Comparison of 3-weekly cisplatin versus 3-weekly carboplatin in patients with locally advanced nasopharyngeal carcinoma receiving concurrent chemoradiotherapy: A multicentre analysis

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Abstract

Background Although concurrent chemoradiotherapy (CCRT) with high-dose cisplatin remains a standard of care for patients with locally advanced nasopharyngeal carcinoma (LA-NPC), carboplatin has alternatively been used, particularly for cisplatin-ineligible patients. However, the comparable efficacy of these two regimens remains unclear. The present study aimed to evaluate the efficacy and tolerability of 3-weekly carboplatin and 3-weekly cisplatin therapies.

Methods From May 2005 to November 2014, we identified patients with LA-NPC treated with CCRT from a Thai multicentre head and neck cancer database. The patients were administered a chemotherapy (CT) regimen of either cisplatin (75–100 mg/m²) or carboplatin (AUC-5 or 6). Patient tolerability and survival were analysed and compared between regimens.

Results Overall, 780 patients with LA-NPC were identified. Of these, the 76 patients (9.7%) treated with carboplatin showed significantly more comorbidity and lower baseline creatinine clearance than those treated with cisplatin. Compared with the cisplatin group, a higher number of patients in the carboplatin group completed three planned cycles of CT during CCRT (88.2% vs 52.0%; $p < 0.001$) and three planned cycles of adjuvant CT (92.1% vs 78.7%; $p = 0.004$). Furthermore, 28% of patients in the cisplatin group, as opposed to only 2.8% in the carboplatin group, required a dose reduction of CT in the subsequent cycle due to toxicities ($p < 0.001$). At the time of analysis, the 5-year disease-free survival rate was 59.0% and 59.0% ($p = 0.935$) and the 5-year overall survival rate was 64.0% and 66.0% ($p = 0.530$), in the cisplatin and carboplatin groups, respectively.

Conclusions Carboplatin provided comparable efficacy to that of cisplatin but with better tolerability and could be considered as an alternative regimen, particularly in cisplatin-ineligible patients with LA-NPC. These findings still warrant a randomised phase III study to compare these two CT regimens.

Background

Nasopharyngeal carcinoma (NPC) is endemic to Southern China, the Middle East, Alaska, Greenland and Southeast Asia, including Thailand (1, 2). Concurrent chemoradiotherapy (CCRT) with high-dose cisplatin followed by three cycles of adjuvant chemotherapy (CT) containing cisplatin plus 5-fluorouracil is considered the standard protocol for patients with locally advanced nasopharyngeal carcinoma (LA-NPC), based upon the significant survival benefits demonstrated by the Intergroup (INT) 0099 study (3). The significant improvement of progression-free survival (PFS) and overall survival (OS) favouring combined modality over radiotherapy (RT) alone group was shown, with the 5-year PFS of 58% and 5-year OS of 67% in the former group. Furthermore, a number of subsequent meta-analyses confirmed the added OS benefit of CCRT over RT alone (4-6). Nevertheless, the compliance rate of chemotherapy administration during CCRT in this protocol was quite low (63%) owing to intolerable toxicities secondary to that of high-dose cisplatin (3). Because of this, alternative chemotherapy regimens have been used, particularly for cisplatin-ineligible patients.

Carboplatin is another platinum-based CT that has been shown to have similar radiosensitising properties but less oto-, renal- and gastrointestinal toxicities compared with cisplatin (7-9). Therefore, carboplatin has alternatively been used, particularly for cisplatin-ineligible patients. A number of studies have demonstrated the survival benefits of CCRT with carboplatin in patients with LA-NPC; however, the majority of the trials were phase II, single-arm studies (10, 11). Only one phase II randomised controlled trial directly compared weekly carboplatin therapy to standard 3-weekly cisplatin therapy and suggested that weekly carboplatin therapy had a non-inferior benefit with better tolerability in patients with LA-NPC (12). Conversely, a phase I/II study of CCRT with weekly carboplatin predicted that survival outcomes would be inferior to those of the experimental arm in the INT 0099 study (13). Taken together, the benefit of carboplatin use with CCRT in patients with LA-NPC needs to be better defined. Therefore, we aimed to evaluate the efficacies and tolerabilities of CCRT between 3-weekly carboplatin and 3-weekly cisplatin therapies in patients with LA-NPC in a multicentre study in Thailand.

Methods

From May 2005 to November 2014, we retrospectively reviewed medical information of newly-diagnosed NPC patients from a large multicentre, multidisciplinary database of Thai head and neck cancer patients encompassing three university hospitals in Thailand: Ramathibodi and Siriraj Hospitals, Mahidol University and Songklanagarind Hospital, Prince of Songkla University. The eligibility criteria for the study included patients with histologically-confirmed, non-metastatic NPC in stages II-IVb according to the 7th edition of the American Joint Committee on Cancer Staging System (AJCC 2010) (14) and those who had received CCRT with either cisplatin (75–100 mg/m²) or carboplatin (AUC-5 or 6). A radical dose of RT was planned for all patients. Major exclusion criteria included patients with distant metastasis or previous radiation and/or chemotherapy, including induction CT for LA-NPC. The variables extracted from the database included patient information (date of birth, sex, vital status, date of death or date of last follow-up and cause of death), diagnosis (primary site and date of diagnosis), treatment (CT regimen, number of cycles of CT received, radiation technique and dose) and recurrence (date of recurrence and site of recurrence). Ethics approval was obtained through either the ethics committee or institutional review board at each study center and all patient information was de-identified.

Statistical analysis

Descriptive statistics were used to compare the data between the two groups of patients. OS was calculated from the date of diagnosis to the date of death from any causes. Disease-free survival (DFS) was calculated from the date of diagnosis to the first documented date of disease recurrence or date of death from any causes. Data for OS and DFS, respectively, were censored for patients who were still alive or free of recurrence at the last date of follow-up visit. Death status was validated and cross-checked with the Thai Social Security Death Index database. The last date of follow-up for censored patients was 11 June 2019. To eliminate imbalance of the follow-up time between the two groups, the total observation

period was 5 years. If the event occurred within the observation period, survival time is the point of event occurrence. On the other hand, if the event did not occur, survival time is equal to 5 years and censored. Survivals were calculated by using the Kaplan–Meier method. A log-rank test was used to compare the survival curves.

We then used propensity score adjusted probability of receiving cisplatin or carboplatin together with known post-treatment prognostic factors for multivariable Cox Regression model to explain the effect of chemotherapy regimens on time-to-event analysis (OS and DFS). The propensity score was calculated based on baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS), comorbidity and baseline creatinine clearance (CCr). A p -value of 0.05 or less was considered statistically significant. All analyses were performed using Stata/MP 16, StataCorp, College Station, TX 77845, USA.

Results

Patients and baseline disease characteristics

Between May 2005 and November 2014, we identified 780 eligible patients with newly-diagnosed LA-NPC who had received definitive CCRT with either 3-weekly cisplatin or 3-weekly carboplatin. **Table 1** summarises the patient demographics and their baseline disease characteristics. A total of 76 of 780 patients (9.7%) were treated with carboplatin during CCRT. Patients who received carboplatin were significantly associated with smoking ($p<0.001$), higher incidences of comorbidity of vascular risk factors including hypertension, diabetes mellitus, dyslipidemia and/or previous vascular events ($p=0.014$) or lower baseline CCr ($p=0.001$). The majority of patients in this cohort were diagnosed with stage IVa or IVb LA-NPC at the time of diagnosis (43.4% and 48.7% in cisplatin and carboplatin groups, respectively). Histogram of propensity score distribution based on patient ECOG PS, comorbidity, and baseline CCr is shown in **Figure 1**.

Treatment

Chemotherapy toxicity and tolerability

More patients in the carboplatin group versus the cisplatin group completed three planned cycles of CT during CCRT (88.2% vs 52.0%, $p<0.001$) and three planned cycles of adjuvant CT (92.1% vs 78.7%, $p=0.004$), as shown in **Table 2**. Eighty-eight percent (624 out of 704) of patients in the cisplatin group and 95% (72 out of 76) in the carboplatin group were able to receive more than one cycle of CT during CCRT. Among these, 28.4% of patients in the cisplatin group, as opposed to only 2.8% in the carboplatin group, required a dose reduction of CT in the subsequent cycle due to toxicities ($p<0.001$). However, there was no difference in the percentage of patients who required switching of CT regimen between the two groups ($p=0.566$).

Radiotherapy

Intensity-modulated radiation therapy (IMRT) technique concurrently with CT as a definitive treatment was used significantly more in the cisplatin group (62.3%) than in the carboplatin group (0%; $p < 0.001$), as shown in **Table 2**. Almost all patients (74 out of 76) in the carboplatin arm received a 2D-technique. Nevertheless, the mean actual dose of RT was not significantly different between the two groups ($p = 0.755$).

Survivals

The median durations of follow-up were 6.1, 5.9, and 10.0 years for overall, patients treated with cisplatin, and carboplatin, respectively. The 5-year DFS of patients treated with cisplatin or carboplatin was 61.0% (95% CI: 57-64%) or 61.0% (95% CI: 49-71%), respectively (**Fig. 2A**). Multivariable Cox regression for DFS with adjustment for propensity score and post-treatment prognostic factors is summarized in **Table 3**. Age ≥ 65 , male, advanced stage at diagnosis, non-IMRT technique and actual dose of radiation < 6600 cGy were associated with poor DFS. DFS was not significantly different between the patients who had received cisplatin or carboplatin (HR 0.66, 95% CI: 0.42–1.04) (**Table 3 and Fig. 2B**).

The 5-year OS of patients treated with cisplatin or carboplatin was 64.0% (95% CI: 60-67%) or 66.0% (95% CI: 54-75%), respectively (**Fig. 3A**). Multivariable Cox regression for OS with adjustment for propensity score and post-treatment prognostic factors is summarized in **Table 4**. Age ≥ 65 , male, advanced stage at diagnosis, non-IMRT technique and actual dose of radiation < 6600 cGy were associated with poor OS. OS was not significantly different between the patients who had received cisplatin or carboplatin (HR 0.65, 95% CI: 0.40–1.05) (**Table 4 and Fig. 3B**).

Discussion

In this study, we compared the clinical characteristics and survival outcomes for patients with LA-NPC who received definitive CCRT with either 3-weekly cisplatin or 3-weekly carboplatin. As expected, more patients in carboplatin group had comorbidity of vascular risk factors and lower baseline CCR; both factors are considered high risk for cisplatin ineligibility (15). In cisplatin-ineligible patients with locally advanced non-NPC head and neck squamous cell carcinoma, cetuximab is recommended for concurrent use with RT (16, 17). However, recommendation for the agent being used in cisplatin-ineligible patients with LA-NPC is limited. In standard guideline, carboplatin has been for decades recommended for concurrent use with RT (18), according to data from phase II studies (10-12). In addition, anti-EGFR monoclonal antibodies such as cetuximab and nimotuzumab were evaluated as radiosensitisers in patients with LA-NPC, albeit with limited data (19-23).

The INT 0099 study was the first landmark trial that demonstrated the survival benefits of CCRT with high-dose cisplatin followed by three cycles of adjuvant chemotherapy over RT alone in patients with LA-

NPC; hence, this protocol has become standard practice (3). In our study, we observed comparable survival outcomes between patients who received cisplatin and those who received carboplatin. The 5-year DFS and 5-year OS of patients treated with cisplatin in our study (61.0% and 64.0%, respectively) were similar to those reported by the INT 0099 study, which indicated a 5-year PFS of 58.0% and 5-year OS of 67.0%. Interestingly, although more patients in our study were able to complete three cycles of adjuvant CT (78.7%) in comparison to those in the INT 0099 study (55.0%), the higher survival outcomes that we anticipated were not observed. A potential explanation might be due to the fact that the survival benefits of adjuvant CT after CCRT remain controversial (24, 25). In particular, the results of a phase III trial showed no significant improvements of survival when adjuvant CT was added to CCRT versus CCRT alone (25, 26). In terms of the carboplatin group, we found a slightly lower 3-year DFS (66.0%) and 3-year OS (75.0%) than those of the previous study (10), which reported a 3-year PFS of 72.7% and 3-year OS of 89.7%. This might be explained by the fact that there was a lower proportion of patients in our study (88.2%) that were able to complete three planned cycles of carboplatin during CCRT as compared to the previous study (98.0%). Hence, this finding might emphasise the importance of cumulative dose of CT.

In this study, we ultimately evaluated the effect of chemotherapy regimens on survival using propensity score adjusted probability of receiving cisplatin or carboplatin together with known post-treatment prognostic factors for multivariable Cox Regression model. We found that after adjustment for propensity score and those prognostic factors, DFS and OS remain comparable between the two groups.

One main issue for high-dose cisplatin is toxicity, leading to the low compliance rate. In our study, patients treated with carboplatin had a better compliance rate for CT than those treated with cisplatin. More patients in the carboplatin group than in the cisplatin group were able to complete planned cycles of CT. This result appeared similar to that of the INT 0099 study, which showed that only 63.0% and 55.0% of patients received three planned cycles of cisplatin during CCRT and adjuvant CT, respectively, and that the main reason for discontinuation of treatment was patient intolerance to toxicities (3). Additionally, we found significantly more patients in the cisplatin group who required a dose reduction for CT due to toxicities. In contrast, a study using 3-weekly carboplatin demonstrated that 98.0% of patients could complete planned cycles of CT (10). Taken together, this affirms a better tolerability of carboplatin over cisplatin in this setting.

IMRT is an advanced mode of RT that is expected to improve survival and reduce local toxicities; however, the superior survival benefits of IMRT over 2D-RT technique remains uncertain (27-32). Although the mean actual dose of RT was not different, the RT technique used was significantly dissimilar between the two arms of our study. IMRT was the most-used technique in the cisplatin group (62.3%), whereas the 2D-RT technique was practised the most in the carboplatin group (97.4%). Though significantly fewer patients in cisplatin group were able to tolerate CT, we found no survival differences between the two arms. It is still hard to conclude whether these findings were affected by the enhanced benefit of IMRT. If the IMRT technique truly improves survival in patients with LA-NPC, the tolerability and survival outcome of patients receiving carboplatin concurrently with IMRT remains unknown because in our study, no patient in this arm received IMRT.

Our study is limited by its retrospective nature and relatively small number of patients in the carboplatin group. The selection bias of treating physicians is unavoidable in a retrospective study. In addition, owing to incomplete control of confounders such as ECOG PS and histology, which may have influenced the outcomes, our results should be interpreted with caution. However, given a larger sample size and longer duration of follow-ups, our study results were consistent with those of previous phase II studies that support the use of carboplatin CCRT in patients with LA-NPC .

Conclusions

Our study demonstrates that carboplatin provided comparable efficacy to that of cisplatin, but with better tolerability. Therefore, 3-weekly carboplatin concurrently with RT could be considered as a viable alternative regimen, particularly in cisplatin-ineligible patients with LA-NPC. Furthermore, carboplatin could serve as a better option in outpatient setting, given its short infusion without required fluid hydration. Importantly, our results still warrant a randomised phase III study to compare these two CT regimens, particularly in use with novel RT techniques such as IMRT.

List Of Abbreviations

CCRT: Concurrent chemoradiotherapy

CI: Confidence intervals

CT: Chemotherapy

DFS: Disease-free survival

HR: Hazard ratios

IMRT: Intensity-modulated radiation therapy

NPC: Nasopharyngeal carcinoma

OS: Overall survival

PFS: Progression-free survival

RT: Radiotherapy

RUN: Research University Network

Declarations

Ethics approval and consent to participate: Ethics approval was obtained through the ethics committee at the Ramathibodi (ID 07-59-48), and Siriraj (ECI 149/2562) hospitals, Mahidol university, and

Songklanagarind hospital (REC.61-007-14-1), Prince of Songkla University, and all patient information was de-identified.

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Authors' contributions

Study concepts: AD, NN

Study design: AD

Data acquisition: PD, RJ, CS, CJ, CP, JS

Quality control of data and algorithms: BS, PP, NN

Data analysis and interpretation: AD, BH, PP, NN

Statistical analysis: AD, TD, SLG

Manuscript preparation: AD

Manuscript editing: RJ, CJ, JS, BS, PP, NN

Manuscript review: All authors

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Tables

Table 1: Patient demographics and baseline characteristics

Characteristics	Treatment group		<i>p</i> -value
	Cisplatin n=704 (%)	Carboplatin n=76 (%)	
Median Age (years)	61	58	0.903
(Range)	(16-77)	(22-80)	
Age ≥ 65	61 (8.7)	7 (9.2)	0.502
Sex			
Male	496 (70.5)	55 (72.4)	0.792
Female	208 (29.5)	21 (27.6)	
ECOG PS			
0	238 (71.3)	60 (90.9)	0.003
1	88 (26.3)	6 (9.1)	
2	8 (2.4)	0	
Missing	370	10	
Smoker	224 (31.8)	46 (60.5)	<0.001
Any Comorbidity	93 (13.2)	18 (23.7)	0.014
Hypertension	72 (10.2)	13 (17.1)	0.057
Diabetes	32 (4.5)	4 (5.3)	0.473
Hyperlipidemia	16 (2.3)	0	0.191
Previous vascular events	8 (1.1)	1 (1.3)	0.605
T stage			
T1	153 (21.8)	11 (14.5)	0.389

T2	213 (30.4)	24 (31.6)	
T3	119 (17.0)	12 (15.8)	
T4	216 (30.8)	29 (38.1)	
Missing	3	0	
N stage			
N0	77 (10.9)	5 (6.6)	0.392
N1	152 (21.6)	14 (18.4)	
N2	358 (50.9)	46 (60.5)	
N3	117 (16.6)	11 (14.5)	
Stage at diagnosis			
II	108 (15.3)	11 (14.5)	0.610
III	289 (41.1)	28 (36.8)	
IVa	190 (27.0)	26 (34.2)	
IVb	117 (16.6)	11 (14.5)	
Histology			
WHO type I	5 (1.4)	0	0.381
WHO type II	204 (55.1)	38 (50.0)	
WHO type III	161 (43.5)	38 (50.0)	
Missing	334	0	
Mean baseline CCr* $\pm$ SD	91 $\pm$ 26	80 $\pm$ 25	0.001
(mL/min/1.73 m ²)			

*CCr – creatinine clearance calculated by Cockcroft-Gault formula

Table 2: Treatment modality and tolerability of LA-NPC patients treated with carboplatin or cisplatin CCRT

	Treatment group		<i>p</i> -value
	Cisplatin n=704 (%)	Carboplatin n=76 (%)	
Patients who completed 3 planned cycles during CCRT	366/704 (52.0)	67/76 (88.2)	<0.001
Patients who required dose reduction of the subsequent cycle during CCRT	177/624 (28.4)	2/72 (2.8)	<0.001
Patients who required chemotherapy regimen switching during CCRT	33/660 (5.0)	2/74 (2.7)	0.566
Patients who completed 3 planned cycles of adjuvant CT	554/704 (78.7)	70/76 (92.1)	0.004
RT technique			
2D	146/692 (21.1)	74 (97.4)	<0.001
3D	115/692 (16.6)	2 (2.6)	
IMRT	65/692 (9.4)	0	
3D+IMRT	366/692 (52.9)	0	
Missing	12	0	
Mean actual dose of RT (cGy)	6955.42±331.90	6942.10±504.71	0.755

Table 3: Multivariable Cox regression with propensity score adjustment for DFS

Variables	HR	[95% CI]		Adjusted HR	[95% CI]	
Age ≥ 65	1.354	0.939	1.953	1.604	1.093	2.354
Male	1.655	1.258	2.178	1.551	1.132	2.126
Smoker	1.856	1.480	2.328	1.159	0.863	1.556
Stage at diagnosis						
stage II	1.000	.	.	1.000	.	.
stage III	1.614	1.021	2.549	1.685	1.053	2.695
stage IVa	2.946	1.872	4.635	3.178	2.003	5.042
stage IVb	5.526	3.487	8.759	6.017	3.775	9.592
Radiation technique						
2D	1.000	.	.	1.000	.	.
3D	0.918	0.663	1.270	0.875	0.606	1.263
IMRT	0.465	0.279	0.776	0.475	0.274	0.821
IMRT+3D	0.516	0.396	0.671	0.471	0.319	0.697
Actual Dose of Radiation (cGy)						
≥ 6600	1.000	.	.	1.000	.	.
< 6600	1.972	1.080	3.602	2.417	1.309	4.461
Chemo regimen						
cisplatin	1.000	.	.	1.000	.	.
carboplatin	1.005	0.685	1.474	0.660	0.420	1.039
Propensity score	3.950	1.525	10.232	0.723	0.185	2.822

Table 4: Multivariable Cox regression with propensity score adjustment for OS

Variables	HR	[95% CI]		Adjusted HR	[95% CI]	
Age ≥ 65	1.470	1.017	2.124	1.640	1.115	2.412
Male	1.707	1.281	2.275	1.665	1.200	2.309
Smoker	1.781	1.408	2.253	1.143	0.844	1.548
Stage at diagnosis						
stage II	1.000	.	.	1.000	.	.
stage III	1.764	1.071	2.904	1.845	1.108	3.072
stage IVa	3.236	1.976	5.299	3.432	2.079	5.664
stage IVb	6.412	3.895	10.554	6.899	4.168	11.419
Radiation technique						
2D	1.000	.	.	1.000	.	.
3D	0.980	0.700	1.373	0.904	0.617	1.324
IMRT	0.494	0.291	0.839	0.514	0.292	0.907
IMRT+3D	0.584	0.444	0.767	0.530	0.353	0.795
Actual Dose of Radiation (cGy)						
≥ 6600	1.000	.	.	1.000	.	.
< 6600	1.710	0.880	3.323	2.088	1.062	4.104
Chemo regimen						
cisplatin	1.000	.	.	1.000	.	.
carboplatin	0.931	0.622	1.393	0.646	0.399	1.045
Propensity score	2.778	1.000	7.723	0.698	0.165	2.959

Figures

Figure 1

Histogram of propensity score distribution

Figure 2

Kaplan-Meier (KM) survival curve for DFS (A) and survival curve in Multivariable Cox regression with propensity score adjustment for DFS (B) of LA-NPC patients treated with carboplatin or cisplatin CCRT

Figure 3

Kaplan-Meier (KM) survival curve for OS (A) and survival curve in Multivariable Cox regression with propensity score adjustment for OS (B) of LA-NPC patients treated with carboplatin or cisplatin CCRT