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ORIGINAL RESEARCH

Bevacizumab versus placebo in combination with paclitaxel and carboplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase II trial

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Background: The value of anti-angiogenesis antibody therapy in recurrent or metastatic nasopharyngeal carcinoma (R/M NPC) remains unknown. We carried out a phase II study to evaluate the addition of bevacizumab to paclitaxel plus carboplatin in R/M NPC.

Materials and methods: A total of 80 patients with previously untreated R/M NPC were randomly assigned (1 : 1) to CPB or CP groups to receive carboplatin (area under the curve 6) and paclitaxel (175 mg/m^2) intravenously every 3 weeks for a maximum of six cycles in combination with or without bevacizumab (7.5 mg/kg), respectively. The primary endpoint was progression-free survival (PFS) as per investigators, and the secondary endpoints were PFS as per independent review committee (IRC), overall survival (OS), objective response rate (ORR), and safety. This study was registered with ClinicalTrials.gov (NCT02250599).

Results: The median PFS as per investigators was 7.5 months [95% confidence interval (CI), 6.53-8.45 months] in the CPB group and 6.5 months (95% CI, 5.53-7.52 months) in the CP group ($P = 0.148$), which were similar to IRC-assessed PFS. The median OS was also alike between CPB and CP arms (21.0 versus 24.7 months; $P = 0.326$). ORRs were 87.2% and 72.5%, respectively ($P = 0.105$). However, the tumor-shrinking rate was higher in the CPB arm than in the CP arm ($P = 0.035$). No differences in grade 3 or higher adverse events between the groups were observed.

Conclusions: Addition of bevacizumab to paclitaxel plus carboplatin as first-line treatment did not prolong PFS and OS in patients with R/M NPC but improved tumor-shrinking rate. These results indicated that bevacizumab plus chemotherapy might be an optional choice for NPC with heavy tumor load or those pursuing short-term efficacy in neoadjuvant and concurrent chemotherapy.

Key words: nasopharyngeal carcinoma, bevacizumab, carboplatin, paclitaxel, first-line

INTRODUCTION

Nasopharyngeal carcinoma is characterized by its unbalanced geographic distribution. About 80% of new cases are in East and Southeast Asia,[1] with the highest incidence of 20-30 per 100 000 in China.[2,3] More than 15% of patients presented distant metastases at the primary diagnosis,[4,5] and ∼20% of early-stage or locoregionally advanced patients developed local recurrence or distant metastases after potentially curative radiotherapies with or without chemotherapy.[6] The outcome for patients with recurrent or primary metastatic nasopharyngeal carcinoma was very poor.

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Due to a randomised, phase III trial, the gemcitabine plus cisplatin regimen has been established as the standard first-line treatment for patients with recurrent or metastatic disease.[7] However, due to the high probability of nausea or appetite loss, this regimen sometimes may affect the patients' quality of life. In previous studies, the combination of paclitaxel and carboplatin demonstrated well-tolerable toxicity profile and promising clinical activity, with an objective response rate (ORR) of ∼60%, which was similar to gemcitabine plus cisplatin.[8-10] Furthermore, paclitaxel plus carboplatin regimen seems more convenient to administrate in clinical practice, with which patients do not require to receive chemotherapy on day 1 and 8. Notably, without maintenance treatment after four to six cycles of platinum-based chemotherapy, most patients would suffer disease progression, with a short median progression-free survival (PFS). Therefore, more effective treatment strategies are urgently needed for this patient population.

In recent years, molecularly targeted drugs have been added to the cytotoxic chemotherapy regimens to seek better survival of patients with other advanced tumor types.[11-13] Among them, anti-angiogenesis is a potentially effective target. However, none of these drugs have been approved for patients with recurrent or metastatic nasopharyngeal carcinoma (R/M NPC). Vascular endothelial growth factor (VEGF) is a constitutively active angiogenic molecule during tumor growth and metastasis.[14,15] VEGF overexpression presents in 60%-67% of nasopharyngeal carcinoma and is related to higher recurrence rate and lower overall survival (OS).[16,17] Several early clinical trials on anti-angiogenesis agents, including multi-targeted tyrosine kinase inhibitors against VEGF receptor (VEGFR) (sunitinib, pazopanib, axitinib, and sorafenib), have shown promising results in patients with locally advanced or metastatic nasopharyngeal carcinoma.[18-21] However, the efficacy of monotherapy of anti-VEGF/VEGFR is limited, with the ORR ranging from 6.1% to 20%. Better efficacy has been seen when anti-angiogenesis drugs were combined with chemotherapy or radiotherapy. We have previously reported the promising activity of sorafenib, a multi-kinase inhibitor against VEGFR, combined with cis-platinum (DDP) and 5-fluorouracil (5-FU) in a phase II study of nasopharyngeal carcinoma, with a feasible efficacy (ORR of 77.8% and median PFS of 7.2 months) and tolerable toxicity.[22] However, all these studies were single-arm trials focusing only on multi-kinase inhibitors. The efficacy and safety of anti-angiogenesis antibody therapy in R/M NPC remain unknown.

Bevacizumab, a recombinant humanized monoclonal antibody against VEGF, was chosen in combination with platinum-based chemotherapy because it has improved response rate and PFS in phase III trials of advanced non-small-cell lung cancer and colorectal cancer.[23,24] Indeed, a phase II study also has revealed promising efficacy of bevacizumab, when combined with chemo-radiation in patients with locally advanced nasopharyngeal carcinoma.[25] However, we noted that there were no randomised controlled trials to assess whether bevacizumab could safely improve the efficacy of paclitaxel plus carboplatin as the first-line treatment for R/M NPC. Whether the lack of a controlled arm affected the reported efficacy or toxicity is unknown. Therefore, we conducted this multicentre, randomised, open-label, phase II study in patients with previously untreated, recurrent, or metastatic nasopharyngeal carcinoma to investigate the efficacy and safety of bevacizumab in combination with chemotherapy.

MATERIALS AND METHODS

Study design and patients

This is a multicentre, randomised, open-label, phase II clinical trial conducted at nine hospitals in China. Patients with histologically confirmed R/M NPC that was unsuitable for local treatment after previous curative treatment at diagnosis were recruited. Other inclusion criteria included that patients had (i) an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, (ii) age 18 years or older, (iii) had an estimated life expectancy of 12 weeks or more, and (iv) at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Patients were excluded if they had (i) received any previous systematic chemotherapy for recurrent or metastatic disease, (ii) history of hemoptysis (more than one-half teaspoon of bright red blood in 3 months before enrolment), (iii) tumors invading major blood vessels, (iv) central nervous system metastases, and (v) uncontrolled hypertension. Full eligibility criteria are listed in the protocol (Supplementary Appendix, available at https://doi.org/10.1016/j.esmoop.2021.100313).

This study was approved by the Ethics Committee of each participating institution and was done in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonization. All patients provided written informed consent.

Randomisation and masking

Eligible patients were randomised (1 : 1) to CPB or CP group by Central Random System to receive carboplatin (area under the curve 6) and paclitaxel (175 mg/m^2) intravenously on day 1 and once every 3 weeks for a maximum of six cycles with (CPB) or without (CP) intravenously injecting bevacizumab (7.5 mg/kg) on day 1 of each cycle. In the CPB arm, bevacizumab (7.5 mg/kg) was maintained on day 1 of every 3 weeks after the finish of chemotherapy until radiographic progression, intolerable toxicity, investigator decision, withdrawal of consent, or death. Random assignment was stratified by sex. Masking was not done in this trial. However, the Independent Review Committee (IRC) and statisticians were blinded.

Study procedures

Tumor responses were assessed by investigators as well as IRC every two cycles (6 weeks) during the chemotherapy phase and the maintenance period according to RECIST 1.1.

After withdrawal, patients were followed up once every 3 months until disease progression, withdrawal of consent, lost to follow-up, or death. Adverse events (AEs) were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Outcomes

The primary endpoint of this study was PFS, defined as the time from randomisation to documented disease progression assessed by investigators or death from any cause, whichever occurred first. Secondary endpoints included PFS assessed by IRC, OS (defined as the time from randomisation to the time of death), ORR [defined as the percentage of patients who had a best overall response of complete response (CR) or partial response (PR)], disease control rate [DCR, defined as the percentage of patients who achieved stable disease (SD) or objective response], and safety.

Statistical analysis and sample size calculation

The hypothesis of this study was that the combination of bevacizumab with CP is superior to CP regarding PFS. Based on previous reports, we assumed that the PFS was 9 months in the CPB group and 6 months in the CP group. With an enrolment period of 1 year and a follow-up period of 9 months, and by taking 10% dropout rate into account, we predicted that we would need a total of 80 participants to achieve 60% power and a one-sided type I error of 5% significance level and hazard ratio (HR) of 0.67.

The efficacy analyses were carried out in the intent-to-treat populations which included all randomly assigned patients. The safety analysis population comprised all patients who underwent randomisation and received at least one dose of the study medication. Kaplan—Meier methods were used to assess median PFS and OS with 95% confidence interval (CI). A stratified Cox regression analysis was used to estimate HRs for PFS and OS with 95% CIs; a log-rank test was used to calculate the *P* value. ORRs and DCRs were compared using the Mantel—Haenszel chi-square test. We further carried out subgroup analyses to explore the effect of the treatment varied according to sex, age, metastasis category, number of liver metastases, and radical chemoradiotherapy history. Analyses were conducted with SPSS software, version 23.0 (IBM Corp., Armonk, NY), and all statistical testing was two-sided. This study is registered at ClinicalTrials.gov, number NCT02250599.

RESULTS

Patient characteristics

Between August 2014 and March 2016, a total of 86 eligible patients from nine hospitals in China were randomly assigned to the CPB group ($n = 43$) and CP group ($n = 43$) at 1 : 1 ratio. One patient in the CPB group and three patients in the CP group withdrew consent before the allocated treatment. Eighty-two (95.3%) patients received study medication treatment. Besides, three patients in the CPB group just received one cycle of study treatment without efficacy evaluation. Overall, 79 patients were included in the efficacy analysis, and 82 patients were included in the safety analysis (Figure 1).

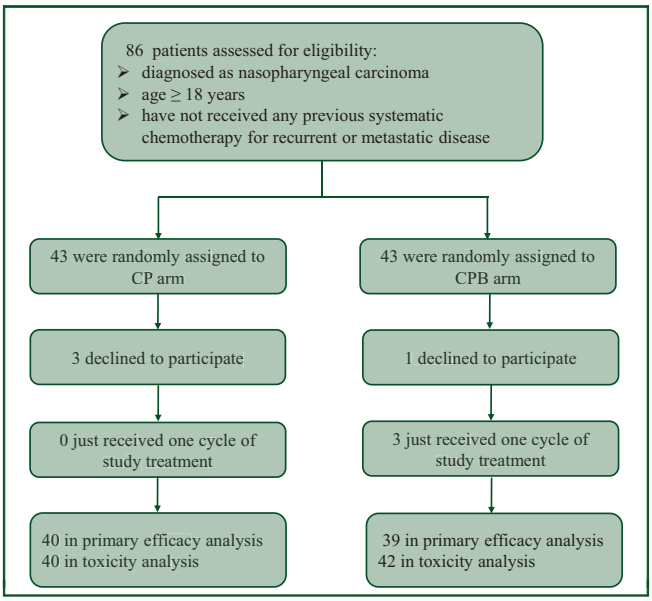

Figure 1. Trial profile.
The cut-off date for progression-free survival was 31 December 2020. All patients randomly assigned to study group were included in the intention-to-treat analysis according to their assigned group. All patients who received at least one dose of study treatment were included in the safety analysis according to the regimen they actually received.
CP, carboplatin and paclitaxel; CPB, carboplatin, paclitaxel, and bevacizumab.
[a] None were on treatment at the time of analysis.

Baseline characteristics were comparable between the two groups (Table 1). The median age of patients was 50 years in the CPB group and 46 years in the CP group. Most patients were non-smokers (69.2% in the CPB group and 60% in the CP group), with an ECOG PS of 1 (82.1% in the CPB group and 87.5% in the CP group). Approximately 65% of patients had received induction or concurrent chemotherapy and radiotherapy.

Treatments

The proportion of patients who completed six cycles of all components of protocol treatment was 82.1% ($n = 32$) in the CPB group and 82.5% ($n = 33$) in the CP group. The median dose intensity was 438.5 mg for bevacizumab, 648 mg versus 663 mg for carboplatin, and 286.5 mg versus 282 mg for paclitaxel in the CPB and CP arms, respectively.

A total of 12 (30.8%) patients in the CPB arm and 28 (70.0%) patients in the CP arm received subsequent anticancer therapy. Among them, chemotherapy was the most common treatment in their choices, including gemcitabine-based and capecitabine-based treatments.

Efficacy

The data cut-off date was 31 December 2020, and the overall median follow-up time was 34.5 months. Thirty-four

Table 1. Baseline characteristics of all enrolled patients

Characteristics	No. of patients (%)		*P* value
	CPB ($n = 39$)	CP ($n = 40$)	
Sex			0.632
Male	32 (82.1)	34 (85.0)	
Female	7 (17.9)	6 (15.0)	
Age (years)			0.716
Median	50.0	46.0	
ECOG performance status			0.732
0	7 (17.9)	5 (12.5)	
1	32 (82.1)	35 (87.5)	
Smoking history			0.322
Smokers	12 (30.8)	16 (40.0)	
Non-smokers	27 (69.2)	24 (60.0)	
Stage[a]			0.556
IVb	1 (2.6)	2 (4.0)	
IVc	38 (97.4)	38 (96.0)	
EBV-DNA copy number			
Baseline >0	30 (76.9)	28 (70.0)	0.106
After one cycle >0	25 (64.1)	24 (60.0)	0.320
Metastatic organs at screening			
Lung	19 (48.7)	19 (47.5)	0.132
Liver	19 (48.7)	20 (50.5)	0.177
Bone	11 (28.2)	8 (20.0)	0.947
History of nasopharyngeal radiation			0.768
Yes	25 (64.1)	26 (65.0)	
No	14 (35.9)	14 (35.0)	
History of chemotherapy			0.899
Yes	22 (56.4)	24 (60.0)	
No	17 (43.6)	16 (40.0)	
Previous chemotherapeutic agents			
Platinum	22 (56.4)	23 (57.5)	0.734
Fluorouracil	11 (28.2)	10 (25.0)	0.866
Paclitaxel	3 (7.7)	5 (12.5)	0.854
Docetaxel	8 (20.5)	15 (37.5)	0.129
No. of liver metastatic sites			0.374
≤3	6 (15.4)	13 (32.5)	
>3	13 (33.3)	7 (17.5)	
Time interval from previous treatment to recruitment			0.899
No treatment history	14 (35.9)	14 (35.0)	
3-6 months	9 (23.1)	3 (7.5)	
>6 months	16 (35.9)	23 (57.5)	
Cavity in tumor after treatment			0.295
Yes	9 (22.1)	5 (12.5)	
No	30 (77.9)	26 (65.0)	

Data are presented as *n* (%) unless otherwise indicated.
CP, carboplatin and paclitaxel; CPB, bevacizumab, carboplatin, and paclitaxel; ECOG, Eastern Cooperative Oncology Group.
[a] According to American Joint Committee on Cancer (AJCC) staging system for nasopharyngeal carcinoma, seventh edition.

(87.2%) of 39 patients in the CPB group and 39 (97.5%) of 40 patients in the CP group had disease progression as per investigator or died. Investigator-assessed PFS showed an improvement trend in the CPB group [median 7.5 months (95% CI, 6.53-8.45 months)] compared with the CP group [median 6.5 months (95% CI, 5.53-7.42 months)], with an HR of 0.71 (95% CI, 0.44-1.13) ($P = 0.148$) (Figure 2A). Median PFS assessed by the IRC was similar to the primary analysis: 7.33 months in the CPB group (95% CI, 5.35-9.30 months) versus 6.9 months in the CP group (95% CI, 6.24-7.56 months) ($P = 0.994$), respectively. The PFS rate at 6 months was 79.5% versus 55.0% in the CPB group and CP group, respectively, which showed a significant difference ($P = 0.031$).

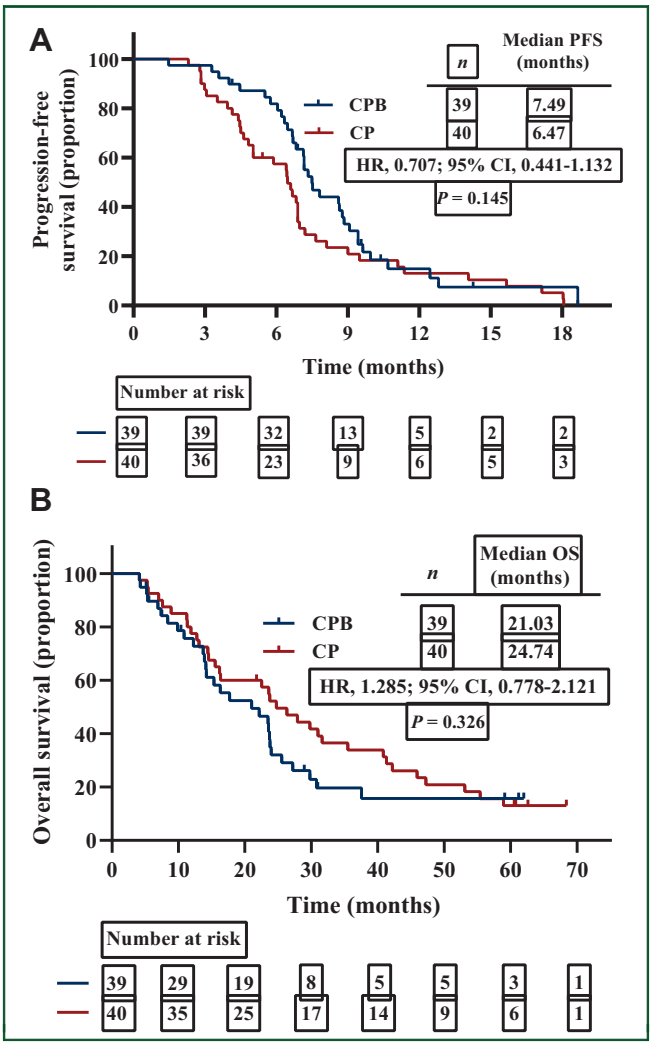

Figure 2. Kaplan–Meier estimated survival by treatment group.
(A) PFS and (B) OS for all patients. CI, confidence interval; CP, carboplatin and paclitaxel; CPB, carboplatin, paclitaxel, and bevacizumab; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

At the time of data cut-off, 10 (25.6%) patients in the CPB group and 6 (15.0%) patients in the CP group were still alive. The addition of bevacizumab did not result in a significant improvement in OS among patients who received at least one dose of study treatment (HR, 1.29; 95% CI, 0.78-2.12). The estimated median OS was 21.0 months (95% CI, 10.80-31.26 months) in the CPB group and 24.7 months (95% CI, 18.33-31.15 months) in the CP group ($P = 0.326$) (Figure 2B).

Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100313, shows unstratified exploratory subgroup analyses of PFS. Compared with that in the CP group, PFS in the CPB group was improved for (i) patients without liver metastasis (HR, 0.50; 95% CI, 0.25-0.99), (ii) patients with little treatment interaction with prior chemotherapy (received >6 months' interval) (HR, 0.48; 95% CI, 0.24-0.96), and (iii) patients had radiotherapy previously (HR, 0.55; 95% CI, 0.30-0.99). In the remaining interactions, HRs for PFS did not favor either arm.

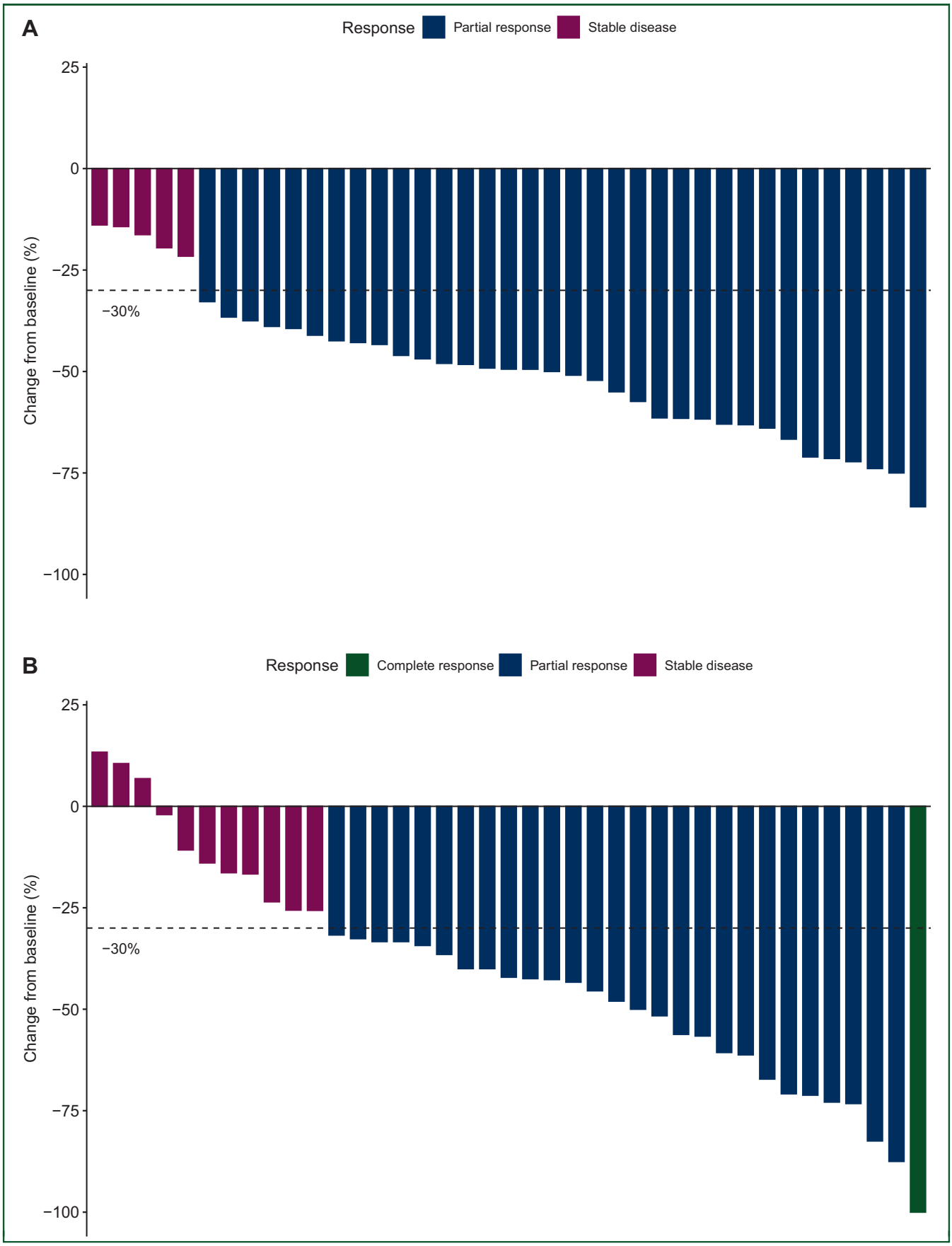

Figure 3. Waterfall plot of the maximum decrease in the sum of the longest diameters of target lesions observed in the CPB (A) and CP (B) groups. Patients are listed in the order of increasing percentage response. CP, carboplatin and paclitaxel; CPB, bevacizumab, carboplatin, and paclitaxel; CR, complete response; PD, progression disease; PR, partial response; SD, stable disease.

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Table 2. Common drug-related adverse events in the safety set ($N = 82$)[a]

	CPB ($n = 42$)			CP ($n = 40$)			*P* value for difference in all grades	*P* value for difference in grades 3 and 4
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4		
Leucopenia	39 (93)	11 (26)	3 (7)	40 (100)	14 (35)	2 (5)	0.241	0.687
Neutropenia	33 (79)	11 (26)	5 (12)	40 (100)	15 (38)	6 (15)	0.002	0.350
Anemia	30 (71)	7 (17)	0	27 (68)	2 (5)	0	0.811	0.168
Thrombocytopenia	23 (55)	1 (2)	0	20 (50)	2 (5)	1 (3)	0.825	0.358
ALT increased	10 (24)	2 (5)	0	12 (30)	0	0	0.621	0.497
AST increased	6 (14)	0	0	9 (23)	0	0	0.399	
Decreased appetite	12 (29)	0	0	8 (20)	0	0	0.445	
Nausea	8 (19)	0	0	8 (20)	0	0	1.000	
Vomiting	3 (7)	0	0	7 (18)	0	0	0.189	
Fatigue	9 (21)	0	0	10 (25)	0	0	0.796	
Muscular stiffness	11 (26)	0	1 (2)	17 (43)	0	0	0.163	1.000
Peripheral nerve toxicity	13 (31)	0	0	21 (53)	0	0	0.072	
Anaphylaxis	10 (24)	0	0	8 (20)	1 (3)	0	0.792	0.488
Bleeding[b]	9 (21)	0	0	3 (8)	0	0	0.117	
Epistaxis	7 (17)	0	0	2 (5)	0	0	0.156	
Hemoptysis	1 (2)	0	0	2 (5)	0	0	0.611	
Proteinuria[b]	1 (2)	0	0	0	0	0	1.000	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CP, carboplatin and paclitaxel; CPB, bevacizumab, carboplatin, and paclitaxel.
[a] Most of the adverse events have an incidence ≥10%.
[b] Drug-related adverse events of special interest related to bevacizumab.

We next investigated the prediction role of Epstein—Barr virus (EBV) DNA. EBV-DNA assay was conducted in 58 patients at the baseline and in 49 patients at both baseline and after one cycle of treatment. Among them, eight patients presented 0 copy/ml of EBV-DNA at both baseline and after one cycle. Therefore, the positive rate of EBV-DNA at baseline was 86.2%. The copy number of EBV-DNA both at baseline and after one cycle failed to predict treatment efficacy and prognosis. We then used the reduction rate of EBV-DNA after one cycle, which was defined as (EBV-DNA after one cycle − EBV-DNA at baseline)/EBV-DNA at baseline, as a group indicator and found 60% was a suitable cut-off value using X-Tile software (Yale University, New Haven, CT). The prognosis was the best for patients with 0 copy/ml at both baseline and after one cycle, with a median PFS of 12.39 months, second-best for patients with EBV-DNA reduction rate >60%, with a median PFS of 7.16 months, poorest for patients with EBV-DNA reduction rate <60%, with a median PFS of only 4.01 months. ($P < 0.001$).

Figure 3 shows the tumor response by treatment. In the CPB group, 34 patients had a PR and 5 had SD (Figure 3A). By contrast, in the CP group, 1 patient achieved CR, 28 had PR, and 11 had SD (Figure 3B). The proportion of patients who achieved an objective response (ORR) was numerically higher in the CPB group than in the CP group (87.2% versus 72.5%), but showed no significant difference ($P = 0.105$). When comparing the deepness of response, we observed that patients in the CPB group showed a higher tumor-shrinking rate than patients in the CP group ($P = 0.035$).

Safety

The safety analysis totally included 82 patients (42 patients in the CPB group and 40 patients in the CP group). Table 2 compares the treatment-related AEs, including hematological and non-hematological toxic events, between the two groups. The most common AEs (incidence >50%, any grade) were hematological events, including leucopenia, neutropenia, anemia, and thrombocytopenia. The incidence of grade 3 or higher AEs was 60% in the CPB group and 61.9% in the CP group. Serious AEs (SAEs) were reported in 6 of 42 patients (14.3%) in the CPB group, of which 4 were hematological toxic events, 1 was diarrhea, and 1 was nose bleeding. By contrast, in the CP group, one patient (2.5%) with nose bleeding was reported as a SAE. All these SAEs were treatment-related.

AEs of special interest related to bevacizumab were generally rare in our study. Only eight cases of grade 1-2 bleeding events (seven epistaxis and one hemoptysis) and one case of grade 2 proteinuria in the CPB group were observed. No bevacizumab-related grade 3 or 4 AEs, especially including bleeding, were observed. No treatment-related deaths occurred in either group.

DISCUSSION

To the best of our knowledge, this is the first multicentre, randomised, controlled, phase II trial conducted to date in patients with R/M NPC to investigate the safety and efficacy of combining bevacizumab with paclitaxel plus carboplatin in the first-line treatment setting. Our results showed that the regimen of bevacizumab plus paclitaxel—carboplatin was tolerable for patients with R/M NPC.

There was no statistically significant improvement with concurrent bevacizumab in endpoint efficacy, including PFS, OS, and ORR. The median PFS was 7.5 months in the CPB arm and 6.5 months in the CP arm (HR, 0.71; 95% CI, 0.44-1.13; $P = 0.15$). Although the improvement trend of PFS and survival advantage at 6 months in the CPB group was observed, they did not translate to OS benefit (HR, 1.29; 95% CI, 0.78-2.12; $P = 0.326$), which were similar to the findings of the trial in recurrent or metastatic

squamous cell carcinoma of head and neck.[26] The reasons for this negative finding are complicated. One potential reason might be that this analysis was a phase II study with a limited population, which hinders reaching a statistical significance. Additionally, the VEGF pathway might not be the main signaling pathway for nasopharyngeal carcinoma development. Thus, inhibiting VEGF/VEGFR would not completely suppress tumor progression. Thirdly, the proportion of patients receiving subsequent anticancer therapy was not balanced, with 12 (30.8%) patients in the CPB arm and 28 (70.0%) patients in the CP arm, as it could have an impact on OS. Fourthly, the dosage of bevacizumab might be insufficient. A phase I clinical trial (BP20689) evaluating the safety and pharmacokinetic characteristics of bevacizumab among Chinese patients with advanced solid tumors adopted three different dosages of bevacizumab, 5 mg/kg/Q2w, 10 mg/kg/Q2w, and 15 mg/kg/Q3w.[27] Pharmacokinetic analysis revealed a linear correlation between plasma bevacizumab concentration and administration doses, and no additional toxicity was found in the high-dose group. Besides, Radiation Therapy Oncology Group (RTOG) 0615 trial adopted 15 mg/kg/Q3w of bevacizumab and demonstrated an eligible toxicity profile.[25] The high incidence of hemorrhage in a phase II trial by Hui et al. indicated that the risk of serious bleeding should be concerned in nasopharyngeal carcinoma patients who had previously received induction or concurrent chemotherapy and radiotherapy during the anti-angiogenic therapy.[19] Therefore, we chose the dosage of 7.5 mg/kg/Q3w of bevacizumab in our study, which was derived from the experience of non-small-cell lung cancer. The AVAiL study found no efficacy difference between high-dose (15 mg/kg/Q3w) and low-dose (7.5 mg/kg/Q3w) groups of bevacizumab.[28] What is more, except for eight cases of grade 1-2 bleeding events and one case of grade 2 proteinuria in the CPB group, no other bevacizumab-related AEs, especially hypertension, were reported in our study, which also suggested insufficient dosage of bevacizumab.

The question about who should receive the anti-angiogenic drug bevacizumab in addition to chemotherapy needs to be explored. Compared with chemotherapy alone, combination with bevacizumab significantly improved tumor-shrinking rate ($P = 0.035$) and PFS advantage at 6 months ($P = 0.031$). The results indicated that the bevacizumab combined regimen might be a choice for those with heavy tumor load or pursuing short-term efficacy such as in neoadjuvant and concurrent chemotherapy.

Bevacizumab combined with chemotherapy was well tolerable. The addition of bevacizumab did not appear to increase the frequency of AEs that are associated with paclitaxel and carboplatin. Moreover, the risk of anti-angiogenesis-related AEs was not higher with bevacizumab—chemotherapy combination therapy than that previously reported in bevacizumab monotherapy studies, including grade 3-4 hemorrhage. The most common AEs were hematological events, including leucopenia, neutropenia, anemia, and thrombocytopenia.

It is well known that EBV infection is an important etiological factor for the pathogenesis of nasopharyngeal carcinoma in epidemic area.[29] Accumualating evidence indicates that plasma EBV-DNA could be applied for early disease detection, and its dynamic change during anticancer treatment, including chemotherapy, chemoradiotherapy, and radiotherapy, strongly correlates with treatment response and prognosis in patients with nasopharyngeal carcinoma.[30-32] However, the prognostic value of EBV-DNA level at baseline and its dynamic change in patients with nasopharyngeal carcinoma undergoing anti-angiogenesis therapy remains confused. In our study, longer PFS was observed in patients with 0 copy/ml plasma EBV-DNA level at both baseline and after one cycle. We also found prolonged PFS in patients with an EBV-DNA reduction rate $>60\%$ ($\geq 60\%$ 12.39 versus $<60\%$ 4.01 months; $P < 0.001$).

Our study has certain limitations. Firstly, as an open-label trial, the primary endpoints could be potentially affected by the investigators' assessment of response and progression. However, the IRC-assessed PFS was similar to the primary analysis, which was assessed by investigators. Furthermore, randomisation was carried out to ensure the balance between the two groups. Secondly, we did not explore different doses of bevacizumab. Since the influence of dose intensity on the efficacy is unclear, a further randomised phase III trial is needed to validate the efficacy of the higher dose of bevacizumab.

Conclusion

In conclusion, the addition of bevacizumab to paclitaxel plus carboplatin did not improve survival compared with paclitaxel plus carboplatin in patients with previously untreated R/M NPC. Given the well-tolerable toxicities and the advantage in tumor-shrinking rate, bevacizumab plus chemotherapy could be considered as an option for nasopharyngeal carcinoma patients with heavy tumor load or pursuing short-term efficacy such as in neoadjuvant and concurrent chemotherapy.

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DISCLOSURE

LZ has received research support from Roche. All other authors have declared no conflicts of interest.

DATA SHARING

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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