Original Article

Gemcitabine Plus Platinum versus Docetaxel Plus Platinum as First-Line Therapy for Metastatic Nasopharyngeal Carcinoma: A Randomized Clinical Study

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Abstract

Background: A well-established first-line chemotherapy standard for metastatic nasopharyngeal carcinoma is yet lacking.

Objectives: To compare the efficacy and safety of gemcitabine plus platinum versus docetaxel plus platinum regimen as first-line therapies for distal metastatic nasopharyngeal carcinoma.

Study Design and Participants: A single center, randomized, open-label, parallel-arm study. The study included 120 patients with metastatic nasopharyngeal carcinoma who met the study requirements.

Interventions: Participants were randomized in a 1:1 ratio through a sealed envelope selection. Gemcitabine 1000 mg/m^2/d intravenously (IV) for >30 min (days 1 and 8) or docetaxel 75 mg/m^2/d IV for 1 h (day 1) were administered to the respective group participants. Nedaplatin 75 mg/m^2/d, IV (day 1), cisplatin 75 mg/m^2/d IV (day 1) or carboplatin (area under the curve set as 5) IV (day 1) were used in both groups. One cycle duration was 21 days, with 4–6 cycles for all participants.

Outcomes: The primary assessed outcomes were progression-free survival (PFS) and overall survival (OS), and the secondary outcomes were short-term efficacy [i.e., response rate (RR) and disease control rate (DCR)] and safety.

Results: Seven patients withdrew from the study, and efficacy and adverse reactions were obtained for 113 patients (gemcitabine: 56; docetaxel: 57). Compared with the docetaxel plus platinum group, the gemcitabine plus platinum group had significantly higher RR (71.4% vs. 52.6%, $P < 0.05$); mPFS (9.7 vs. 7.8 months, $P < 0.05$), and mOS (20.6 vs. 16.8 months, $P < 0.01$). The significance was not associated with increased adverse reactions, as both groups showed similar Grades 3 and 4 adverse reactions ($P > 0.05$). DCR was non-significantly higher in the gemcitabine group (85.7% vs. 75.4%, $P > 0.05$). Multivariable analysis revealed that time to disease progression, number of involved organs, liver metastasis, and grouping were associated with mPFS and mOS (all $P < 0.05$).

Conclusion: The combination of gemcitabine with platinum is likely superior to that of docetaxel with platinum as first-line treatment for metastatic nasopharyngeal carcinoma.

Keywords: Chemotherapy, docetaxel, gemcitabine, metastatic nasopharyngeal carcinoma, platinum, prognostic factors, survival

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INTRODUCTION

Nasopharyngeal carcinoma is a malignancy more commonly found in East Asia and Africa,[1] and approximately 87,000 new cases and 51,000 deaths are reported each year worldwide.[2] Radiotherapy with or without chemotherapy has been used as a major treatment for treatment-naïve nasopharyngeal carcinoma without distant metastasis, with a 5-year local recurrence-free survival of 78.4–86.8%.[3,4] The 15–20% patients who are not responsive to this therapy usually develop distant metastases.[5-7] Those patients' prognosis is affected by factors such as location of metastasis and number of involved organs,[8] and the median overall survival (mOS) of patients with metastatic nasopharyngeal carcinoma is only 11–22 months.[9,10]

Platinum-based chemotherapy is recommended as the first-line treatment for metastatic nasopharyngeal carcinoma. The 5-fluorouracil and cisplatin (PF) regimen has been previously adopted for patients with advanced metastatic nasopharyngeal carcinoma with low remission rate and short overall survival.[11-13] However, there is need for a chemotherapy regimen with higher efficacy and better tolerance. Gemcitabine or docetaxel represent a potential approach for recurrent or metastatic nasopharyngeal carcinoma.[14-16]

Gemcitabine is a specific anti-metabolite that mainly works on tumor cells during the S phase. It can also prevent cell cycle progression from the G1 to the S phase. Gemcitabine plus platinum lead to long-term complete remission of metastatic nasopharyngeal carcinoma.[12,17] As first-line therapy, gemcitabine plus platinum has a response rate (RR) of 52–73%, median progression-free survival (mPFS) of 7–10.6 months and mOS of 15–29 months for recurrent/metastatic nasopharyngeal carcinoma.[12,17] The main adverse reactions reported are Grades 3/4 leukopenia (29–60%) and thrombocytopenia (13–20%). Those adverse reactions are well tolerated, and the patients' lives could be restored to normal after symptomatic measures, such as bone marrow stimulation and pro-platelet therapy.

Docetaxel is a specific drug that binds to β-tubulin to block the G2 and M phases, which, as a result, interferes with cell division and proliferation. It has been reported to be effective for locally advanced or metastatic nasopharyngeal carcinoma,[18-21] with a RR of 22–65%, mPFS of 5.6–7.9 months and mOS of 12–16 months. The main adverse reactions were Grades 3-4 leukopenia (15%) and rare peripheral nerve damages.

Although studies have demonstrated the safety and efficacy of the gemcitabine plus platinum regimen and the docetaxel plus platinum regimen for metastatic nasopharyngeal carcinoma, there is no consensus on which regimen is superior.[22-24] This study was conducted with the objective of comparing the efficacy and safety of these two regimens as first-line therapies for distal metastatic nasopharyngeal carcinoma. The findings of this study will help determine the more suitable first-line therapy for patients with metastatic nasopharyngeal carcinoma.

METHODS

Study design and participants

In this open-label, parallel-arm study, nasopharyngeal carcinoma patients who were newly diagnosed with distant metastasis and treated at the Fourth Affiliated Hospital of Guangxi Medical University, Liuzhou, China, between January 2011 and December 2015 were randomized into two treatment groups in a 1:1 ratio. This study was approved by the local ethics committee and is a preliminary study of the "S-1 (AiYi) maintenance therapy for metastatic nasopharyngeal carcinoma patients that received gemcitabine plus platinum chemotherapy" project (Ethical approval No.: PJK2016001, Chinese Clinical Trial Registry No.: ChiCTR-IOR-16007939). All patients enrolled provided written consent for participation.

The inclusion criteria were as follows: (1) pathological diagnosis with non-keratinizing (differentiated and undifferentiated) squamous cell carcinoma of the nasopharynx; (2) new diagnosis of distant metastases after induction chemotherapy combined with concurrent chemoradiotherapy, concurrent chemoradiotherapy alone, concurrent chemoradiotherapy with adjuvant chemotherapy or radiotherapy alone; (3) 18–70 years of age; (4) ECOG score of 0–1; (5) at least one measurable lesion based on the response evaluation criteria in solid tumors version 1.1 (RECIST 1.1); and (6) laboratory results meeting the following criteria: neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and liver (glutamic-pyruvic transaminase, aspartate aminotransferase, and bilirubin) and renal (creatinine and urea nitrogen) function indicators within 1.5 times the upper limits of normal (ULN).

The exclusion criteria were as follows: (1) any other malignancies; (2) life-threatening medical problems or severe infections; (3) metastases to the central nervous system; (4) peripheral neuropathy; (5) metastases limited to the bones; (6) allergies to any component contained in gemcitabine, docetaxel or platinum; or (7) active hemorrhage or coagulation dysfunction (partial thromboplastin time >1.5 × ULN or international normalized ratio >1.5). Female patients who were either pregnant/lactating or

potentially pregnant (not using contraception) were also excluded.

Randomization

Eligible patients were allocated to the gemcitabine plus platinum group (gemcitabine group; n = 60) or the docetaxel plus platinum group (docetaxel group; n = 60) using simple randomization. Participants picked a sealed envelope that randomly assigned them to either group.

Intervention

Patients in the gemcitabine group received gemcitabine 1000 mg/m^2/d intravenously (IV) for >30 min (days 1 and 8). Patients in the docetaxel group received docetaxel 75 mg/m^2/d IV for 1 h (day 1). The choice of platinum for the two groups was nedaplatin 75 mg/m^2/d, IV (day 1), cisplatin 75 mg/m^2/d IV (day 1) or carboplatin (area under the curve [AUC] set as 5) IV (day 1). The duration of one cycle was 21 days, and all patients initially received 4–6 cycles of first-line therapy unless there was disease progression or intolerable adverse reaction. Up to six cycles of therapy, patients were evaluated immediately and monitored for disease progression without a maintenance therapy.

Efficacy evaluation was performed every two cycles after initial treatment, which included physical examination, blood routine, blood biochemistry tests and imaging examinations such as B-type ultrasound, spiral computed tomography (CT) and magnetic resonance imaging (MRI).

Patients with liver and lung diseases did not undergo local treatment for metastatic lesions. Antitumor efficacy evaluation was based on RECIST 1.1. Adverse reactions were evaluated using the National Cancer Institute–Common Terminology Criteria Adverse Events Version 3.0 (NCI-CTC3.0). Evaluation was performed every 2 weeks. After treatments, follow-up was performed every 3 months for clinical symptoms, adverse reactions (neutropenia, leukopenia, anemia, thrombocytopenia, vomiting, elevated ALT, elevated AST, elevated creatinine, peripheral nerve damage, etc.), and hematological and imaging examinations.

Outcomes

Primary outcomes were progression-free survival (PFS) and overall survival (OS), and secondary outcomes were short-term efficacy [response rate (RR) and disease control rate (DCR)] and safety. PFS was defined as the time from the first day of treatment to the day of either disease progression, cancer-related death, or unexplained deaths during treatment. PFS was censored at the end of follow-up if no disease progression was found. OS was defined as the time from the first day of treatment to the day of death due to any causes. OS was censored at the end of follow-up if no death occurred. RR was defined as the proportion of patients whose tumors were reduced to a certain size for a certain time, including complete remission (CR) and partial remission (PR). DCR was defined as the proportion of patients whose tumors were reduced for a certain time, including CR, PR, and stable disease (SD) cases.

Adverse events

Symptomatic therapies such as antiemetic, gastric protection, and liver protection were given during chemotherapy, as per routine practice. Hydration and alkalinization were administered during cisplatin treatment. Leukopenia and thrombocytopenia during the treatment were treated with hematopoietic colony-stimulating factors (CSFs) and recombinant human thrombopoietin (rhTPO).

The dose of gemcitabine or docetaxel was reduced by 20% when either Grades 3-4 hematological/non-hematological toxicity occurred. If severe neutropenia appeared, the use of gemcitabine was either reduced on day 8, delayed for 7 days or withdrawn. In the case of renal dysfunction, the dose of platinum was calculated based on creatinine clearance unless platinum treatment needed to be terminated.

Follow-up

Patients were followed-up by telephone annually for 3 years. Hospital visits were recommended as needed, but no clinical examinations were offered during the telephonic follow-up.

Statistical analysis

In the current study, PFS was the primary point for increase more than 10% as margin. A 0.05 alpha and a 0.20 beta value were used. After accounting for an estimated 10% dropout, the number of participants in each group was found to be 60 (N = 120). SPSS 20.0 (IBM, Armonk, NY, USA) was used for statistical analyses. The Kolmogorov-Smirnov test was used to analyze continuous data for normal distribution. Normally distributed continuous data were presented as means ± standard deviations and analyzed using the Student t-test, while non-normally distributed continuous data were presented as median (range) and analyzed using the Mann–Whitney U test. Categorical variables were presented as frequencies and analyzed using the Chi-square test. Survival was analyzed using the Kaplan–Meier method and the log-rank test. The Cox multivariable analysis was used to determine the factors independently associated with survival. Differences with

two-sided *P* values of < 0.05 were considered statistically significant.

RESULTS

Characteristics of the patients

Of the 120 patients included, 7 withdrew from the study after randomization but before treatment initiation; therefore, the study reports the efficacy and adverse reactions of 113 patients (56 in the gemcitabine group and 57 in the docetaxel group) [Figure 1]. The median age was 51 years (30–68 years), and the male to female ratio was 2:1 (male: $n = 77$; female: $n = 36$). Table 1 shows the baseline characteristics of the patients. A total of 605 chemotherapy cycles were completed for the 113 patients, with 2–6 cycles for each patient [Table 2]. The median number of chemotherapy cycles was 6 in both groups.

Survival

All patients were followed-up in the clinics for 1 year (up to December 30th, 2016), and then through phone calls for 3 years during which period no clinical follow-up was mandated. The follow-up rate was 95%, and the median follow-up period was 15.8 (6.5-35.7) months. Twenty-six patients died in the gemcitabine group and 40 died in the docetaxel group. All the deaths in this study were disease related. Kaplan–Meier analysis showed that mPFS and mOS were both significantly longer in the gemcitabine group compared with the docetaxel group (gemcitabine vs. docetaxel, 9.7 vs. 7.8 months, $P < 0.05$; 20.6 vs. 16.8 months, $P < 0.01$, respectively) [Figure 2]. RR (CR + PR) was also significantly higher in the gemcitabine group than in the docetaxel group (71.4% vs. 52.6%, $P < 0.05$). DCR (CR + PR + SD) was higher in the gemcitabine than in the docetaxel group, although the difference was not statistically significant (85.7% vs. 75.4%, $P > 0.05$) [Table 3].

Adverse events

Chemotherapy-related toxic and adverse events are listed in Table 4. No significant differences were found in Grades 1-2 gastrointestinal reactions, bone marrow suppression, and liver and kidney dysfunction between the two groups. No significant differences were found in Grades 3-4 gastrointestinal reactions between the two groups (all $P > 0.05$). No significant difference was found in Grades 3-4 bone marrow suppression between the gemcitabine and docetaxel groups (all $P > 0.05$). No Grades 2–4 peripheral neurotoxicity was observed. However, the docetaxel group showed significantly more severe Grade 1 peripheral nerve damage than the gemcitabine group ($P < 0.05$).

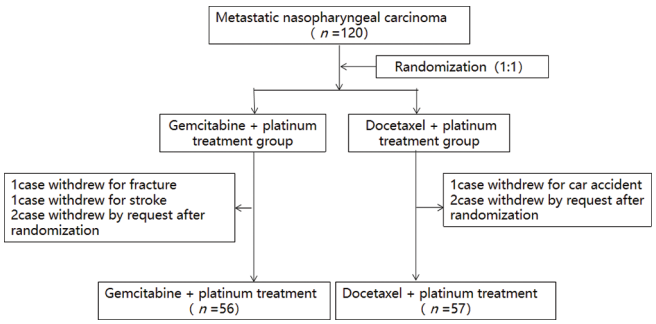

Figure 1: Study flowchart

Univariate analyses

Univariable analyses indicated that time to disease progression, liver metastasis, number of involved organs, and grouping were associated with both mPFS [Table 5] and mOS [Table 6], while gender, age, previous treatment, ECOG score and lung metastasis were not associated with them. Patients with time to disease progression after radical treatment (TTP) of >1 year had significantly better mPFS and mOS than those with TTP of <1 year (mPFS: 9.9 vs. 4.5 months, $P < 0.001$; mOS: 19.9 vs. 12.5 months, $P < 0.001$). Patients without liver metastasis had significantly superior mPFS and mOS over those with liver metastasis (mPFS: 9.8 vs. 5.8 months, $P < 0.01$; mOS: 21.3 vs. 15.6 months, $P < 0.001$). Patients with single organ

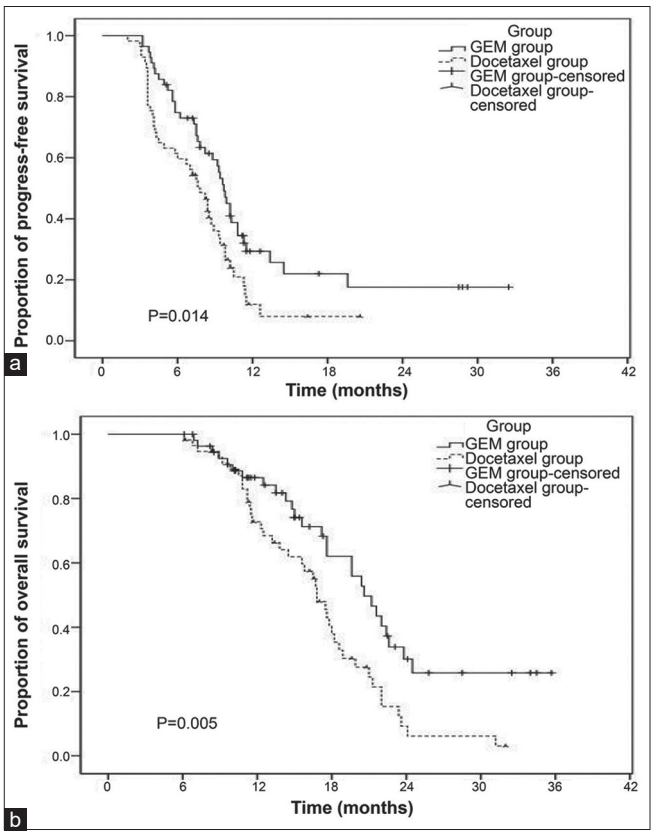

Figure 2: (a) Progression-free survival analysis of the gemcitabine and docetaxel groups. (b) Overall survival analysis of the gemcitabine and docetaxel groups. Kaplan–Meier survival analysis

Table 1: Characteristics of study participants

Characteristic	Total, *n* (%)	Gemcitabine + platinum (*n*=56), *n* (%)	Docetaxel + platinum (*n*=57), *n* (%)	*P*
Median age (years)	51 (30-68)	48.5 (30-68)	54 (33-68)	0.157
Gender				
Male	77 (68.1)	39 (69.6)	38 (66.7)	0.734
Female	36 (31.9)	17 (30.4)	19 (33.3)	
Previous treatment				
IC + CCRT	75 (66.4)	33 (58.9)	42 (73.7)	0.424
CCRT	26 (23.0)	16 (28.6)	10 (17.5)	
CCRT + AC	7 (6.2)	4 (7.1)	3 (5.3)	
IMRT	5 (4.4)	3 (5.4)	2 (3.5)	
Time to disease progression (years)				
≤1	40 (35.4)	16 (28.6)	24 (42.1)	0.133
>1	73 (64.6)	40 (71.4)	33 (57.9)	
ECOG score				
0	6 (5.5)	3 (5.4)	3 (5.3)	0.982
1	107 (94.5)	53 (94.6)	54 (94.7)	
Organ involved				
Liver	8 (7.1)	5 (8.9)	3 (5.3)	0.542
Lung	16 (14.2)	9 (16.1)	7 (12.3)	
Nonregional lymph nodes	1 (0.9)	1 (1.8)	0	
Multiple sites	88 (77.8)	41 (73.2)	47 (82.4)	
Organ involvement				
Single organ	24 (21.2)	14 (25.0)	10 (17.5)	0.333
Multiple organs	89 (78.8)	42 (75.0)	47 (82.5)	
Liver metastasis				
Yes	62 (54.9)	29 (51.8)	33 (57.9)	0.514
No	51 (45.1)	27 (48.2)	24 (42.1)	
Lung metastasis				
Yes	73 (64.6)	34 (60.7)	39 (68.4)	0.392
No	40 (35.4)	22 (39.3)	18 (31.6)	
Platinum selection				
NDP	96 (85.0)	46 (82.1)	50 (87.7)	0.708
DDP	5 (4.4)	3 (5.4)	2 (3.5)	
CBP	12 (10.6)	7 (12.5)	5 (8.8)	

IC – Induction chemotherapy; CCRT – Concurrent chemoradiotherapy; AC – Adjuvant chemotherapy; IMRT – Intensity modulated radiotherapy; NDP – Nedaplatin; DDP – Cisplatin; CBP – Carboplatin; ECOG – Eastern cooperative oncology group

Table 2: Number of cycles of chemotherapy in the study participants

Cycles of chemotherapy	Therapeutic regimen	
	Gemcitabine + platinum (*n*=56)	Docetaxel + platinum (*n*=57)
2	2	6
3	0	2
4	5	11
5	1	2
6	48	36

involvement had significantly better mPFS and mOS than those with multiple organ involvements (mPFS: 13.4 vs. 7.8 months, $P < 0.001$; mOS: 23.4 vs. 17.2 months, $P < 0.001$). Patients receiving gemcitabine plus platinum as first-line therapy had significantly superior mPFS and mOS than those receiving docetaxel plus platinum treatment (mPFS: 9.7 vs. 7.8 months, $P < 0.05$; mOS: 20.6 vs. 16.8 months, $P < 0.0$).

Univariable analyses indicated that docetaxel group reduced the mPFS and mOS in metastatic nasopharyngeal carcinoma patients that had TTP of <1 year, multiple organ involvements and liver metastasis (all $P < 0.05$) [Figures 3-4].

Cox multivariate analysis

Results from the Cox multivariable analysis indicated that TTP, ECOG score, liver metastasis, number of involved organs and grouping were independently associated with mOS, while TTP, liver metastasis, lung metastasis, number of involved organs, and grouping were independently associated with mPFS. Gender and age were not correlated with either mPFS or mOS. Patients with TTP of >1 year had significantly better mPFS and mOS than those with TTP of <1 year ($P < 0.001$). Patients without liver metastasis had significantly superior mPFS and mOS over those with liver metastasis ($P < 0.001$ and $P < 0.05$). Patients with single organ involvement had significantly better mPFS and mOS than those with multiple organ involvements ($P < 0.05$ and $P < 0.01$). Patients receiving gemcitabine plus platinum as first-line treatment had significantly superior mPFS and mOS over those receiving docetaxel plus platinum ($P < 0.001$ and $P < 0.05$). Patients with ECOG score of 0 point had better prognosis than those with ECOG score of 1 point ($P < 0.05$). Patients with lung metastasis had better mPFS than those without lung metastasis ($P < 0.05$) [Table 7].

Table 3: Comparison of efficacy between the gemcitabine and docetaxel groups

	Therapeutic regimen (*n*=113)		*P*
	Gemcitabine + platinum (*n*=56), *n* (%)	Docetaxel + platinum (*n*=57), *n* (%)	
Treatment response			
CR	1 (1.8)	1 (1.8)	0.21
PR	39 (69.6)	29 (50.9)	
SD	9 (16.1)	13 (22.8)	
PD	7 (12.5)	14 (24.6)	
RR	40 (71.4)	30 (52.6)	0.04
DCR	49 (87.5)	43 (75.4)	0.099

CR – Complete remission; PR – Partial remission, SD – Stable disease; PD – Progressive disease; RR – Response rate; DCR – disease control rate

Table 4: Toxicity and adverse reactions between the gemcitabine and docetaxel groups, *n* (%)

Toxicity (grade)	Gemcitabine + platinum (*n*=56), *n* (%)	Docetaxel + platinum (*n*=57), *n* (%)	*P*
Leucopenia			
0	0	0	0.483
1-2	40 (71.4)	44 (77.2)	
3-4	16 (28.6)	13 (22.8)	
Anemia			
0	3 (5.4)	2 (3.5)	0.633
1-2	53 (94.6)	55 (96.5)	
3-4	0	0	
Thrombocytopenia			
0	0	2 (3.5)	0.159
1-2	49 (87.5)	52 (91.1)	
3-4	7 (12.5)	3 (5.4)	
Vomiting			
0	0	0	0.775
1-2	51 (91.1)	51 (89.5)	
3-4	5 (8.9)	6 (10.5)	
Renal damage			
0	52 (92.9)	54 (94.7)	0.679
1	4 (7.1)	3 (5.3)	
2-4	0	0	
Liver function damage			
0	48 (85.7)	50 (87.7)	0.753
1	8 (14.3)	7 (12.3)	
2-4	0	0	
Sensory neuritis			
0	55 (98.2)	50 (87.7)	0.03
1	1 (1.8)	7 (12.3)	
2-4	0	0	

DISCUSSION

The findings of this randomized study indicate that gemcitabine combined with platinum as first-line treatment is superior to docetaxel combined with platinum regarding RR, mPFS and mOS. No differences were observed in adverse reactions.

Few randomized controlled studies have previously compared gemcitabine plus platinum with docetaxel plus platinum as first-line treatment in metastatic nasopharyngeal carcinoma. One such study was conducted by Jin *et al*.,[25] who found that patients receiving gemcitabine plus platinum had a RR of 71.1%, a DCR of 78%, a mPFS of 6.6 months, and a mOS of 21.5 months, while those with docetaxel plus platinum had a RR of 61.7%, a DCR of 68%, a mPFS of 5.5 months, and a mOS of 21 months. The study found that gemcitabine plus platinum had a better short-term efficacy, but those differences were not statistically significant.

In the present study, mPFS and mOS were significantly higher in the gemcitabine group than those in the docetaxel group (9.7 vs. 7.8 months, and 20.6 vs. 16.8 months, respectively). RR and DCR in the gemcitabine group were significantly higher than those in the docetaxel group (71.4% vs. 52.6%, 87.5% vs. 75.4%). Compared to the study by Jin *et al.,*[25] the RR of the docetaxel group in the present study was lower than that in their paclitaxel + cisplatin (TP) group, but the DCR of the gemcitabine group in this study was higher than that of their gemcitabine + cisplatin (GP) group. mPFS in the gemcitabine group from our study is higher than that in the GP group from the study by Jin *et al*., while mOS in the docetaxel group from our study was lower than that in their TP group. Our results are consistent with

Table 5: Univariate analysis of the median progression-free survival in patients with metastatic nasopharyngeal carcinoma

Characteristic	*n* (%)	mPFS	95% CI	HR	*P*
Total	113 (100)	8.2			
Gender					
Male	77 (68.1)	9.2	7.968-10.432	0.855	0.494
Female	36 (31.9)	7.6	6.196-9.004		
Age (years)					
≤50	55 (48.7)	7.8	6.276-9.324	0.984	0.940
>50	58 (51.3)	9.3	8.094-10.506		
Previous treatment					
Neoadjuvant or adjuvant chemotherapy					
Yes	82 (72.6)	7.8	6.804-8.796	0.664	0.100
No	31 (27.4)	9.8	8.858-10.742		
Time to disease progression (years)					
≤1	40 (35.4)	4.5	3.510-5.490	3.020	0.000
>1	73 (64.6)	9.9	8.941-10.859		
ECOG score					
0	6 (5.3)	12.6	9.447-15.753	0.573	0.266
1	107 (94.7)	8.4	6.944-9.854		
Organ involvement					
Single organ	24 (21.2)	13.4	9.918-16.882	0.29	0.000
Multiple organs	89 (78.8)	7.8	6.920-8.680		
Liver metastasis					
Yes	62 (54.9)	5.8	3.762-7.838	0.555	0.007
No	51 (45.1)	9.8	8.858-10.742		
Lung metastasis					
Yes	73 (64.6)	7.8	6.831-8.769	0.688	0.108
No	40 (35.4)	9.4	8.483-10.317		
Grouping					
Gemcitabine + platinum	56 (49.6)	9.7	8.844-10.556	0.585	0.014
Docetaxel + platinum	57 (50.4)	7.8	6.447-9.153		

mPFS – Median progression-free survival; CI – Confidence interval; HR – Hazards ratio; ECOG – Eastern cooperative oncology group

Table 6: Univariate analysis of the median overall survival in patients with metastatic nasopharyngeal carcinoma

Characteristic	*n* (%)	mOS	95% CI	HR	*P*
Total	113 (100)	18.0			
Gender					
Males	77 (68.1)	18.0	16.654-19.346	0.837	0.483
Females	36 (31.9)	17.5	12.593-22.407		
Age (years)					
≤50	55 (48.7)	16.7	12.834-20.566	1.187	0.479
>50	58 (51.3)	18.2	17.205-19.195		
Previous treatment					
Neoadjuvant or adjuvant chemotherapy					
Yes	82 (72.6)	17.6	16.835-18.365	0.633	0.101
No	31 (27.4)	21.3	18.136-24.464		
Time to disease progression (years)					
≤1	40 (35.4)	12.5	9.877-15.123	2.734	0.000
>1	73 (64.6)	19.9	21.939		
ECOG score					
0	6 (5.3)	20.6	16.876-24.324	0.817	0.694
1	107 (94.7)	17.6	16.109-19.091		
Organ involvement					
Single organ	24 (21.2)	23.4	18.828-27.972	0.302	0.001
Multiple organs	89 (78.8)	17.2	16.141-18.259		
Liver metastasis					
Yes	62 (54.9)	15.6	13.509-17.691	0.428	0.001
No	51 (45.1)	21.3	20.099-22.502		
Lung metastasis					
Yes	73 (64.6)	17.6	16.064-19.136	0.918	0.733
No	40 (35.4)	19.6	15.972-23.228		
Grouping					
Gemcitabine + platinum	56 (49.6)	20.6	17.966-23.234	0.503	0.005
Docetaxel + platinum	57 (50.4)	16.8	15.504-18.096		

mOS – Median overall survival; CI – Confidence interval; HR – Hazards ratio; ECOG – Eastern cooperative oncology group

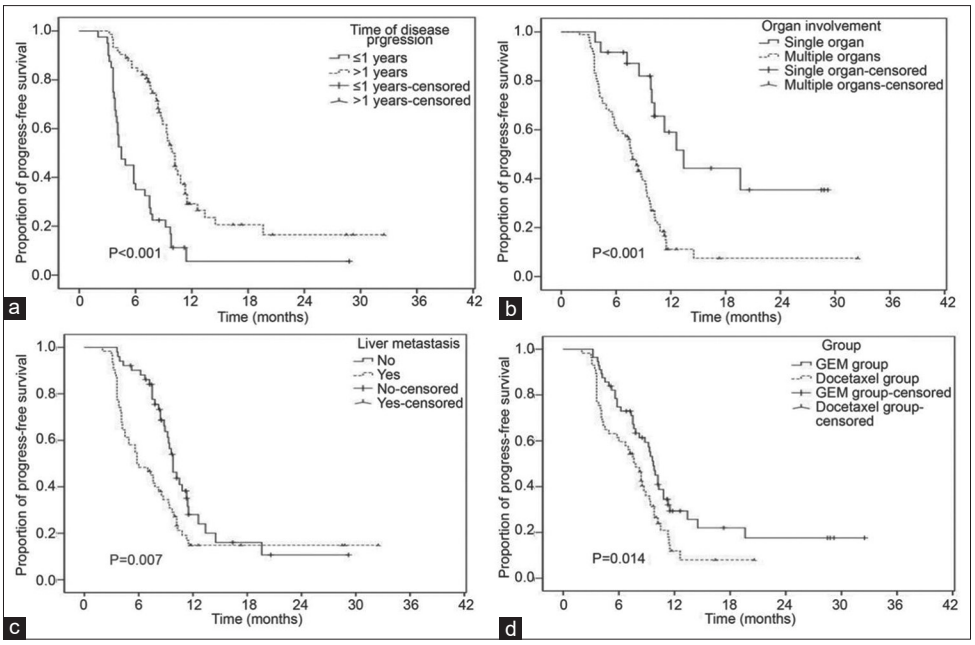

Figure 3: Univariable analysis of the median progression-free survival between the gemcitabine and docetaxel groups. (a) Disease progression >1 year and versus <1 year. (b) Single organ involvement vs. multiple organ involvement. (c) Liver metastasis vs. without liver metastasis. (d) Gemcitabine group versuss. docetaxel group. Kaplan–Meier survival analysis

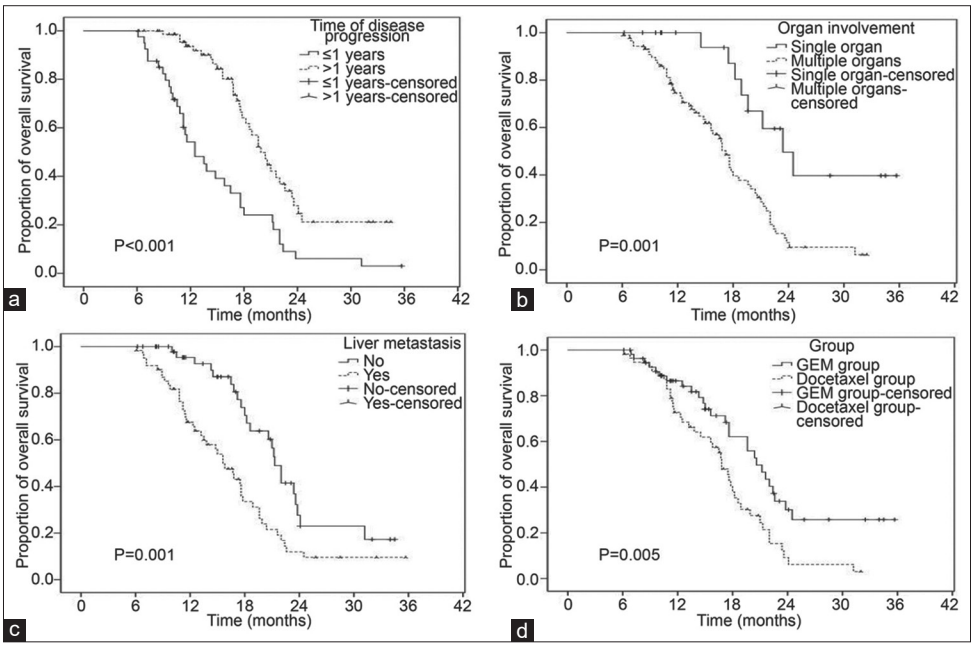

Figure 4: Univariable analysis of median overall survival between the gemcitabine and docetaxel groups. (a) Time to disease progression >1 year versus <1 year. (b) Single organ involvement vs. multiple organ involvement. (c) Liver metastasis versuss without liver metastasis. (d) Gemcitabine group versus docetaxel group

the findings of Zhang *et al*.[12] and Hsieh *et al*.,[17] wherein use of gemcitabine + cisplatin as first-line treatment was found to prolong mPFS for metastatic nasopharyngeal carcinoma. Differences between study findings could be because of disparities in patient characteristics, as Jin *et al*. included recurrent and elderly patients, while the current study did not.

The main adverse reactions in the two chemotherapy regimens used in the present study were bone marrow suppression and gastrointestinal reactions. No significant liver or kidney dysfunction was observed, demonstrating that both regimens were well tolerated. Nevertheless, due to the biological characteristics of the drugs, Grade 1 peripheral nerve damage was more frequently observed

Table 7: Multivariate cox regression analysis for the patients with metastatic nasopharyngeal carcinoma

Characteristic	All patients (*n*=113)					
	mOS			mPFS		
	HR	95%CI	*P*	HR	95%CI	*P*
Gender						
Males	1.517	0.887-2.594	0.128	1.448	0.896-2.340	0.131
Females						
Age (years)						
≤50	0.879	0.478-1.616	0.678	1.072	0.624-1.840	0.802
>50						
Time to disease progress						
≤1 year	0.372	0.214-0.646	0.000	0.307	0.185-0.511	0.000
>1 year						
ECOG score						
0	0.262	0.074-0.921	0.037	0.602	0.200-1.813	0.367
1						
Organ involvement						
Single	2.478	1.095-5.609	0.029	2.632	1.315-5.267	0.006
Multiple						
Lung metastasis						
Yes	1.309	0.787-2.178	0.299	1.736	1.073-2.809	0.025
No						
Liver metastasis						
Yes	3.449	1.715-6.934	0.001	1.891	1.122-3.185	0.017
No						
Grouping						
Gemcitabine + platinum	2.650	1.469-4.783	0.001	1.768	1.052-2.973	0.032
Docetaxel + platinum						

mPFS – Median progression-free survival; mOS – Median overall survival; CI – Confidence interval; HR – Hazards ratio; ECOG – Eastern cooperative oncology group

in the docetaxel group than that in the gemcitabine group (12.3% vs. 1.8%). As the treatment continued, hand and foot numbness gradually and significantly reduced. No significant differences were found in Grades 3-4 adverse reactions between the two groups, similar to the observations of Jin *et al*.[25]

The multivariable analysis indicated that TTP of <1 year, multiple organ involvement, liver metastasis, and grouping were independently associated with the prognosis of patients with metastatic nasopharyngeal carcinoma, as supported by Li *et al*.[8] and Toumi *et al*.[26]

Few limitations of this study were that the sample size was relatively small, the patients were from a single institution, biochemical markers of disease progression were not assessed, and the follow-up period was short. Future studies should be carried out with more patients from multiple institutions and with longer follow-up.

CONCLUSION

This study found that gemcitabine + platinum is more effective than docetaxel + platinum in the treatment of patients with metastatic nasopharyngeal carcinoma; both regimens are well tolerated. Further studies are required to validate the findings of this study.

Ethical considerations

This study was approved by the local ethics committee and is a preliminary study of "S-1 (AiYi) maintenance therapy for metastatic nasopharyngeal carcinoma patients that received gemcitabine plus platinum chemotherapy" project (Reference no.: PJK2016001; Chinese Clinical Trial Registry No.: ChiCTR-IOR-16007939). The study was conducted in accordance with the Declaration of Helsinki, 2013. All participants provided written informed consent at the time of enrollment.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

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Conflicts of interest

There are no conflicts of interest.

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