharyngeal carcinoma using intensity-modulated radiotherapy-the national cancer centre singapore experience. Int J Radiat Oncol Biol Phys 2009;75:1481–6.
24. Lee N, Harris J, Garden AS, Straube W, Glisson B, Xia P, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. J Clin Oncol 2009;27:3684–90.
25. Wee J, Tan E, Tai B, Wong H, Leong S, Tan T, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. J Clin Oncol 2005;23:6730–8.
26. Lee A, Tung S, Chua D, Ngan R, Chappell R, Tung R, et al. Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy vs radiotherapy alone for regionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst 2010;102:1188–98.
27. Zhang Y, Chen L, Hu G-Q, Zhang N, Zhu X-D, Yang K-Y, et al. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. N Engl J Med 2019;381:1124–35.
28. Pfister DG, Spencer S, Adelstein D, Adkins D, Anzai Y, Brizel DM, et al. Head and neck cancers, version 2.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2020;18:873–98.
29. Lee A, Chow J, Lee N. Treatment deescalation strategies for nasopharyngeal cancer: a review. JAMA Oncol 2020[Online ahead of print].
30. Tang L, Chen D, Guo L, Mo H, Huang Y, Guo S, et al. Concurrent chemoradiotherapy with nedaplatin versus cisplatin in stage II-IVB nasopharyngeal carcinoma: an open-label, non-inferiority, randomised phase 3 trial. Lancet Oncol 2018;19:461–73.
31. Chen Y, Liu MZ, Liang SB, Zong JF, Mao YP, Tang LL, et al. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of China. Int J Radiat Oncol Biol Phys 2008;71:1356–64.
32. Sharma A, Mohanti BK, Thakar A, Bahadur S, Bhasker S. Concomitant chemoradiation versus radical radiotherapy in advanced squamous cell carcinoma of oropharynx and nasopharynx using weekly cisplatin: a phase II randomized trial. Ann Oncol 2010;21:2272–7.
33. Bauml JM, Vinnakota R, Anna Park YH, Bates SE, Fojo T, Aggarwal C, et al. Cisplatin every 3 weeks versus weekly with definitive concurrent radiotherapy for squamous cell carcinoma of the head and neck. J Natl Cancer Inst 2019;111:490–97.
34. Liu F, Jin T, Liu L, Xiang Z, Yan R, Yang H. The role of concurrent chemotherapy for stage II nasopharyngeal carcinoma in the intensity-modulated radiotherapy era: a systematic review and meta-analysis. PLoS One 2018;13:e0194733.
35. Liang H, Lv X, Wang L, Wu Y-S, Sun R, Ye Y-F, et al. The plasma Epstein–Barr virus DNA level guides precision treatment for nasopharyngeal carcinoma in the intensity-modulated radiotherapy era: a large population-based cohort study from an endemic area. Ther Adv Med Oncol 2018;10:1758835918782331.
36. Lin JC, Wang WY, Chen KY, Wei YH, Liang WM, Jan JS, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. N Engl J Med 2004;350:2461–70.

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A Randomized Controlled Trial Comparing Two Different Schedules for Cisplatin Treatment in Patients with Locoregionally Advanced Nasopharyngeal Cancer

Wei-Xiong Xia, Xing Lv, Hu Liang, et al.

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