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Original Research

Anti-PD1 checkpoint inhibitor with or without chemotherapy for patients with recurrent and metastatic nasopharyngeal carcinoma

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ABSTRACT

Purpose: To compare the efficacy and safety of anti-PD1 checkpoint inhibitor plus chemotherapy with anti-PD1 checkpoint inhibitor alone in recurrent and metastatic nasopharyngeal carcinoma (R/M NPC) progressing after first or subsequent-line therapy.
Methods and materials: A total of 67 patients with recurrent and metastatic nasopharyngeal carcinoma from our hospital were included. All patients were sorted into two arms: anti-PD1 checkpoint inhibitor+ chemotherapy arm and anti-PD1 checkpoint inhibitor arm. We retrospectively estimated objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) in patients of both arms. Chi-square test and Kaplan–Meier methodology were used to analyze.
Results: From September 2018 to March 2020, this research included 67 patients. For anti-PD1 checkpoint inhibitor+ chemotherapy arm, partial response and stable disease were observed in fourteen and 11 patients, respectively, for an ORR of 53.8%. For anti-PD1 checkpoint inhibitor arm, complete response and partial response were observed in one and 5 patients, respectively, for an ORR of 14.6%. The incidence of hyperprogressive disease was higher in the anti-PD1 checkpoint inhibitor group compared with anti-PD1 checkpoint inhibitor+ chemotherapy group (39.0% vs 3.8%, $p<0.05$). Univariable analyses discovered that 6-month PFS and OS benefits were observed for anti-PD1 checkpoint inhibitor+ chemotherapy arm compared to anti-PD1 checkpoint inhibitor arm (65.4% vs. 28.6%, $P = 0.001$; 100.0% vs. 73.5%, $P = 0.014$).
Conclusion: In present study, we revealed that adding chemotherapy to anti-PD1 checkpoint inhibitor significantly improved 6-month PFS and OS for patients with R/M NPC progressing after first-line therapy. It warrants further study.

Introduction

In 2018, it was estimated that about 129,000 new patients with nasopharyngeal carcinoma (NPC) were diagnosed throughout the world. Near half of the patients were occurring in China [1]. NPC is highly sensitive to chemotherapy and radiotherapy. Due to the improvements of imaging diagnostic machine such as magnetic resonance imaging (MRI), radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), treatment protocols such as induction chemotherapy (IC) plus concurrent chemoradiotherapy (CCRT), the local and regional control rates reached ≈90% at 3 years after treatment for stage III–IVB (Seventh Editon of the AJCC Cancer Staging) NPC [2–4]. However, near 1/5 of patients with stage III–IVB (Seventh Edition of the AJCC Cancer Staging) NPC still fail state-of-the-art care due to distant metastasis [2,5].

The standard care for patients with recurrent or metastatic nasopharyngeal carcinoma (R/M NPC) not amenable to curative treatment is to offer palliative systemic chemotherapy using platinum-based doublet chemotherapy [6,7]. In 2016, Zhang et al. [8] revealed that cisplatin plus gemcitabine (GC) was more effective than cisplatin/fluorouracil (PF) in the treatment of R/M NPC. Due to the results of the above multicenter, randomized, phase-3 clinical trial, GC is the standard first-line treatment for R/M NPC. However, the median time to progression was still only 7 months which did not improve substantially compared to previous two-drug regimens [9,10]. Given the limited improves in chemotherapeutic drugs, there is an urgent need to develop targeted therapies for R/M NPC that potentially reduce toxicity and improve progression-free survival (PFS) and overall survival (OS).

One strategy to improve duration of response/survival benefit in patients with M-NPC is to combine anti-PD1 checkpoint inhibitor and chemotherapeutic drugs. Fang et al. [11] assess the addition of cam-

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Table 1

Baseline Demographics and Clinical Characteristics of the 67 patients in each treatment arm.

Variable	Anti-PD1 checkpoint inhibitor + chemotherapy ($n = 26$)	Anti-PD1 checkpoint inhibitor ($n = 41$)	$\chi2$	P-value*
Sex			2.239	0.135
Male	22 (84.6%)	28 (68.3%)		
Female	4 (15.4%)	13 (31.7%)		
Age			1.728	0.189
<60	15 (57.7%)	30 (73.2%)		
≥60	11 (42.3%)	11 (26.8%)		
ECOG PS			0.000	1.000
0–1	22 (84.6%)	35 (85.4%)		
2	4 (15.4%)	6 (14.6%)		
Recurrence or metastasis			0.034	0.581
Recurrence	6 (23.1%)	6 (14.6%)		
metastasis	20 (76.9%)	35 (85.4%)		
Sites of metastatic disease			6.284	0.099
Lung	9 (34.6%)	16 (39.0%)		
Liver	4 (15.4%)	20 (48.8%)		
Bone	7 (26.9%)	6 (14.6%)		
Distant lymph nodes	6 (23.1%)	8 (19.5%)		
Number of recurrent or metastatic sites			0.001	0.977
Oligo	5 (19.2%)	8 (19.5%)		
Multiple	21 (80.8%)	33 (80.5%)		
No. of prior lines of chemotherapy, median (range)			12.131	0.002
1	14 (53.8%)	6 (14.6%)		
2	8 (30.8%)	19 (46.3%)		
>2	4 (15.4%)	16 (39.0%)		
Median (range)	2 (2–6)	3 (2–7)		
No. of Anti-PD1 checkpoint inhibitor cycles, median (range)	5.5 (2–14)	3 (2–23)		

* calculated using the χ^2 test. Values are shown as n (%) .

relizumab (a humanized anti-PD1 IgG4 antibody) to GC chemotherapy showed that 91% evaluable patients had an overall response. with a median follow-up time of 10.2 months, This phase I trial also indicated improved PFS when compared to historical control of GC regimen (6-month PFS, 86% vs. 66%; 12-month PFS, 61% vs. 20%). Three randomized, multicenter, phase-3 clinical trials are conducted to confirm the above results (NCT 03581786; NCT 03707509; NCT 03924986).

Nowadays, there is no standard second-line treatment for R/M NPC. Investigators also evaluated the antitumour activity of anti-PD1 checkpoint inhibitor alone for patients with R/M NPC whose prior standard therapy was ineffective. KEYNOTE-028 Study [12] and NCI-9742 Study [13] revealed that 26.3% evaluable patients receiving Pembrolizumab and 20.5% evaluable patients receiving Nivolumab had an overall response. Although the unsatisfactory overall outcomes, current NCCN guidelines still recommend Pembrolizumab or Nivolumab as a treatment option besides chemotherapy for patients with R/M NPC whose prior standard therapy was ineffective (category 2B) [14].

As we stated earlier, immunotherapy and chemotherapy combination showed promising antitumour activity as the first-line treatment for patients with R/M NPC. Whether the combination of immunotherapy and chemotherapy is superior to immunotherapy alone for patients with R/M NPC whose prior standard therapy was ineffective is still unknown, therefore, we did a retrospectively research to compare the efficacy and safety of anti-PD1 checkpoint inhibitor plus chemotherapy with anti-PD1 checkpoint inhibitor alone in R/M NPC.

Materials and methods

Patients

The present research was a non-randomized hypothesis-generating study. To confirm the value of adding chemotherapy to immunotherapy, the inclusion criteria of our present research were (1) pathologically biopsy-proven NPC (WHO class II/III), (2) age 18–70 years; (3) measurable disease at baseline on the basis of RECIST v1.1 (4) Eastern Cooperative Oncology Group performance status of 0 or 1; (5) adequate organ function as determined by laboratory testing; (6)receiving

at least one prior line of platinum-based chemotherapy for recurrent and/or metastatic disease and have adequate organ function; (7) receiving *at least two cycles of* anti-PD1 checkpoint inhibitor With or Without Chemotherapy treatment.

The exclusion criteria of our present research were (1) prior targeted therapy or any anticancer therapy within one month of study start; (2) known additional malignancy that was progressing or that required active treatment; (3) corticosteroid therapy within one week of study start; (4) therapy with any other immune checkpoint inhibitor; (6)active autoimmune disease; (7) interstitial lung disease.

From September 2018 to March 2020, this research included 67 patients treated with anti-PD1 checkpoint inhibitor+ chemotherapy ($n = 26$) or anti-PD1 checkpoint inhibitor alone ($n = 41$). The patient and tumor characteristics are listed in Table 1.

Chemotherapy and immunotherapy

Patients in the anti-PD1 checkpoint inhibitor+ chemotherapy group received chemotherapy regimens including docetaxel/paclitaxel and nedaplatin/carboplatin (TP), gemcitabine and carboplatin (GP), docetaxel/paclitaxel alone, capecitabine alone, gemcitabine alone, repeated every three weeks. Patients in anti-PD1 checkpoint inhibitor+ chemotherapy group or anti-PD1 checkpoint inhibitor group received immunotherapy regimens including Camrelizumab (200 mg) on day 1 every two or three weeks, Toripalimab (240 mg) on day 1 every three weeks, penpulimab (200 mg) on day 1 every two weeks or tislelizumab (200 mg) on day 1 every three weeks.

Statistical analysis

OS was defined as the duration from the date of starting treatment to the date of death from any cause or the censoring of the patient at the date of the last follow-up. PFS was defined as the date of starting treatment to first failure at any site or death of any cause or patient censoring at the date of last follow-up. We used Kaplan–Meier survival curves to analyze the time-to-event endpoints, and the log-rank test to compare the differences between two groups. Chi-squared tests were

Table 2
Comparison of the treatment outcome of the different treatments.

Variable	Anti-PD1 checkpoint inhibitor + chemotherapy ($n = 26$)	Anti-PD1 checkpoint inhibitor ($n = 41$)	χ^2	*P*-value*
ORR (CR + PR)	14 (53.8)	6 (14.6)	11.683	0.001
CR	0 (0.0)	1 (2.4)		
PR	14 (53.8)	5 (12.2)		
SD	11 (42.3)	12 (29.3)		
PD	1 (3.8)	23 (56.1)		
Disease progression	11 (42.3)	31 (75.6)	4.456	0.035
Disease progression≤2 months	1 (9.1)	16 (51.6)		
Disease progression>2 months	10 (90.9)	15 (48.4)		
Death	2 (7.7)	12 (29.3)	4.481	0.034

* calculated using the χ^2 test. Values are shown as *n* (%) .

used to compare categorical variables. Analyses were performed using the statistical software package SPSS for Windows version 21.0 (IBM Corp., Armonk, NY, USA). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Among the 67 patients with recurrent or metastatic NPC, 26 patients received Anti-PD1 checkpoint inhibitor + chemotherapy and 41 patients received Anti-PD1 checkpoint inhibitor alone. In the anti-PD1 checkpoint inhibitor + chemotherapy group, The male-to-female ratio was 2.2:1. The proportional distribution of sex, number of recurrent or metastatic sites, PS scores, and age between the two arms were not significant different (all $P > 0.05$). Compared to anti-PD1 checkpoint inhibitor + chemotherapy group, There were significantly more patients with hepatic metastases in anti-PD1 checkpoint inhibitor group (48.8% vs 15.4%). Compared to anti-PD1 checkpoint inhibitor + chemotherapy group, There were significantly more patients receiving at least three prior lines of therapy for advanced disease in anti-PD1 checkpoint inhibitor group (48.8% vs 15.4%, $p = 0.019$). Table 1 showed the comparison of the balance of patient clinicopathologic characteristics in the two groups.

Antitumor activity

There were no complete responses and 14 (53.8%) partial responses in the checkpoint inhibitor + chemotherapy group while 1 (2.4%) complete responses and 5 (12.2%) partial responses in the checkpoint inhibitor group. Compared to anti-PD1 checkpoint inhibitor group, the objective response rate was much higher in anti-PD1 checkpoint inhibitor + chemotherapy group (14.6% vs 53.8%, $p = 0.001$). Table 2 showed the comparison of the treatment outcome of the different treatments. Fig. 1 showed the CT example of patients with regression, hyperprogression and stable disease and Fig. 2 showed the longitudinal change from baseline in tumor size for patients receiving anti-PD1 checkpoint inhibitor+ chemotherapy and anti-PD1 checkpoint inhibitor alone.

Survival outcomes

At a median follow-up of 7 months (2 to 19 months), 2 patients died in the checkpoint inhibitor + chemotherapy group and 12 patients died in the checkpoint inhibitor group. Overall, the 6-, and 12-month OS rates of all patients were 84.4, and 75.9% (Fig. 1A), while the 6-, and 12-month PFS rates of all patients were 43.3, and 30.9% (Fig. 1B), respectively. The median PFS were 3 months (95% CI, 2.276 to 3.724 months) in the checkpoint inhibitor group and 11 months (95% CI, 4.120 to 17.880 months) in the checkpoint inhibitor + chemotherapy group. Univariate analysis indicated that the 1-year OS and PFS were significantly worse in the checkpoint inhibitor group compared with that

in the checkpoint inhibitor + chemotherapy group (65.4% vs. 91.3%, $P = 0.014$, Fig. 1C; 20.5% vs. 40.5%, $P = 0.001$, Fig. 1D). The survival curves are shown in Fig. 3.

Adverse events

All of the patients in the two group finished at least two cycles of treatments. there were less 3 or 4 hematologic adverse events occurred in the checkpoint inhibitor group compared with checkpoint inhibitor + chemotherapy group (Thrombocytopenia: 0% vs 34.6%, $P <0.001$; Neutropenia: 2.4% vs 42.3%, $P <0.001$; Anemia: 2.4% vs 38.5%, $P <0.001$). Grade 3 or 4 liver dysfunction occurred in 11.5% of the checkpoint inhibitor + chemotherapy group and 2.4% of the checkpoint inhibitor group ($P = 0.316$) and grade 1 or 2 kidney dysfunction in 7.7% of the checkpoint inhibitor + chemotherapy group and 2.4% of the checkpoint inhibitor group ($P = 0.684$). As for *non-hematologic toxicity,* Grade 1 or 2 Anorexia occurred in 84.6% of the checkpoint inhibitor + chemotherapy group and 9.8% of the checkpoint inhibitor group ($P <0.001$) and grade 1 or 2 Peripheral neuropathy in 38.5% of the checkpoint inhibitor + chemotherapy group and 0% of the checkpoint inhibitor group ($P <0.001$). The detail of the side-effects in the two arms was shown in Table 3.

Ethical statement

Our study had been granted an exemption from requiring ethics approval by our the institutional ethics committee because our study just retrospectively analysed routine clinical data (IRB-2020-297).

Discussion

According to what we have learned, this is the first study comparing the antitumour activity and side effects between anti-PD1 checkpoint inhibitor alone and combined with chemotherapy for patients with recurrent and metastatic nasopharyngeal carcinoma progressing after first or subsequent-line therapy. Our study demonstrate that Anti-PD1 checkpoint inhibitor alone or combined with Chemotherapy are well-tolerated safety profiles. Adding chemotherapy to anti-PD1 checkpoint inhibitor significantly improved 6-month PFS and OS for patients with recurrent and metastatic nasopharyngeal carcinoma progressing after first or subsequent-line therapy.

Platinum-based doublet chemotherapy regimens are generally considered the first-line standard of care for patients with recurrent or metastatic nasopharyngeal carcinoma. However, no consensus has been reached regarding treatment following progression after first or subsequent-line therapy. Many phase II studies have demonstrated that the use of new oral fluoropyrimidine such as capecitabine and S-1 produced an objective response rates (ORR) between 23.5 and 30.7%, median PFS between 4.9 and 5.6 months while OS between 7.6 and 14 months [15,16]. The use of gemcitabine produced an ORR 43.8%, median PFS 5.1 months while median OS 16 months [17]. The use of
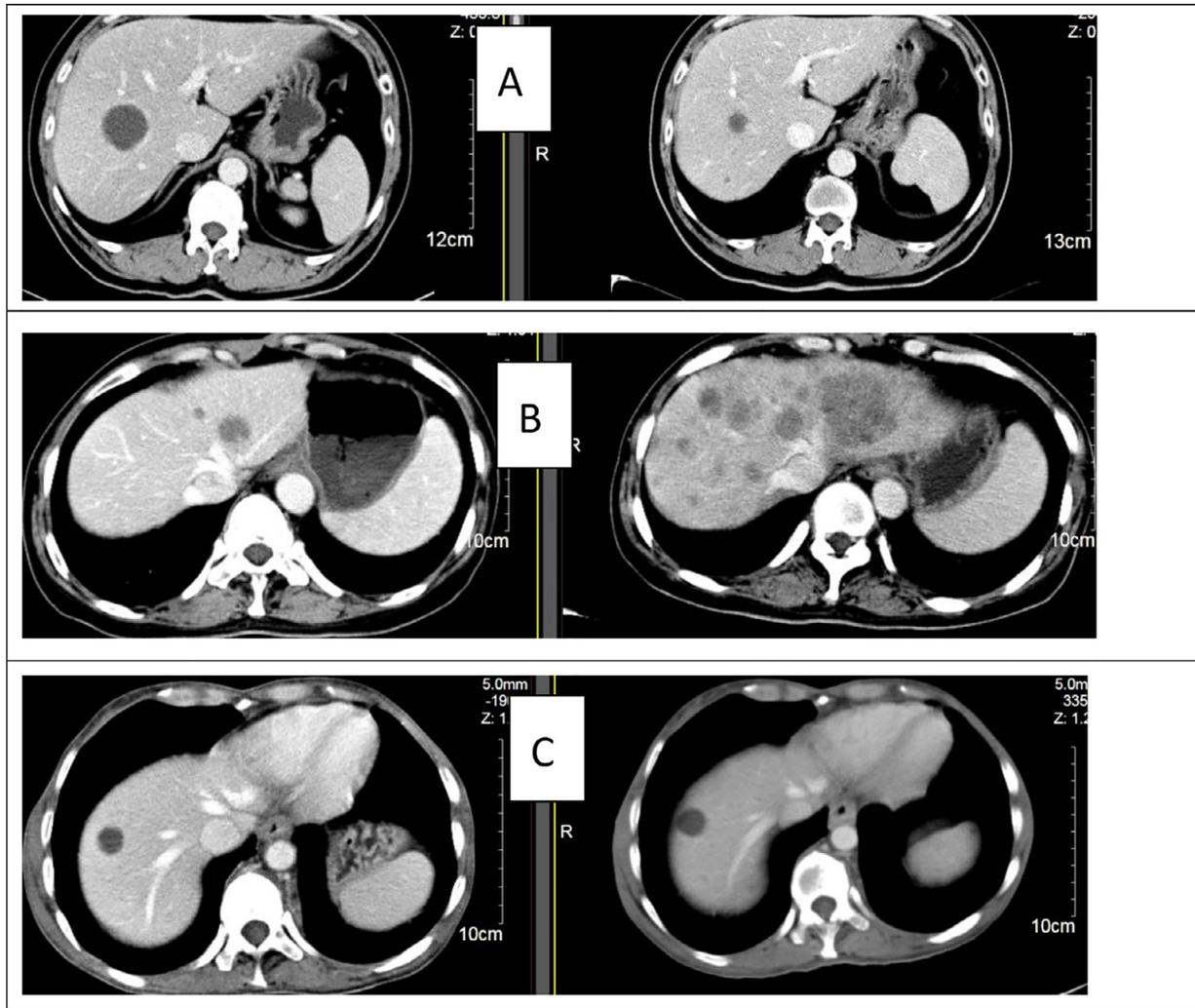
Fig. 1. CT example of patients with regression (A), hyperprogression (B) and stable disease (C).
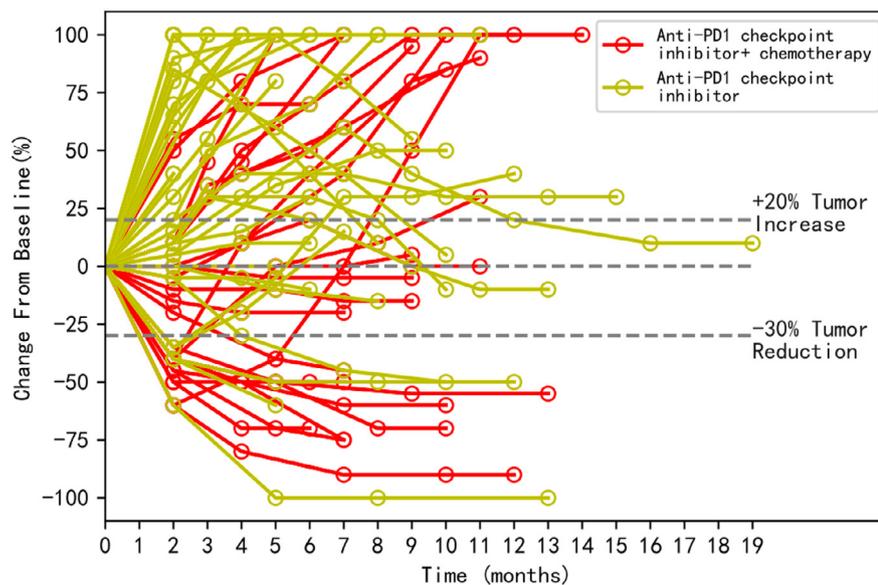

Fig. 2. Longitudinal change from baseline in tumor size for patients receiving anti-PD1 checkpoint inhibitor+ chemotherapy and anti-PD1 checkpoint inhibitor alone.
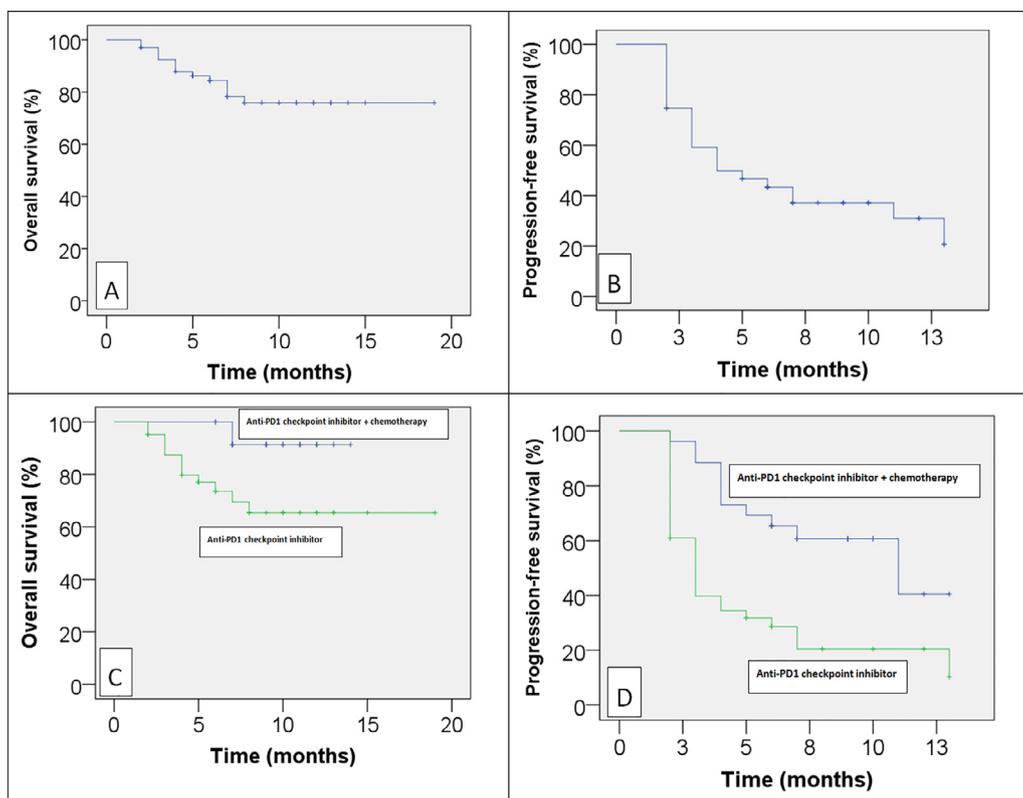
Fig. 3. Kaplan–Meier estimates of (A) Overall survival for all patients. (B) Progression-free survival for all patients. (C) Overall survival for patients receiving anti-PD1 checkpoint inhibitor+ chemotherapy and anti-PD1 checkpoint inhibitor alone ($p = 0.014$). (D) Progression-free survival for patients receiving anti-PD1 checkpoint inhibitor+ chemotherapy and anti-PD1 checkpoint inhibitor alone ($p = 0.001$).

Table 3
Adverse events.

Variable	Anti-PD1 checkpoint inhibitor + chemotherapy ($n = 26$)	Anti-PD1 checkpoint inhibitor ($n = 41$)	χ^2	P-value*
Any (grade 1–5)	26 (100%)	41 (100%)		
Hematologic				
Anemia (grade 1 or 2)	26 (100%)	5 (12.2%)	49.341	< 0.001
Anemia (grade 3 or 4)	10 (38.5%)	1 (2.4%)	12.535	< 0.001
Thrombocytopenia (grade 3 or 4)	9 (34.6%)	0 (0.0%)	13.553	< 0.001
Neutropenia (grade 3 or 4)	11 (42.3%)	1 (2.4%)	14.596	< 0.001
Liver dysfunction (grade 3 or 4)	3 (11.5%)	1 (2.4%)	1.006	0.316
Kidney dysfunction (grade 1 or 2)	2 (7.7%)	1 (2.4%)	0.166	0.684
Anorexia (grade 1 or 2)	22 (84.6%)	4 (9.8%)	37.546	< 0.001
Rash (grade 1 or 2)	2 (7.7%)	8 (19.5%)	0.943	0.331
Pruritus (grade 1 or 2)	1 (3.8%)	2 (4.9%)	0.000	1.000
Herpes zoster (grade 1 or 2)	2 (7.7%)	1 (2.4%)	0.166	0.684
Myalgia (grade 1 or 2)	1 (3.8%)	1 (2.4%)	0.000	1.000
Peripheral neuropathy (grade 1 or 2)	10 (38.5%)	0 (0.0%)	15.630	< 0.001
Hypothyroidism (grade 1 or 2)	2 (7.7%)	3 (7.3%)	0.000	1.000
Fatigue (grade 1 or 2)	11 (42.3%)	21 (51.2%)	0.506	0.477
Hyperglycaemia (grade 1 or 2)	3 (11.5%)	1 (2.4%)	1.006	0.316
pneumonitis (grade 1 or 2)	2 (7.7%)	2 (4.9%)	0.000	1.000
diarrhea (grade 1 or 2)	3 (11.5%)	1 (2.4%)	1.006	0.316
Proteinuria (grade 1 or 2)	3 (11.5%)	4 (9.8%)	0.000	1.000

* Calculated using the χ^2 test.

newer agents such as paclitaxel or docetaxel produced an ORR between 21.7 and 37%, median PFS between 5.3 and 7.5 months while median OS between 12 and 12.8 months [18,19]. Ifosphamide based doublet combination chemotherapy regimens such as ifosphamide plus 5-fluorouracil or doxorubicin produced an ORR between 30 and 56%, median PFS between 4 and 7 months [20–22]. Vinorelbine plus gemcitabine produced an ORR between 36 and 37.7%, median PFS between 5.2 and 5.6 months [23]. Nedaplatin plus capecitabine produced an ORR 41.7%, median PFS 5.8 months and median OS 12.4 months [24].

Polychemotherapy regimens such as paclitaxel+cisplatin+5-fluorouracil produced an ORR 78.9%, median PFS 9.1 months and median OS between 27.2 months but this was associated with a high rate of grade 5 adverse events (nearly 10%) [25,26]. Given the limited improves in chemotherapeutic drugs, there is an urgent need to develop targeted therapies for R/M NPC that potentially reduce toxicity and improve PFS and OS. KEYNOTE-028 Study [12] and NCI-9742 Study [13] revealed that 26.3% evaluable patients receiving Pembrolizumab and 20.5% evaluable patients receiving Nivolumab had an overall response.

Table 4

Baseline Demographics and Clinical Characteristics of the 41 patients in Anti-PD1 checkpoint inhibitor group.

Variable	HPD ($n = 16$)	No HPD ($n = 25$)	$\chi2$	P-value*
Sex			2.034	0.154
Male	13 (81.2%)	15 (60.0%)		
Female	3 (18.8%)	10 (40.0%)		
Age			0.000	1.000
<60	12 (75.0%)	18 (72.0%)		
≥60	4 (25.0%)	7 (28.0%)		
ECOG PS			0.349	0.555
0–1	13 (81.2%)	22 (88.0%)		
2	3 (18.8%)	3 (12.0%)		
Liver metastases			0.586	0.444
NO	7 (43.7%)	14 (56.0%)		
YES	9 (56.3%)	11 (44.0%)		
Number of recurrent or metastatic sites			3.343	0.067
Oligo	1 (6.2%)	7 (28.0%)		
Multiple	15 (93.8%)	18 (72.0%)		
No. of prior lines of chemotherapy, median (range)			14.272	<0.001
≤ 2	4 (25.0%)	21 (84.0%)		
> 2	12 (75.0%)	4 (16.0%)		

* calculated using the χ^2 test. Values are shown as n (%) .

In our present study, median PFS was 3 months (95% CI, 2.276 to 3.724 months) with anti-PD1 checkpoint inhibitor alone, which is similar with the result in the pembrolizumab study (3.7 [2.1–13.4] by central review) and the nivolumab study (2.8 months [1.8–7.4]). It seems that a lower proportion of patients had an overall response (14.6%) with anti-PD1 checkpoint inhibitor monotherapy in our study than patients in the KEYNOTE-028 study (26%) [12] and NCI-9742 study (21%) [13]. The most likely reasons are the different proportion of Asians and ECOG PS 2 between the three studies and different drugs used in the three studies. Anti-PD1 checkpoint inhibitor combined with chemotherapy produced an ORR 53.8% and median PFS 11 months. By comparing the above-mentioned data, anti-PD1 checkpoint inhibitor combined with chemotherapy got better ORR and median PFS than anti-PD1 checkpoint inhibitor alone, single-agent chemotherapy and doublet combination chemotherapy regimens and better median PFS than polychemotherapy regimens. It should be noted that there were more patients with hepatic metastases (48.8% vs. 15.4%, $p<0.05$) and receiving >2 lines of chemotherapy (39.0% vs. 15.4%, $p<0.05$) in the Anti-PD1 checkpoint inhibitor group compared with Anti-PD1 checkpoint inhibitor + chemotherapy group. As we all know, liver metastasis is a negative prognostic factor and patients who had received several lines of chemotherapy may be skewed towards a more treatment-resistant disease.

In our present study, we defined hyperprogressive disease (HPD) as 'the acceleration of tumor cells proliferation exceeding twice as much or as many based on three point of time (pre-treatment, baseline, post/under-treatment)' or 'time-to-treatment failure ≤2 months'. in the Anti-PD1 checkpoint inhibitor group, the incidence of HPD has been as high as 39.0%. in the Anti-PD1 checkpoint inhibitor + chemotherapy group, the incidence of HPD has been as low as 3.8%. After we retrospectively analysed the data, we found that patients in the Anti-PD1 checkpoint inhibitor group with HPD had three mainly characteristics: 87.5% serum lactate dehydrogenase (LDH) above the upper normal limit, 93.8% multiple metastatic sites, 56.3% liver metastases. The above three characteristics had been proved significantly associated with HPD by a A high-quality Meta-Analysis [27]. What is more surprising is that most of the patients in the Anti-PD1 checkpoint inhibitor group without HPD also had above three characteristics: 72% serum lactate dehydrogenase (LDH) above the upper normal limit, 72% multiple metastatic sites, 44% liver metastases. It is an urgent problem to find the baseline patient factors which are significantly associated with HPD and underlying molecular mechanisms and predictive biomarkers of HPD. In the Anti-PD1 checkpoint inhibitor arm, it should be noted that there were more patients receiving >2 lines of chemotherapy (75%

vs. 16%, $p<0.001$) in the HPD group compared with no HPD group. Table 4 showed the comparison of the balance of patient clinicopathologic characteristics in the two groups. Such huge survival benefit seen in the Anti-PD1 checkpoint inhibitor + chemotherapy group compared with Anti-PD1 checkpoint inhibitor group may be due to the prevention of hyperprogressive disease by early using cytotoxic chemotherapy, which would otherwise have led to HPD. Although this is not confirmed by multiple, high-quality prospective, randomized clinical trials, selectively administrating chemotherapy plus Anti-PD1 checkpoint inhibitor after identifying patients with high risk of HPD may prove to be a effect treatment method.

The safety profile of Anti-PD1 checkpoint inhibitor alone or combined with chemotherapy observed in our present study was generally consistent with that reported for other anti-PD-1 antibodies. Most of the side effects in our study were well tolerated and manageable. In the Anti-PD1 checkpoint inhibitor combined with chemotherapy group, the most common treatment-related side effects were hematological toxicities. Grade 3–4 hematological toxicities was mainly attributed to chemotherapy, which is comparable to other chemotherapy schemes that reported elsewhere. The safety profile of our study indicate that the Anti-PD1 checkpoint inhibitor combined with chemotherapy regimen is generally manageable in patients with recurrent or metastatic nasopharyngeal carcinoma progressing after first-line therapy.

There were several limitations associated with the present study: First, it was a retrospective analysis; second, The expression of programmed death-ligand 1 (PD-L1) was not detected in our study; last, the proportion of patients with hepatic metastases and receiving >2 lines of chemotherapy was not balanced between the two groups. Nevertheless, our report is noteworthy, because it is the first Real World Study to show that adding chemotherapy to anti-PD1 checkpoint inhibitor significantly improved 6-month PFS and OS for patients with recurrent and metastatic nasopharyngeal carcinoma progressing after first-line or subsequent-line therapy.

In conclusion, in present study, we revealed that adding chemotherapy to anti-PD1 checkpoint inhibitor significantly improved 6-month PFS and OS for patients with recurrent and metastatic nasopharyngeal carcinoma progressing after first-line therapy or subsequent-line therapy. It warrants further study. Therefore, well-designed phase 3, multi-center, prospective, randomized, controlled trials should be carried out for further verification.

We suggest that future clinical trials concentrating on appropriate patient selection, optimal chemotherapy regimen selection, appropriate chemotherapy cycles selection, biomarker identification, optimal Targeted drugs in combination with immunotherapy selection, as well as

the development of new drugs that can be used to overcome the resistance of anti-PD1 checkpoint inhibitor.

Declarations of Competing Interest

None.

Authors' contributions

Ting Jin, Qi-Feng Jin and Yong-Hong Hua carried out the cases collection, Ting Jin and Qun Zhang analyzed results. Xiao-Zhong Chen conceived of the study, participated in its design and coordination and helped to draft the manuscript.

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