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Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: Randomised, non-inferiority, open trial

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ABSTRACT

Purpose: This single centre, open labelled, randomised non-inferiority trial compared concurrent chemoradiotherapy with carboplatin versus standard concurrent chemoradiotherapy with cisplatin in patients with locoregionally advanced nasopharyngeal cancer (NPC).
Patients and methods: From August 1999 to December 2004, 206 patients with locally advanced NPC were randomised with 101 to cisplatin arm and 105 to carboplatin arm. Planned radiotherapy was the same in both groups. All the patients were evaluated for toxicity and survival according to the as-treated principle.
Results: With a median follow-up of 26.3 months (range 3–74.6 months), 59% of patients in the cisplatin arm completed the planned concurrent chemoradiation treatment, compared to 73% in the carboplatin arm. Forty-two percent of cisplatin patients completed the 3 cycles of adjuvant therapy compared to 70% in the carboplatin group. There were more renal toxicity, leucopenia, and anaemia in the cisplatin group, and more thrombocytopenia in the carboplatin arm. The 3 year disease free survival rates were 63.4% for the cisplatin group and 60.9% for the carboplatin group ($p = 0.9613$) (HR 0.70, 95% confidence interval (CI): 0.50–0.98). The 3 year overall survival rates were 77.7% and 79.2% for cisplatin and carboplatin groups, respectively ($p = 0.9884$) (HR 0.83, 95% CI: 0.63–1.010).
Conclusion: We concluded that the tolerability of carboplatin based regimen is better than that of the cisplatin regimen. Moreover, the treatment efficacy of carboplatin arm is not different from the standard regimen in the treatment of locoregional advanced stage NPC.

1. Introduction

A total of 1355 new cases of nasopharyngeal cancer were diagnosed in Thailand in 2002 (961 males, 394 females) and 860 died of the disease.[1] An Intergroup trial using concurrent and adjuvant chemotherapy with radiotherapy (RT) showed improved overall survival (OS) favouring the combined modality arm with an interim analysis showing a 3 year overall survival of 76% in the experimental arm and 46% in the RT alone arm, with fewer locoregional failures and distant metastases in the combined modality arm.[2] An update in 2001 reported overall survival rates of

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67% and 37% at 5 years in the experimental and RT alone arm, respectively.[3]

Carboplatin, another platinum-based drug, has been shown to have similar radiosensitising properties to those of cisplatin, and it is typically associated less with renal and gastrointestinal toxicities.[4–8] Weekly carboplatin given concurrently with radiation has also been tested in locally advanced head and neck cancer. Eisenberger's use of carboplatin at 60, 75 or 100 mg/m^2/week in advanced head and neck cancers indicated that a dose of 100 mg/m^2/week of carboplatin was reasonably well tolerated and all treatment could be given without significant delays or dosage reduction.[9] Although concomitant plus adjuvant cisplatin is proven to improve both disease-free-survival (DFS) and overall survival, however, compliance is low due to serious side effects in a particularly vulnerable patient group who are already suffering the side effects of high-dose radiotherapy. In an attempt to demonstrate that a new treatment is equivalent to a standard therapy with regard to a specific clinical end-point and has an intrinsic benefit for other clinical end-points and to decrease the problem of hospital bed limitation in our centre, and reduce the work associated with cisplatin administration, therefore, this was designed as a non-inferiority trial. We selected to compare the derivative of cisplatin; carboplatin, concurrent with radiotherapy, followed by 3 cycles of adjuvant carboplatin and 5-FU every 4 weeks after the completion of initial chemoradiotherapy versus a cisplatin regimen as given in the Intergroup study. The primary end-point of this study was to compare the efficacy of carboplatin with that of cisplatin in locally advanced nasopharyngeal carcinoma in terms of disease-free survival. The secondary end-points included overall survival, toxicity and tolerability of the two chemotherapy regimens in locally advanced nasopharyngeal cancer. The protocol was approved by the Faculty of Medicine, Chiang Mai University Institutional Review Board and ethics committee. Written informed consent was obtained from all patients.

2. Patients and methods

Patients who had histologically confirmed WHO types II–III nasopharyngeal carcinoma that was locally (T2b or more) and/or regionally advanced (N1 with a unilateral lymph node of greater than 3 cm in dimension or N2–N3b) by AJCC staging 1997,[10] without evidence of systemic metastasis, were eligible for this study. Other eligibility criteria included age between 16 and 70 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leqslant$ 2; adequate haematologic function (WBC >3000/μL, platelet count >100,000 μL, and haemoglobin >10 g/L); and adequate hepatic and renal function (bilirubin <1.5 mg/dL, AST and ALT <3× upper limit of normal, and creatinine <1.5× upper limit of normal). Patients were not eligible if they had received prior chemotherapy and/or radiotherapy, had active infection, or had had a second malignancy other than carcinoma-in situ of the cervix or basal cell skin carcinoma.

Before enrolment, all patients underwent a full history review, physical examination, CBC with differential count, electrolytes, liver function test, BUN/Cr, CT scan of the nasopharynx, chest X-ray, liver ultrasound and bone scan. During the concurrent phase, patients were clinically assessed weekly for chemotherapy and radiotherapy toxicity and CBC, BUN/Cr.

2.1. Concurrent and adjuvant chemotherapy

Patients were randomised to receive:

Arm I. Cisplatin at 100 mg/m^2 infusion over 3 h was given on days 1, 22 and 43 concurrently with radiotherapy. Adjuvant chemotherapy consisting of cisplatin 80 mg/m^2 intravenously and 5-FU infusion at 1000 mg/m^2/day by 96 h infusion was given every 4 weeks for a total of 3 cycles, beginning 4 weeks after the end of radiation therapy.

Arm II. Carboplatin at 100 mg/m^2 infusion for 1 h was given on days 1, 8, 15, 22, 29 and 36 concurrently with radiotherapy. Adjuvant chemotherapy consisting of carboplatin at AUC 5 intravenously and 5-FU infusion at 1000 mg/m^2/day by 96 h infusion was given every 4 weeks for a total of three cycles, beginning 4 weeks after the end of radiation therapy. During chemotherapy, all patients were assessed for toxicity according to the World Health Organization (WHO) grading system.[11]

2.2. Dose modification for concurrent cisplatin

Chemotherapy was not administered until the absolute neutrophil count was $\geqslant$1500/μL and the platelet count was $\geqslant$100,000/μL. If the absolute neutrophil count nadir was between 1000 and 1499/μL and/or the platelet count between 50,000 and 74,999/μL, during RT, cisplatin was decreased to 80 mg/m^2. If the absolute neutrophil count was less than 1000/μL and/or the platelet count less than 50,000/μL, chemotherapy was withheld until the white blood cell count and platelet counts were greater than 3000 and 100,000/μL, and cisplatin was then decreased to 60 mg/m^2. If the creatinine concentration was $\leqslant$1.5 mg/dL, no dose modification was made. If the creatinine concentration was 1.6–2.0 mg/dL, cisplatin was reduced to 80 mg/m^2 for the next cycle. If the creatinine concentration was greater than 2.0 mg/dL, no further cisplatin was given.

2.3. Dose modification for concurrent carboplatin

If the absolute neutrophil count nadir was between 1000 and 1499/μL and/or the platelet count between 50,000 and 74,999/μL, during RT, carboplatin was decreased to 80 mg/m^2. If the absolute neutrophil count was less than 1000/μL and/or the platelet count less than 50,000/μL, chemotherapy was withheld until the white blood cell count and platelet counts were greater than 3000 and 100,000/μL, and carboplatin was then decreased to 60 mg/m^2.

2.4. Radiotherapy

For tumour localisation, a CT scan was used to assess the extent of the primary tumour, as well as the neck nodes. Megavoltage machines with cobalt-60 or 6 MV were used. The treatment volume included the primary tumour site and the neck nodes down to the clavicle. The primary tu-

mour and the upper neck were treated with two lateral fields. The field arrangement was individualised. The lower neck and supraclavicular fields were treated with a single anterior field with shielding to the larynx and spinal cord. Radiotherapy was given to the patients five times a week with 2 Gy per fraction to a total dose of 70 Gy in both arms. After treating the nasopharynx and upper cervical lymph nodes with 40–44 Gy, the fields were reduced to exclude the spinal cord, and 26 Gy was added using these reduced fields. The bulky nodal area was boosted using a posteroanterior neck field of cobalt-60 or an electron beam of appropriate energy. During the course of radiotherapy, all patients were observed weekly to assess the grade of radiation toxicity using the Radiation Therapy Oncology (RTOG) acute morbidity scoring criteria.[12]

2.5. Dose modification for adjuvant chemotherapy

Chemotherapy was not administered until the absolute neutrophil counts were $\geqslant$1500 μL and the platelet counts >100,000/μL. If the absolute neutrophil count nadir was $\geqslant$1500/μL and/or the platelet count nadir >75,000/μL, no dose modification was made. If the absolute neutrophil count nadir was between 1000 and 1499/μL and/or the platelet neutrophil nadir between 50,000 and 74,999/μL, cisplatin was decreased to 60 mg/m^2, the last dose of carboplatin was decreased to 25% and 5-FU decreased to 800 mg/m^2. If the absolute neutrophil count was less than 1000/μL and/or the platelet nadir less than 50,000/μL, chemotherapy was withheld until the WBC count and platelet counts were greater than 1500 and 100,000/μL, respectively; cisplatin was decreased to 40 mg/m^2, the last dose of carboplatin was decreased to 25%, and 5-FU was decreased to 600 mg/m^2, respectively. The dose of cisplatin was adjusted according to the value of creatinine after the last cycle. If the creatinine concentration was $\leqslant$1.5 mg/dL, no dose adjustment was required. If the creatinine concentration increased to 1.6–2.0 mg/dL, cisplatin is reduced to 60 mg/m^2 for the next course. No cisplatin was administered until complete recovery from renal toxicity occurred. If the creatinine concentration was greater than 2 mg/dL, no further cisplatin was given.

2.6. Criteria of discontinuation for chemotherapy

Chemotherapy treatment was discontinued for the following reasons: serious adverse events (including inter-current illness and unacceptable toxicity), which render further chemotherapy treatment on protocol detrimental to patients, delay of more than 2 weeks for blood counts to recover or for renal toxicity to improve to grade 2 or less, or at request from the patient.

2.7. Follow-up

The first follow-up visit was 2 months after the last cycle of adjuvant chemotherapy. Patients were evaluated by radiation oncologists and otolaryngologists for locoregional control, complications and survival. Every patients underwent endoscopic examination of the nasopharynx, with a biopsy, if necessary. An evaluation was done at 2 month intervals for the first year, 3–4 month intervals for the second and third year and 6 month intervals thereafter. Late effects were recorded if they occurred or persisted for more than 6 months after complete chemoradiation, and they were graded using the Radiation Therapy Oncology Group (RTOG) late radiation morbidity scoring criteria.[13]

2.8. Statistical analysis

Efficacy variables were analysed on an intent-to-treat basis and on an as-treated basis. In the as-treated analysis, only data from patients continuing randomised treatment were considered for analysis, and based on the time from random assignment to death. As-treated analysis, is recommended to provide the more conservative approach for the non-inferiority assessment.[14–16] Given the results of the Intergroup study,[3] we expected a 3 year overall survival of 76% in both cisplatin and carboplatin arms. In order to determine with 80% power, using a one-sided type I error of 0.20, to test the non-inferiority at 3 year overall survival of two treatment arms, at least 103 patients per group were needed to be observed for overall survival analysis. Categorical variables were tested with χ^2-tests. Fisher's exact test was used when a small sample size existed. Testing difference between two proportions was used to compare two proportions. Survival estimates were calculated according to Kaplan–Meier method.[17] The significant difference between the survival curve was calculated using the log-rank test and a p-value of <0.05 was considered statistically significant.[18] An arbitrary clinical cutoff of an increased risk of 25% was used; that is ruling out a hazard ratio for survival of not more than 1.25 for the experimental drug versus control would be considered evidence of effectiveness.

3. Results

Between August 1999 and December 2004, 220 patients randomly assigned to this protocol and 206 eligible patients were enrolled to this study (101 cisplatin and 105 carboplatin). The CONSORT trial flow diagram for locally advanced nasopharygeal cancer is shown in Fig. 1. Patient characteristics are given

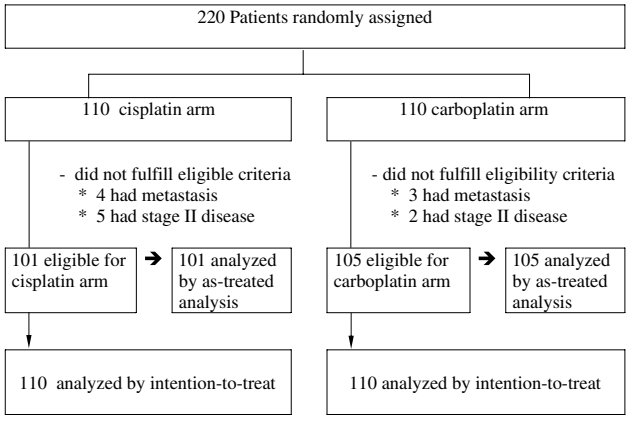

Fig. 1 – CONSORT trial flow diagram for locally advanced nasopharyngeal cancer patients.

Table 1 – Patient and tumour characteristics (n = 206)

Characteristics	Cisplatin arm (%)	Carboplatin arm (%)	*p*-Value
Total patients	101 (49)	105 (51)	
Median age (range)	46 (16–69)	50 (16–70)	
Sex			
Male	57 (56)	69 (67)	$p = 0.6$
Female	44 (44)	36 (35)	
ECOG PS			
0	65 (64)	72 (69)	$p = 0.6$
1	36 (36)	33 (31)	
T stage (1997 AJCC)			
T1–T2	59 (58)	65 (62)	$p = 0.7$
T3–T4	42 (42)	40 (38)	
N stage (1997 AJCC)			
N0–N1	51 (50)	42 (40)	$p = 0.1$
N2–N3	50 (50)	63 (60)	
Disease stage (1997 AJCC)			
Stage III	36 (36)	33 (31)	$p = 0.5$
Stage IVA	25 (25)	24 (23)	
Stage IVB	40 (40)	48 (46)	
Histology			
WHO type II	29 (29)	26 (25)	$p = 0.6$
WHO type III	72 (71)	79 (75)	

in Table 1. There was comparability in both arms, including age, performance status, tumour staging, and histology.

3.1. *Disease free survival and overall survival*

The median follow-up time for all patients was 26.3 months (range 3–74.6 months), and 27 months for surviving patients (range 3–74.6 months). For as-treated analysis, the actuarial 3 year disease free survival rates were 63.4% and 60.9% for cisplatin and carboplatin, respectively ($p = 0.9613$). The hazard ratio was 0.70 (95% CI: 0.50–0.98) for carboplatin versus cisplatin. (Fig. 2). The actuarial 3 year overall survival rate was 77.7% for the cisplatin arm and 79.2% for the carboplatin one ($p = 0.9884$). The hazard ratio was 0.83 (95% CI: 0.63–1.01) for carboplatin versus cisplatin (Fig. 3). For intent-to-treat analysis in 220 patients, the 3 year disease free survival rates

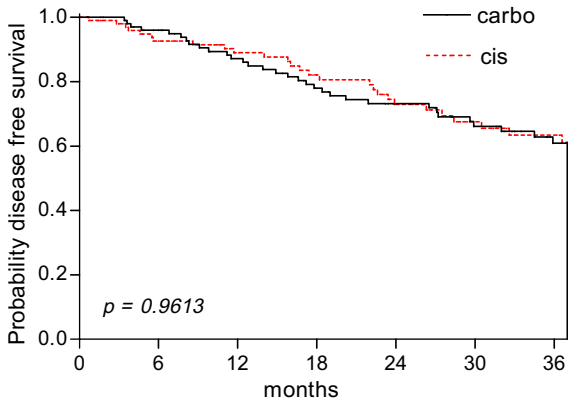

Fig. 2 – The 3 year disease free survival by as-treated analysis carboplatin = 60.9 (95% CI: 50.8–71.1) cisplatin = 63.4 (95% CI: 51.6–75.2).

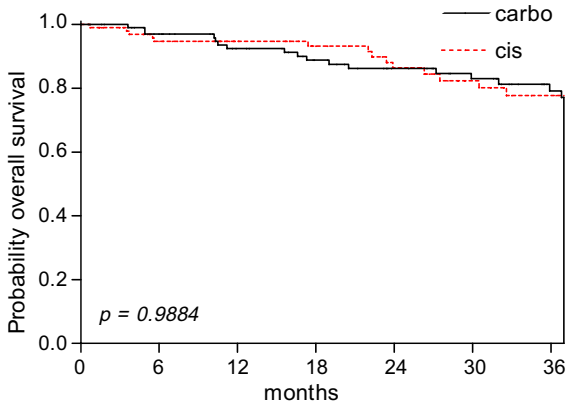

Fig. 3 – The 3 year overall survival by as-treated analysis carboplatin = 79.2 (95% CI: 69.8–88.6) cisplatin = 77.7 (95% CI: 67.6–87.8).

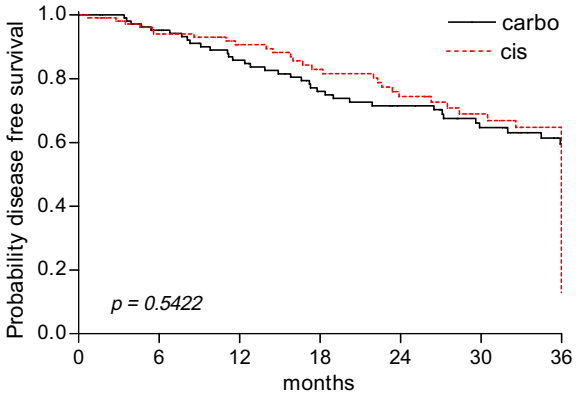

Fig. 4 – The 3 year disease free survival by intent-to-treat analysis carboplatin = 59.6 (95% CI: 48.8–70.4) cisplatin = 64.7 (95% CI: 53.1–76.3).

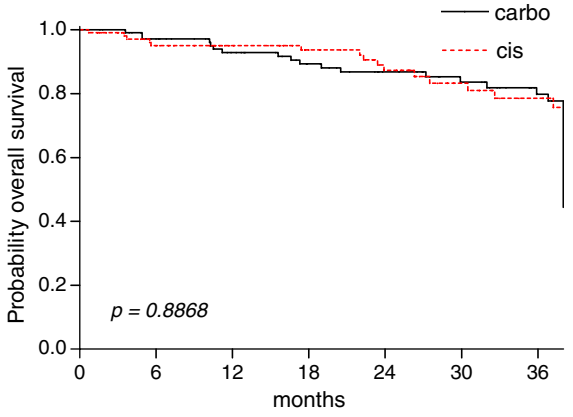

Fig. 5 – The 3 year overall survival by intent-to-treat analysis carboplatin = 79.8 (95% CI: 70.5–89.1) cisplatin = 78.6 (95% CI: 67.9–89.3).

were 64.7% and 59.6% for cisplatin and carboplatin, respectively ($p = 0.522$) (Fig. 4). The 3 year overall survival rates were 78.6%. and 79.8% for cisplatin and carboplatin, respectively ($p = 0.08868$) (Fig. 5).

3.2. Failure patterns

Thirty-five patients died during follow-up as follows: cisplatin arm 16/101 (15.8%); carboplatin arm 19/105 (18.1%). Twenty-one patients (10.2%) had loco-regional recurrence as follows: cisplatin arm 9/101 (8.9%); carboplatin arm 12/105 (11.4%). Thirty-one patients had distant metastases as follows: cisplatin arm 16/101(15.8%); carboplatin arm 15/105 (14.3%).

3.3. Toxicity and tolerability

All 206 patients were evaluated for acute toxicity from radiochemotherapy. Acute toxic effects of chemotherapy according to the WHO criteria are listed in Table 2. Acute toxic effects of radiotherapy according to the RTOG acute radiation morbidity scoring criteria are also listed in Table 2.

3.4. Cisplatin arm

There was one patient who had fatal toxicity related to treatment, due to severe grade 4 mucositis, grade 4 leucopenia and thrombocytopenia during her third cycle of concurrent cisplatin. The cause of death was septicemia. The most common non-haematologic toxicities in patients receiving cisplatin concurrent with radiotherapy were mucositis, skin toxicity and pharyngoesophagitis. A higher incidence of nausea and vomiting was observed in patients on the cisplatin arm ($p = 0.05$). Four patients (4%) had grades 3–4 nephrotoxicity, but overall 26% of patients had some measurable level of nephrotoxicity. Grades 3–4 haematologic toxicity occurred in 28 patients. Fifty percent of patients lost more than 10% of their weight during the course of concurrent treatment. These data are shown in Table 2.

3.5. Carboplatin arm

The most common non-haematologic toxicities in patients receiving carboplatin concurrent with radiotherapy were mucositis, skin toxicity and pharyngoesophagitis. No patients had nephrotoxicity. The incidence of nausea and vomiting was lower in the carboplatin arm. In the case of haematologic toxicity, the incidence of severe thrombocytopenia was higher in the carboplatin arm but was non-statistically significant. Twenty percent of patients lost more than 20% of their weight during the concurrent carboplatin and radiotherapy. These data are shown in Table 2.

3.6. Treatment completion rates

3.6.1. Radiation therapy

The expected duration of the radiation therapy is 7 weeks. Eighty-three patients (83%) completed radiotherapy within 8 weeks in the cisplatin arm, and 90 patients (86%) in the carboplatin arm ($p = 0.9$). Eighteen patients (18%) and 15 patients (14%) ($p = 0.8$) completed between 8 and 9 weeks in the cisplatin and carboplatin arms, respectively.

3.6.2. Chemotherapy

During concurrent chemoradiation, 59 patients (59%) received 3 cycles of chemotherapy in the cisplatin arm, whereas 77 patients (73%) received 6 cycles of carboplatin. For adjuvant chemotherapy, 42 patients (42%) in the cisplatin group received all 3 cycles of adjuvant cisplatin plus 5-FU, whereas 73

Table 2 – Acute toxicity of radiochemotherapy (WHO grading system/RTOG acute radiation morbidity scoring criteria)

Acute toxicity	Cisplatin arm ($n = 101$) (%)	Carboplatin arm ($n = 105$) (%)	p-Value all grades
Leucopenia			
Grade 2	29 (29)	23 (22)	$p = 0.2982$
Grade 3	9 (9)	11 (10)	
Grade 4	2 (2)	0	
Anaemia			
Grade 2	33 (33)	17 (16)	$p < 0.0001$
Grade 3	14 (14)	2 (2)	
Grade 4	0	0	
Thrombocytopenia			
Grade 2	1 (1)	4 (4)	$p = 0.7225$
Grade 3	1 (1)	6 (6)	
Grade 4	2 (2)	2 (2)	
Nausea/vomiting			
WHO grade 1	39 (39)	26 (25)	$p = 0.0537$
Grade 2	19 (19)	9 (9)	
Grade 3	1 (1)	0	
Nephrotoxicity			
WHO grade 1	13 (13)	0	$p = 0.0002$
Grade 2	9 (9)	0	
Grade 3	3 (3)	0	
Grade 4	1 (1)	0	
Mucous membrane			
RTOG grade 1	54 (53)	40 (38)	$p = 0.0514$
Grade 2	46 (46)	60 (57)	
Grade 3	0	5 (5)	
Grade 4	1 (1)	0	
Skin			
RTOG grade 1	60 (59)	51 (48)	$p = 0.2295$
Grade 2	35 (35)	44 (42)	
Grade 3	3 (3)	6 (6)	
Grade 4	3 (3)	4 (4)	
Pharynx and oesophagus			
RTOG grade 1	43 (42)	37 (35)	$p = 0.1029$
Grade 2	44 (44)	52 (50)	
Grade 3	10 (10)	4 (4)	
Grade 4	4 (4)	0	
Weight loss			
>10% at week 3 of RT	15 (15)	3 (3)	$p < 0.0001$
>10% at week 6 of RT	35 (35)	18 (17)	
Need nasogastric tube	48 (48)	23 (22)	$p = 0.0002$

Table 3 – Chart of maximum number of cycles of concurrent and adjuvant cisplatin completed by each patient

Cisplatin	No adjuvant	Adjuvant 1 cycle	Adjuvant 2 cycles	Adjuvant 3 cycles	Total
Concurrent 1 cycle	8	0	0	0	8
Concurrent 2 cycles	11	3	4	16	34
Concurrent 3 cycles	13	5	15	26	59
Total	32	8	19	42	101

Table 4 – Chart of maximum number of cycles of concurrent and adjuvant carboplatin completed by each patient

Carboplatin	No adjuvant	Adjuvant 1 cycle	Adjuvant 2 cycles	Adjuvant 3 cycles	Total
Concurrent 1 cycle	2	0	0	0	2
Concurrent 2 cycles	2	0	0	0	2
Concurrent 3 cycles	3	0	0	1	4
Concurrent 4 cycles	7	1	0	3	11
Concurrent 5 cycles	1	1	1	6	9
Concurrent 6 cycles	8	4	3	62	77
Total	23	6	4	72	105

patients (70%) completed 3 cycles of adjuvant carboplatin and 5-FU. Only 26% of the patients in the cisplatin arm fully complied with the protocol treatment (3 cycles of concurrent chemotherapy and 3 cycles of adjuvant chemotherapy), whereas 62% of the patients in the carboplatin arm completed all 6 cycles of concurrent carboplatin and 3 cycles of adjuvant treatment ($p < 0.001$). Tables 3 and 4 demonstrate the maximum number of cycles of concurrent and adjuvant chemotherapy without cisplatin, and carboplatin, respectively.

3.7. *Late radiation toxicity in cisplatin arm*

Late complications of radiotherapy were evaluated in patients who had completed at least 6 months follow-up after the end of radiotherapy. Seventeen patients (17%) were lost to follow-up after the end of treatment. Eighty-four patients in the cisplatin arm were evaluated for late radiation toxicities. Four patients (5%) developed grade 3 xerostomia. Two patients (2%) developed grade 3 skin fibrosis and also had grade 3 subcutaneous complications. No patient had grades 3–4 laryngeal toxicity. Three patients (4%) had grade 2 late pharynx and oesophageal toxicity. These data are shown in Table 5.

3.8. *Late radiation toxicity in carboplatin arm*

Ninety-six patients (91%) in this arm completed 6 months follow-up after the end of radiotherapy and were evaluated for late radiation toxicities. Nine patients (8%) were lost to follow-up after the end of treatment. Three patients (3%) developed grade 3 xerostomia. One patient (1%) developed grade 3 skin fibrosis. No patient developed grades 3–4 laryngeal toxicity, and none had grades 2–3–4 pharyngeal toxicity. These data are shown in Table 5.

4. Discussion

The INT 0099 study demonstrated a regimen for patients with locally advanced NPC. Our single centre prospective study did not seek to confirm the efficacy of this standard regimen, but sought to evaluate the efficacy and feasibility of the similar regimen with carboplatin; the derivative of cisplatin that is easier to administer. This is important since this disease is more common in East Asian countries which may have very limited hospital resources.

The baseline characteristics (age, sex and performance status) distributions of our patients were similar as the INT 0099 trial, but our study populations were less stage IV (65% in cisplatin group, 69% in carboplatin group and 90% in INT 0099 trial). Furthermore, our patients had 100% WHO histologic types II and III, but only 65% in the INT 0099 study. However, there are no biologic reasons to expect these differences to result in tolerability of treatment, but WHO histologic Type I is thought to have a different natural history in comparison to others.[26]

In the recently published individual patient data meta-analysis of eight randomised trials and 1753 patients, chemotherapy was confirmed to lead to a small but significant benefit for overall survival and event-free survival. The pooled hazard ratio of death was 0.82 (95% CI, 0.71–0.94; $p = 0.006$), corresponding to an absolute survival benefit of 6% at 5 years from the addition of chemotherapy (from 56% to 62%). The pooled hazard ratio of tumour failure or death was 0.76 (95% confidence interval, 0.67–0.86; $p < 0.0001$), corresponding to an absolute event-free survival benefit of 10% at 5 years from the addition of chemotherapy (from 42% to 52%).[19] Chemotherapy has been given sequentially before or after radiotherapy or concurrently with radiotherapy. All of these studies have shown improvement in disease free survival, but no improvement in overall survival[20–25] apart from the Intergroup 0099 trial which demonstrated an improvement in all aspects including local control, freedom from distant metastasis, progression free survival and overall survival.[2] Survival benefit was still seen after 5 years of follow-up.[3] When concurrent cisplatin and radiotherapy was followed by adjuvant chemotherapy, the overall survival rates were 78% and 67% at 3 year and 5 year, respectively. The results of our study are comparable with the Intergroup trial and other phase III trials,[20–25] with our overall survival rate in

Table 5 – Late radiation toxicity (RTOG late radiation morbidity scoring criteria)

Late-radiation toxicity	Cisplatin arm ($n = 84$) (%)	Carboplatin arm ($n = 96$) (%)	p-Value all grade
Skin			
Grade 1	53 (63)	54 (56)	$p = 0.0230$
Grade 2	8 (10)	2 (2)	
Grade 3	2 (2)	1 (1)	
Grade 4	0	0	
Mucous membrane			
Grade 1	42 (50)	51 (53)	$p = 0.0637$
Grade 2	14 (17)	4 (4)	
Grade 3	0	0	
Grade 4	0	1 (1)	
Salivary gland			
Grade 1	49 (58)	51 (53)	$p = 0.6821$
Grade 2	24 (29)	23 (24)	
Grade 3	4 (5)	3 (3)	
Grade 4	0	0	
Larynx			
Grade 1	29 (34)	32 (33)	$p = 0.8478$
Grade 2	1 (1)	2 (2)	
Grade 3	0	0	
Grade 4	0	0	
Pharynx and oesophagus			
Grade 1	37 (44)	36 (38)	$p = 0.01024$
Grade 2	3 (4)	0	
Grade 3	0	0	
Grade 4	0	0	

the cisplatin arm of 77.7% at 3 years. Our percentages are a little lower than a Taiwanese study, which reported a 3 year DFS and 3 year OS rates of 81.4% and 88.8%, respectively.[25] However, there was a higher percentage of stage IV patients in our study when compared with the Taiwanese one; 46% and 45% in our cisplatin and carboplatin arms, respectively, and 29% in the Taiwanese trial. Using an as-treated analysis, no significant difference in efficacy was found between the two arms. The 3 year disease free survival rate was 60.9% for the carboplatin arm and 63.4% for the cisplatin arm (Fig. 1) ($p = 0.9613$). The hazard ratio was 0.70 (95% CI: 0.50–0.98) for carboplatin versus cisplatin. The 3 year overall survival rate was 79.2% for the carboplatin arm and 77.7% for the cisplatin arm (Fig. 2) ($p = 0.9884$). The hazard ratio was 0.83 (95% CI: 0.63–1.01) for carboplatin versus cisplatin. Because the upper bounds of the 95% CIs for both end-points were less than 1.25, we concluded that carboplatin concurrent radiotherapy and adjuvant carboplatin plus 5-FU were not inferior when compared with standard cisplatin regimen.

One issue for cisplatin containing regimens is the toxicity and tolerability of the drug limiting the number of patients who manage to complete the full course of treatment. In our study, only 59% of patients completed all 3 cycles of concurrent cisplatin with radiation. Our findings are consistent with the results of the phase III randomised trial conducted by the Intergroup,[2] in which 63% of patients completed 3 cycles of cisplatin plus radiotherapy. However, our study had an even higher compliance rate than the Canadian one,[26] in which only 43% of patients received all three courses of cisplatin. In contrast, we found much higher compliance rate in the carboplatin arm of our study with 77% of patients completing all 6 cycles of concurrent carboplatin with radiotherapy. Considering the adjuvant part of the treatment regimens, we found a lower adjuvant treatment completion rate for cisplatin plus 5-FU than the INT group and the Canadian study (42% versus 55% versus 61%). However in our carboplatin arm, 72% of patients completed all 3 cycles of adjuvant carboplatin plus 5-FU infusion. We found a major difference between the two treatment arms; the ability to administer the treatment, with only 26% of the patients being able to receive all of the cisplatin courses (concurrent and adjuvant) compared to 62% of the patients treated with carboplatin ($p < 0.01$). As expected the patients in our study experienced a significant higher incidence of anaemia and renal toxicity in patients with cisplatin arm ($p < 0.001$ and $p = 0.0002$, respectively) (Table 2). For radiation toxicity, we found that almost all the patients of both the cisplatin and the carboplatin experienced grades 1–2 mucositis, pharyngoesophagitis and skin toxicity. But as for the rates of grades 3 and 4 toxicities – there were actually 14 (14%) for pharynx and oesophagus for the cisplatin versus 4 (4%) for the carboplatin. We also found that patients who received carboplatin had a significantly lower incidence of severe weight loss relative to patients in cisplatin arm (Table 2). In our centre, we did not give a prophylactic feeding tube at baseline. However, in this study we had a higher percent of patients in cisplatin arm compared with carboplatin (48% versus 22%) who need feeding tubes to minimise weight loss and improve quality of life. All the studies that use the Intergroup regimen have confirmed that it is difficult to deliver due to toxicity of the gastrointestinal tract, bone marrow and kidney,[26,27] and it is also difficult to administer in our centre.

In summary, because the tolerability of the carboplatin regimen was better than that of the cisplatin regimen, and it enabled more patients to complete the planned course of therapy. Moreover, the treatment efficacy of carboplatin regimen has not deviated from the standard regimen in the treatment of locoregional advanced stage nasopharyngeal cancer in terms of disease free survival and overall survival. The substitution of carboplatin for cisplatin is feasible and should be considered as an alternative regimen in this group of patients.

Conflict of interest statement

None.

REFERENCES

1. Ferlay J, Bray F, Pisani P, Parkin DM. *GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC Cancer Base No. 5, version 2.0.* Lyon: IARC Press; 2002 http://www-depdb.iarc.fr/globocan/GLOBOframe.htm.
2. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced

nasopharyngeal cancer: Phase III randomized Intergroup study 0099. *J Clin Oncol* 1998;**116**:1310–7.
3. Al-Sarraf M, Le Blanc M, Giri PG, et al. Superiority of five-year survival with chemo-radiotherapy (CT-RT) vs radiotherapy in patients with locally advanced nasopharyngeal carcinoma. Intergroup (0099) (SWOG 8892, RTOG 8817, ECOG 2388) Phase III study: final report [abstract]. *Proc Am Soc Clin Oncol* 2001;**20**:905.
4. Douple EB, Richmond RC, O'Hara JA, et al. Carboplatin as a potentiator of radiation therapy. *Cancer Treat Rev* 1985;**12**(Suppl. A):111–24.
5. Coughlin CT, Richmond RC. Biologic and clinical developments of cisplatin combined with radiation: Concepts, utility, projections for new trials, and the emergence of carboplatin. *Semin Oncol* 1989;**16**:31–43.
6. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst* 1999;**91**:2081–6.
7. Calais G, Le Floch O. Concomitant radiotherapy and chemotherapy in the treatment of cancer of the upper respiratory and digestive tracts. *Bull Cancer Radiother* 1996;**83**:321–9.
8. Muggia FM. Overview of carboplatin: Replacing complementing and extending the therapeutic horizons of cisplatin. *Semin Oncol* 1989;**16**(Suppl. 5):7–13.
9. Eisenberger M, Jacobs M. Simultaneous treatment with single-agent chemotherapy and radiation for locally advanced cancer of head and neck. *Semin Oncol* 1992;**4**(Suppl. 11): 41–6.
10. Fleming I, Cooper J, Henson D, et al. In: Fleming I, Cooper J, Henson D, et al., editors. *AJCC Cancer staging manual*. Philadelphia: Lippincott-Raven; 1997. p. 31–9.
11. Miller AB, Hoogstraten B, Stagnet M, et al. Reporting results of cancer treatment. *Cancer* 1981;**47**:207–14.
12. RTOG acute radiation morbidity scoring criteria. <http://www.rtog.org/members/toxicity/acute.html>.html [accessed December 1, 2002].
13. RTOG Late radiation morbidity scoring criteria. <http://www.rtog.org/members/toxicity/late.html> [accessed December 1, 2002].
14. Piaggio G, Elbourne DR, Altman DG, Pocock SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006;**295**:1152–60.
15. European Medicines Agency. ICH harmonised tripartite guideline Topic E9: statistical principles for clinical trials. http://www.emea.eu.int/03639n.pdf [accessed February 23, 2006].
16. Armitage P, Colton T, editors. *Encyclopedia of biostatistics*. New York: John Wiley; 1998. p. 1367–72.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;**53**:457–81.
18. Fleiss JL, editor. *Statistical methods for rates and proportions*. New York, NY: Wiley; 1981. p. 138–43.
19. Baujat B, Audry H, Bourhis J, 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.
20. Rossi A, Molinari R, Boracchi P, et al. Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubincin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study. *J Clin Oncol* 1988;**6**:1401–10.
21. Cvitkovic E. Neoadjuvant chemotherapy with epirubicin, cisplatin, bleomycin in undifferentiated nasopharyngeal cancer: preliminary results of international phase III trial (Abstr). *Proc Am Soc Clin Oncol* 1994;**13**:283.
22. International Nasopharynx Cancer Study Group. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV(>or = N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free survival. VUMCA I trial. *Int J Radiat Oncol* 2001;**20**:227a.
23. Chan AT, Teo PM, Leung TW, et al. A prospective randomized study of chemotherapy adjunctive to definitive radiotherapy in advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 1995;**33**:569–77.
24. Chua DT, Sham JS, Choy D, et alfor the Asian-Oceanian Clinical Oncology Association Nasopharynx Cancer Study Group. Preliminary report of the Asian-Oceanian Clinical Oncology Association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer* 1998;**83**:2270–83.
25. Cheng SH, Jian JJ-M, Tsai SYC, et al. Long-term survival of nasopharyngeal carcinoma following concomitant radiotherapy and chemotherapy. *Int J Radiat Oncol Biol Phys* 2000;**48**:1323–30.
26. Bahl M, Siu LL, Pond GR, et al. Tolerability of the Intergroup 0099 (INT 0099) regimen in locally advanced nasopharyngeal cancer with a focus on patients' nutritional status. *Int J Radiat Oncol Biol Phys* 2004;**60**:1127–36.
27. Wee J, Tan EH, Tai BC, 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;**20**:6730–8.