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Induction chemotherapy plus camrelizumab combined with concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma in non-endemic areas: a phase 2 clinical trial in North China

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Abstract

Background Immunotherapy has been confirmed efficient in recurrent or metastatic nasopharyngeal carcinoma (NPC), but its role in the locoregionally advanced setting is undetermined. Previous evidence in non-endemic areas of NPC is also lacking. This study evaluated the efficacy and safety of induction chemotherapy plus camrelizumab followed by concurrent chemoradiotherapy (CCRT) for patients with locoregionally advanced NPC in non-endemic areas.

Methods In this phase 2 trial, patients born and living in North China with untreated stage III to IVa NPC were enrolled. All patients received two 21-day cycles of camrelizumab (200 mg) plus docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2), followed by intensity modulated radiotherapy and concurrent cisplatin (80 mg/m^2 for two 21-day cycles). After CCRT, patients received camrelizumab maintenance for 12 cycles. The primary endpoint was 3-year disease-free survival (DFS) rate.

Results From February 2021 to September 2023, a total of 57 patients were included for analysis. The objective response rate was 92.8% after induction therapy and 100% after CCRT. With a median follow-up time of 21 months, the 3-year DFS rate was 84%. The 3-year locoregional recurrence-free survival, distant metastasis-free survival, and overall survival rates were 95.8%, 90.9%, and 89.5%, respectively. The most common grade 3 or 4 treatment-related adverse events were leukopenia and neutropenia during induction therapy, and weight loss and lymphopenia during CCRT.

Conclusions Induction immunochemotherapy combined with CCRT shows promising antitumor activity with a manageable safety profile in patients with locoregionally advanced NPC from non-endemic areas, which deserves further validation.

Trial registration ClinicalTrials.gov Identifier: NCT04782765.

Keywords Camrelizumab, Induction chemotherapy, Chemoradiotherapy, Nasopharyngeal carcinoma, Non-endemic areas

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Background

Nasopharyngeal carcinoma (NPC) is an epithelial cancer arising from the nasopharynx epithelium, which is characterized by distinct geographical distribution and highly prevalent in East and Southeast Asia, particularly in South China [1]. In endemic areas, a combination of genetic, ethnic, and environmental factors is always considered contributory to affect the pathogenesis of NPC. The non-keratinising pathological subtype constitutes most cases (> 95%) and is predominantly associated with Epstein-Barr virus (EBV) infection [2]. During these years, thousands of clinical trials have been spurred to revise the guidelines and improve the management of NPC in endemic areas [3]. However, clinical data collected from non-endemic areas (such as North China) often goes unnoticed and overlooked.

Dietary and pronunciation pattern as well as socioeconomic status vary largely in South and North China, leading to potential different tumorigenesis mechanisms of NPC from these different risk areas in China. For example, a previous epidemiological study showed that the EBV serostatuses in endemic areas were significantly higher than those in non-endemic areas [4]. Given that the current reliable evidence is lacking, questions on pathogenesis and clinical management of NPC in North China remain to be addressed, optimizing treatment strategies for these patient subgroups is of great importance.

More than 70% of NPC are classified with locoregionally advanced disease at the first diagnosis. For these patients, induction chemotherapy (IC) combined with concurrent chemoradiotherapy (CCRT) constitutes the therapeutic backbone, and has substantially improved locoregional control [5]. However, a high proportion of patients still suffered from disease relapse after receiving the standard treatment. Immune checkpoint blockade therapies have been confirmed efficient in patients with recurrent or metastatic NPC. However, several clinical trials of anti-programmed cell death-1 (PD-1) antibody in patients with locoregionally advanced NPC are quite heterogeneous in design and patient selection, and no robust evidence has been reported and accepted currently, especially in the non-endemic areas of NPC [6–8].

Here we designed a phase 2 study in North China to evaluate the efficacy and safety of IC plus camrelizumab followed by CCRT as a curative approach in patients with locoregionally advanced NPC, with the goal of significantly decreasing risk of local failure and distant metastasis for patients outside the endemic areas of NPC.

Methods

Study design and participants

This study was an open-label, single-arm, phase 2 study conducted at Tianjin Medical University Cancer Institute & Hospital between January 2019 and March 2023. The trial protocol was approved by the Chinese Ethics Committee of Registering Clinical Trials and registered at ClinicalTrials.gov (NCT04782765). Written informed consent was obtained from all participating patients before enrollment. This trial was conducted according to the Declaration of Helsinki and the standards of Good Clinical Practice.

Patients aged 18–70 years, born and living in North China (Tianjin, Hebei province, Shanxi province, Shandong province, Inner Mongolia Autonomous Region, Heilongjiang province, Jilin province, Liaoning province, and Henan province), with previously untreated, histologically proven stage III to IVa NPC (by the American Joint Committee on Cancer tumor staging system, 8th edition) were enrolled, regardless of tumor programmed cell death-ligand 1 (PD-L1) status. All patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate bone marrow, liver and renal function. The key exclusion criteria included stage T3–4N0 and T3N1 NPC; a history of previous radiotherapy, chemotherapy, or surgery for the primary tumor or lymph nodes; any severe comorbidities; previous malignancy apart from non-melanoma skin cancer or carcinoma in situ of the uterine cervix; pregnancy or lactation; uncontrolled active infection; a history of protocol-specified autoimmune disease and active autoimmune disease. The full eligibility criteria are available in the Additional file 1.

Procedures

All eligible patients received two 21-day cycles of camrelizumab (200 mg intravenously on day 1) in combination with IC (docetaxel 75 mg/m^2 intravenously on day 2, and cisplatin 25 mg/m^2 intravenously on days 2–4), followed by CCRT (intensity modulated radiotherapy with concurrently two 21-day cycles of cisplatin 80 mg/m^2 intravenously on day 1). The radiotherapy protocol is provided in the Additional file 1. For the gross target volume of nasopharynx (GTVnx) and lymph nodes (GTVnd), a total radiation dose of 69.96 Gy was administered in 33 fractions (five fractions per week). Clinical target volume (CTV) of high-risk region and low-risk region were administered a respective dose of 60.06 Gy in 33 fractions and 50.96 Gy in 28 fractions [9]. After CCRT, patients received 200 mg camrelizumab maintenance once every 3 weeks for 12 cycles. Dose modification of camrelizumab was not permitted. If a grade 3 adverse

event (AE) was related to camrelizumab as judged by the investigator, treatment was delayed until the AE recovered to grade 1. If the grade 3 AE did not relieve within 6 weeks, or a grade 4 camrelizumab-related AE occurred, camrelizumab treatment was permanently discontinued.

Tumor response was evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST; version 1.1) at 1 week after induction therapy and 12 weeks after CCRT were completed. Physical examinations, flexible nasopharyngoscopy, magnetic resonance imaging (MRI) of the nasopharynx and neck, thoracic and abdominal computed tomography (CT) scan, biochemistry test, and blood cell counts were done every 3 months for 2 years and every 6 months thereafter. CT was performed if patients had contraindication for MRI. Nasopharyngoscopic biopsy was performed 2 weeks prior to CCRT. Patients were withdrawn from the study if they had tumor progression or severe comorbidities developed during treatment, or withdrew consent at any time during the study period. AEs were recorded and graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 5.0) and the Radiation Therapy Oncology Group (RTOG) criteria.

Outcomes

The primary endpoint was 3-year disease-free survival (DFS), defined as the duration from treatment to disease recurrence (locoregional or distant) or death from any cause. Secondary endpoints included objective response rate (ORR; defined as the proportion of patients with the best response of complete response [CR] or partial response [PR]), locoregional recurrence-free survival (LRFS; defined as duration from diagnosis to locoregional recurrence), distant metastasis-free survival (DMFS; defined as duration from diagnosis to distant metastasis), overall survival (OS; defined as duration from diagnosis to death from any cause or last follow-up), and safety.

Statistical analysis

Sample size calculation employed Fleming's one-sample, multiple-testing procedure ($\alpha = 0.05$, $\beta = 0.20$). Given previous treatment data [3, 5, 6], we proposed an 80% threshold for 3-year DFS as the primary endpoint. A 95% confidence interval (CI, width 20%, upper limit 90%) was established. Statistical analysis indicated a required cohort of 53 patients to achieve desired power and precision. Accounting for a 10% drop-out rate, the minimum sample size was determined to be 59 subjects.

Results were expressed as frequencies (percentages) for categorical variables and as medians (ranges or interquartile ranges [IQRs]) for continuous variables. Time-to-event data was estimated using the Kaplan–Meier method and the corresponding 95% CIs were calculated using the Greenwood's formula. Time-to-event data were compared between subgroups using the log-rank test. SPSS version 24.0 (IBM SPSS Statistics, Armonk, NY: IBM Corp) was used for the statistical analysis.

Results

Patients and treatment compliance

From February 2021 to September 2023, a total of 61 patients from North China (mainly Tianjin, Hebei province and Shandong province) were enrolled (Fig. 1A). Among these patients, one patient died before receiving treatment, one patient with stage II tumor was mistakenly enrolled, two patients withdrew consent after one cycle of induction therapy, one patient refused CCRT after induction therapy, and one patient discontinued radiotherapy after receiving 9 fractions due to personal reason. Therefore, 55 (90.2%) of 61 patients were finally included in the efficacy analysis and 57 (93.4%) in the safety analysis (Fig. 1B). Table 1 lists the baseline characteristics.

Fifty-four (98.2%) of 55 patients completed 2 cycles of induction therapy without dose modification, while one (1.8%) patient only completed one cycle due to abnormal liver function. During CCRT phase, all the patients completed the entire radiation therapy plan; 46 (83.6%) of 55 patients completed 2 cycles of cisplatin treatment without dose modification, eight (14.6%) patients received one cycle due to leukopenia or mucositis, and one patient did not receive chemotherapy due to tumor-associated dermatomyositis. Of the 55 patients, 27 received 12 cycles of camrelizumab maintenance after CCRT, 2 received 2 cycles, while 26 refused due to personal reasons, including being too far from the hospital or lack of money. Characteristics of patients who received or refused camrelizumab maintenance are shown in Additional file2: Table 1.

Efficacy

Overall, after the completion of induction therapy and before CCRT initiated, 51 (92.8%) of 55 patients had an objective response (Table 2). For primary tumors, 15 (27.3%) patients had complete response (CR), 36 (65.5%) had partial response (PR), and 4 (7.2%) had stable disease (SD). For lymph nodes, 8 (14.6%) patients had CR, 46 (83.6%) had PR, and 1 (1.8%) had SD (Additional file2: Fig.S1). Among the 10 stage T4 patients, 1 (10.0%) had CR of nasopharyngeal lesions and 9 (90.0%) had PR. Among the 16 stage N3 patients, 1 (6.25%) patient had CR of lymph nodes, 14 (87.5%) had PR and 1 (6.25%) had SD. Seventeen (30.9%) of 55 patients had detectable pre-treatment plasma EBV DNA with a median level of 1157.66 (IQR, 628.24–2432.52) copies/mL. The

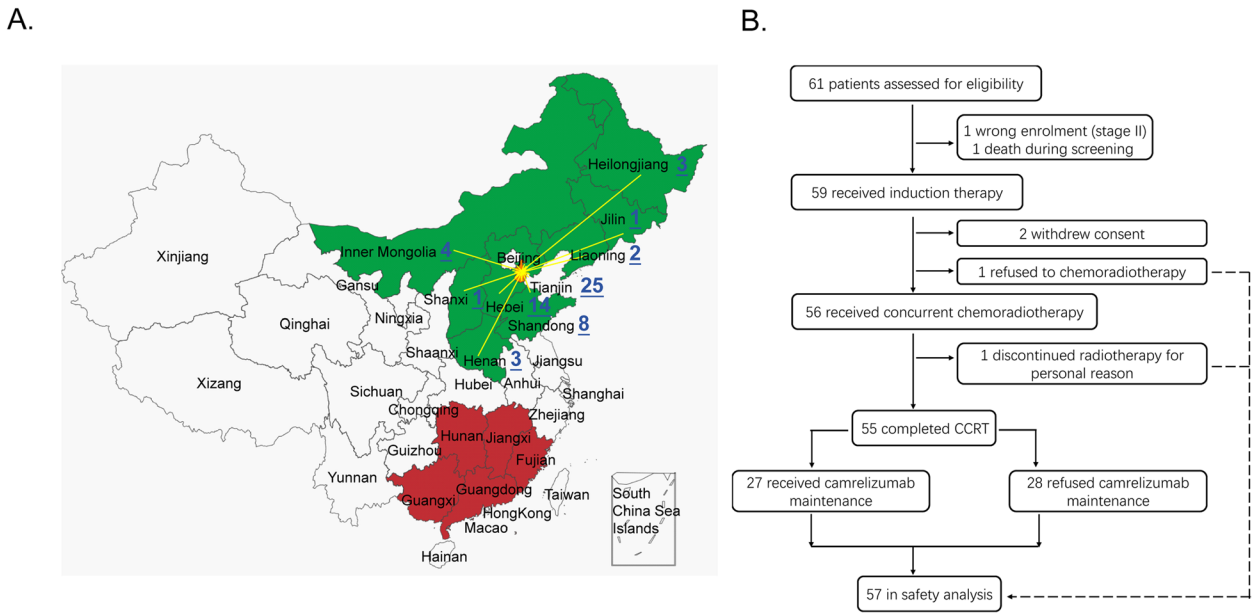

Fig. 1 (**A**) Distribution of enrolled patients. Red color indicates endemic regions of nasopharyngeal carcinoma in China. Green color indicates origin of enrolled patients from non-endemic regions. Number presents patients enrolled from each province. **B** Trial profile

EBV DNA levels became persistently undetectable in all of these patients (100%) after the completion of induction therapy. Thirty-three (86.8%) of 38 patients with available endoscopic biopsy samples from the nasopharyngeal lesions had negative pathological findings (Additional file2: Fig.S2). Characteristics of patients who received or refused biopsy are shown in Additional file2: Table 2. At 3 months after CCRT, the overall ORR was 100% (55/55). For primary tumors, 51 (92.8%) patients had CR and 4 (7.2%) had PR. For lymph nodes, all the 55 (100%) patients achieved CR. Among the stage T4 patients, 80.0% (8/10) of them had CR of nasopharyngeal lesions and 20.0% (2/10) had PR. All the stage N3 patients (16/16, 100%) achieved CR of lymph nodes.

Median follow-up time was 21 months (IQR, 15–33). Median DFS was 43 months (95% CI, 41–45). The 2-year and 3-year DFS rates were 87.7% (95% CI, 82.4–93.0) and 84.0% (95% CI, 77.8–90.2), respectively. Both the 2-year and 3-year LRFS rates were 95.8% (95% CI, 91.7–99.9). Both the 2-year and 3-year DMFS rates were 91.7% (95% CI, 86.8–95.4) and 90.9% (95% CI, 85.7–96.1), respectively. During the follow-up, 1 patient died of liver metastases, 3 died of nasopharyngeal massive hemorrhage, and 1 died of intracranial infection. The 2-year and 3-year OS rates were 93.4% (95% CI, 89.7–97.1) and 89.5% (95% CI, 84.3–94.7), respectively (Fig. 2A-D).

Of the 55 patients, 27 received 12 cycles of camrelizumab maintenance after CCRT, while 26 refused and 2 received only 2 cycles. Improvements in disease control and trend of benefit in survival were observed with camrelizumab maintenance (Fig. 2E-H). All the progression and death events were reported in the observation subgroup. Notably, the camrelizumab maintenance subgroup showed better DFS (p = 0.009) and OS benefit (p = 0.035). There was also a tendency of improvement in locoregional recurrence ($p = 0.277$) and distant metastasis ($p = 0.092$).

Adverse events

Treatment-related AEs (TRAEs) are listed in Table 3. During induction therapy, the most common TRAEs of any grade were leukopenia, neutropenia, lymphopenia, nausea, anemia, vomiting, constipation, anorexia, hypothyroidism and reactive cutaneous capillary endothelial proliferation (RCCEP). Twenty-six (45.6%) of 57 patients had grade 3 or 4 TRAEs, with the most common being leukopenia (7 [12.3%]) and neutropenia (6 [10.5%]). During CCRT, the most common TRAEs of any grade were leukopenia, neutropenia, lymphopenia, anemia, nausea, vomiting, constipation, thrombocytopenia, anorexia, xerostomia, oral mucositis, dermatitis and weight loss. Twenty-three (41.1%) of 56 patients had grade 3 or 4 TRAEs, with the most common being weight loss (6 [10.7%]) and lymphopenia (5 [8.9%]). The most common late TRAEs were impaired hearing, dental disorders and hypogeusia.

RCCEP was observed in 33 (57.9%) patients during the induction therapy, and newly developed in six (10.9%) patients during the maintenance therapy. One patient developed a large mass in the contralateral neck after

Table 1 Patient characteristics

Characteristics	No. (% of patients), N = 57
Age (years)	51 (range 29–70)
Gender (male/female)	
Male	45 (78.9%)
Female	12 (21.1%)
ECOG perform status[a]	
0	51 (89.5%)
1	6 (10.5%)
T stage	
T1	2 (3.5%)
T2	15 (26.3%)
T3	30 (52.6%)
T4	10 (17.6%)
N stage	
N1	7 (12.3%)
N2	34 (59.6%)
N3	16 (28.1%)
Stage[b]	
III	31 (54.4%)
IVa	26 (45.6%)
Histology classification	
Non-keratinising differentiated	29 (50.9%)
Non-keratinising undifferentiated	27 (47.4%)
Keratinizing squamous carcinoma	1 (1.7%)
Positive plasma EBV DNA[c]	17 (29.8%)
Smoking (current or past)	21 (36.8%)

[a] Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability

[b] Tumor category refer to the T stage according to the TNM staging system (American Joint Committee on Cancer, 8th edition)

[c] Shown are the data of pretreatment plasma Epstein-Barr virus (EBV) DNA level which were based on a lower limit of detection cutoff value of 400 copies/mL

the first cycle of induction therapy, which was later confirmed to be soft tissue inflammation through biopsy (Additional file2: Fig.S3). Two patients developed easily ulcerated and bleeding-prone lesions in the nasopharyngeal region after CCRT about 8 months later, and disappeared on their own 3 months later by re-examining with nasopharyngoscopy (Additional file2: Fig.S4). Another one patient developed maculopapular rash and tachycardia. All of these AEs were grade 1 or 2, which were deemed related to camrelizumab. No patients discontinued camrelizumab because of immune-related AEs (irAEs). No patients had dose reduction of chemotherapy during treatment.

Discussion

This study is the first phase 2 trial to evaluate the efficacy and safety of anti-PD-1 immunotherapy combined with IC followed by CCRT in patients with locoregional advanced NPC in the non-endemic areas. Our findings suggest that 2 cycles of induction immunochemotherapy (camrelizumab plus docetaxel and cisplatin) had efficient and fast local control. After CCRT, promising local and distant control were further observed with acceptable safety profile. The 3-year DFS rate was 84%, which was better than previous reports [5, 6, 10].

NPC is characterized by high PD-L1 expression (up to 90% of tumor cells), which renders patients potentially suitable for immune checkpoint blockade therapies [2, 11]. To date, a total of three anti-PD-1 antibodies (including camrelizumab, toripalimab, and tislelizumab) have been confirmed efficient and approved as first-line standard treatment for recurrent or metastatic NPC in China [12–14]. Our results validated the clinical benefits of camrelizumab for locoregionally advanced NPC, especially in non-endemic areas. It was reported that in patients with locoregionally advanced NPC, the CR, PR, and SD rates after the recommended IC (docetaxel plus cisplatin and fluorouracil) were 11%, 78%, and 9% respectively. ORR was 90%, and the 3-year failure-free survival rate was 80% [10]. Our results showed a consistently high ORR rate of 92.8%, with a higher CR rate of 27.3% after

Table 2 Response to treatment [no. /total no. (%)]

		III to IVa Stage	III to IVa Stage		T4 stage	N3 stage
			nasopharyngeal lesion	lymph node	nasopharyngeal lesion	lymph node
Response to induction phase	OR	51/55 (92.8%)	51/55 (92.8%)		10/10 (100%)	15/16 (93.75%)
	CR	4/55 (7.2%)	15/55 (27.3%)	8/55 (14.6%)	1/10 (10.0%)	1 /16 (6.25%)
	PR	47/55 (85.6%)	36/55 (65.5%)	46/55 (83.6%)	9 /10 (90.0%)	14/16 (87.5%)
	SD	4/55 (7.2%)	4/55 (7.2%)	1/55 (1.8%)	0	1/16 (6.25%)
Response to radiation phase	OR	55/55 (100%)	55/55 (100%)	55/55 (100%)	10/10 (100%)	16/16 (100%)
	CR	51/55 (92.8%)	51/55 (92.8%)	55/55 (100%)	8/10 (80.0%)	16/16 (100%)
	PR	4/55 (7.2%)	4/55 (7.2%)	0	2/10 (20.0%)	0
	SD	0	0	0	0	0

OR Objective response, *CR* Complete response, *PR* Partial response, *SD* Stable disease

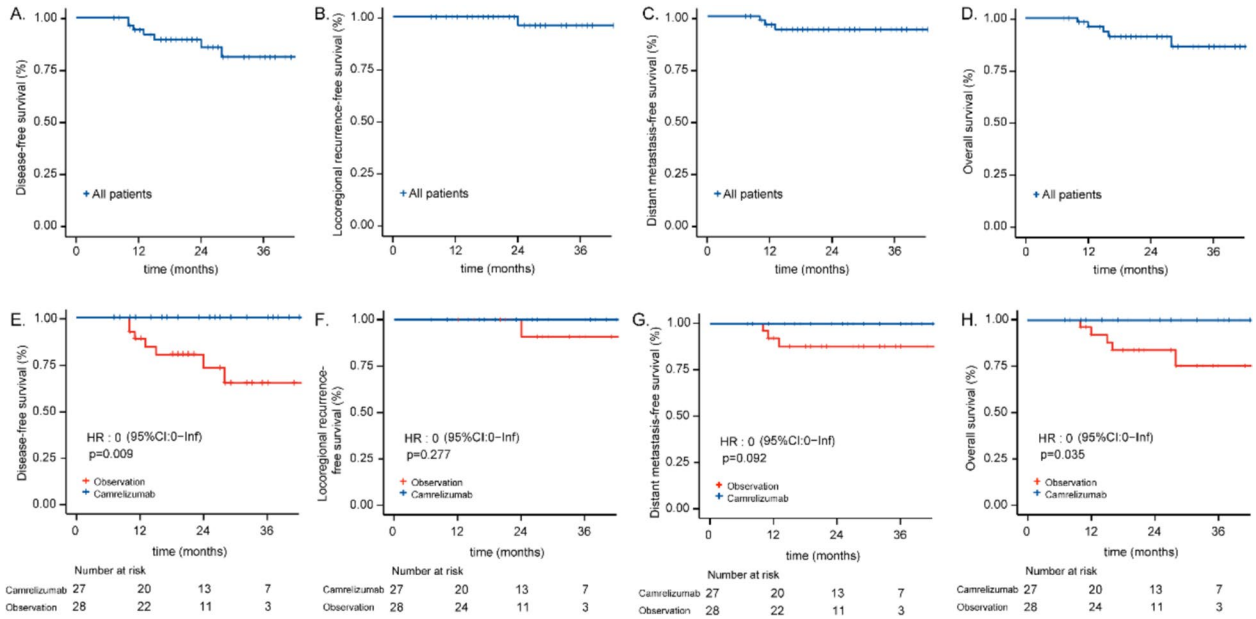

Fig. 2 Kaplan–Meier analysis of survival outcomes. (A) Disease-free survival of all patients. (B) Locoregional recurrence-free survival of all patients. (C) Distant metastasis-free survival of all patients. (D) Overall survival of all patients. (E) Disease-free survival in camrelizumab maintenance subgroup vs. observation subgroup. (F) Locoregional recurrence-free survival in camrelizumab maintenance subgroup vs. observation subgroup. (G) Distant metastasis-free survival in camrelizumab maintenance subgroup vs. observation subgroup. (H) Overall survival in camrelizumab maintenance subgroup vs. observation subgroup

IC plus camrelizumab, compared with the historical CR rate of 11% for IC, indicating a good antitumor activity besides chemotherapy alone. None of the patients represented with detectable EBV DNA, and 86.8% of biopsied primary tumor samples had negative pathological findings. DMFS and DFS were even higher. Moreover, it was reported that the non- keratinizing subtype of NPC accounts for > 95% of cancers in endemic areas (invariably associated with EBV infection,), and for 75% in the United States [2]. The proportion of keratinizing and non- keratinizing subtype in this study is fairly equal, both being around 50%. The proportions of non-keratinizing subtype and EBV DNA positive were far lower than the data from endemic areas and regions in America. While this regimen still showed a favorable overall outcome. All of these results indicate that the combination of IC plus camrelizumab maybe strong enough to eradicate tumor load and micrometastatic lesions for patients with locoregionally advanced NPC in non-endemic areas.

Multiple large-scale randomized controlled trials from the 1990s have demonstrated the benefit of IC in locoregionally advanced NPC, which is now recommended as a preferred treatment strategy in guidelines [3, 9, 15]. In this study, we used docetaxel plus cisplatin as IC regimen rather than traditionally used regimens (gemcitabine plus cisplatin, cisplatin plus 5-fluorouracil, or docetaxel plus cisplatin and fluorouracil) [16–18], and administered for 2 cycles rather than 3 cycles. For the concurrent phase, a reduced-dose and reduced-course of cisplatin was administrated as chemotherapy during radiotherapy (80 mg/m^2 once every 3 weeks for 2 cycles rather than 3). The dose of cisplatin during the concurrent phase had significant impact on locoregional tumor control and survival. The typical study demonstrated the importance and adequacy of a dose of cumulative cisplatin 200 mg/m^2 in two concurrent cycles for locoregional control and survival of locoregionally advanced NPC was documented by Lee AW in 2010, which was conducted in endemic regions [19]. The locoregional- and distant- failure free rate for patients who received 0–100 mg/m^2 dose of cisplatin was significantly lower than those who received 200 mg/m^2 dose of cisplatin. And three-weekly cisplatin was demonstrated comparably efficient to weekly cisplatin, with significantly fewer acute and late-onset auditory loss toxicities [20]. In further study conducted by Anthony T.C. Chan, patients who received more than 200 mg/m^2 dose of cisplatin (administrated at a fixed dose of 40 mg/m^2/week for more than 5 cycles) had better OS than those who received less cycles. Cut-off values of cycles number was chosen as 5. However, more than 5 cycles of cisplatin, not > 4 cycles or > 6 cycles, was found actually only associated with death, but not disease recurrence or metastasis [21]. Thus many subsequent randomized studies in

Table 3 Adverse events [No. (% of patients)]

Event	Cumulative TRAEs (*N* = 57)		Induction phase (*N* = 57)		Concurrent phase (*N* = 56*)	
	Grade1/2	Grade3/4	Grade1/2	Grade3/4	Grade1/2	Grade3/4
Any acute adverse event						
leukopenia	30 (52.6%)	8 (14.0%)	19 (33.3%)	7 (12.3%)	17 (30.4%)	2 (3.6%)
neutropenia	19 (33.3%)	6 (10.5%)	13 (22.8%)	6 (10.5%)	11 (19.6%)	0
lymphopenia	41 (71.9%)	5 (8.8%)	15 (26.3%)	0	33 (58.9%)	5 (8.9%)
anemia	44 (77.2%)	0	36 (63.2%)	0	30 (53.6%)	0
thrombocytopenia	20 (5.1%)	1 (1.8%)	9 (15.8%)	1 (1.8%)	14 (25%)	0
blood creatinine elevation	5 (8.8%)	0	5 (8.8%)	0	1 (1.8%)	0
transaminase elevation	6 (10.5%)	1 (1.8%)	5 (8.8%)	1 (1.8%)	2 (3.6%)	0
hyponatremia	5 (8.8%)	2 (3.5%)	3 (5.3%)	2 (3.5%)	2 (3.6%)	0
hypochloremia	4 (7.0%)	2 (3.5%)	2 (3.5%)	2 (3.5%)	2 (3.6%)	0
hypokalemia	3 (5.3%)	3 (5.3%)	2 (3.5%)	3 (5.3%)	1 (1.8%)	0
hypomagnesemia	2 (3.5%)	0	2 (3.5%)	0	0	0
hyperkalemia	1 (1.8%)	0	1 (1.8%)	0	0	0
lactate dehydrogenase elevation	1 (1.8%)	0	1 (1.8%)	0	0	0
amylase elevation	1 1.8(%)	0	1 (1.8%)	0	0	0
diarrhea	3 (5.3%)	1 (1.8%)	3 (5.3%)	1 (1.8%)	0	0
nausea	57 (100%)	2 (3.5%)	43 (75.4%)	1 (1.8%)	40 (71.4%)	2 (3.6%)
vomiting	39 (68.4%)	1 (1.8%)	28 (49.1%)	1 (1.8%)	32 (57.1%)	1 (1.8%)
constipation	25 (43.9%)	0	15 (26.3%)	0	13 (23.2%)	0
anorexia	40 (70.2%)	1 (1.8%)	18 (31.6%)	1 (1.8%)	26 (46.4%)	2 (3.6%)
weight loss	45 (78.9%)	6 (10.5%)	4 (7.0%)	0	44 (78.6%)	6 (10.7%)
xerostomia	45 (78.9%)	2 (3.5%)	-	-	45 (80.4%)	2 (3.6%)
oral mucositis	53 (93.0%)	2 (3.5%)	-	-	53 (94.6%)	2 (3.6%)
dermatitis	42 (73.7%)	1 (1.8%)	-	-	42 (75.0%)	1 (1.8%)
Any immune-related adverse events						
RCCEP	33 (57.9%)	0	33 (57.9%)	0	-	-
rash	9 (15.8%)	0	9 (15.8%)	0	-	-
dermatomyositis	1 (1.8%)	0	1 (1.8%)	0	-	-
hyperthyroidism	4 (7.0%)	0	4 (7.0%)	0	-	-
allergic reaction	1 (1.8%)	0	1 (1.8%)	0	-	-
hypothyroidism	21 (38.2%)	0	21 (38.2%)	0	-	-
pneumonia	0	0	0	0	-	-
Any late adverse event						
nasopharyngeal necrosis	1 (1.8%)	0	-	-	-	-
hypogeusia	14 (24.6%)	1 (1.8%)	-	-	-	-
impaired hearing	13 (22.8%)	1 (1.8%)	-	-	-	-
dental disorders	16 (28.0%)	0	-	-	-	-
dysphagia	8 (14.0%)	0	-	-	-	-
peripheral neuropathy	3 (5.3%)	0	-	-	-	-

* Due to one patient declined concurrent chemoradiotherapy after induction phase, there were 56 patients for safety analysis in concurrent phase. Patients may have had more than one event. RCCEP, reactive cutaneous capillary endothelial proliferation

these disease setting confirmed the backbone of concurrent cisplatin to 200 mg/m^2, administered for 2 cycles every 3 weeks. However, all the studies were performed in endemic patients. It has not been evaluated whether less dose of cisplatin, i.e. 160–200 mg/m^2, can take effect, especially in significantly different patient setting from non-endemic region, like population in our study. And our data showed that 2 cycles of IC plus 2 cycles of three-weekly concurrent cisplatin with a total dose of 160 mg/m^2 was feasible. For patients in non-endemic

areas, it reduced toxicity by avoiding unnecessary overdose, and maintained efficacy without affecting prognosis. And we noticed that in T4 and N3 patients, their CR rate was much lower than that of patients in our groups. This dose not rule out a relationship with the choice of the docetaxel-cisplatin regimen over conventional gemcitabine-cisplatin and the reduced cumulative cisplatin dose. But the overall efficacy is still favorable and acceptable. Indeed, this regimen with reduced cycle and dose of chemotherapy could be introduced to patients from non-endemic areas, and nevertheless, further larger clinical trials and follow-up are warranted.

Immno-maintenance therapy following radical treatment is commonly applied in clinical trials focus on immunotherapy (i.e. NCT03121716, NCT03700476, and NCT03581786) [7, 12, 13]. The duration of maintenance is different, ranged from six cycles (18 weeks) in NCT03121716 to 36 cycle (2 years) in NCT03581786. Compared with developed southern areas such as Guangdong province and Hong Kong, which is also NPC endemic areas, the economic level in many northern China is relatively backward, and the living standards are low. The cost effectiveness is a very important factor affecting treatment decisions in routine practice. In our study, nearly half of the patients did not receive camrelizumab maintenance due to their personal reason, i.e. being too far from the hospital or lack of money. We must admit that this violation might result in an insufficient sample size to some extent. Camrelizumab maintenance showed a trend of advantages of disease control and survival in this phase 2 study, aligns with global trends in other cancer types. But we must take note that all the negative events which contributed to the poor prognosis were reported in the observation subgroup. And the DFS, LRFS, DMFS and OS rate in the observation subgroup at 2 year was 80.3%, 90.9%, 87.9% and 83.9% respectively, indeed comparable with the data reported in previous studies [16, 22]. Therefore, head-to-head phase 3 clinical trials are still indeed necessary to verify whether immno-maintenance therapy plays a positive role in efficacy and ultimately survival.

Our data indicate that this combination regimen is more suitable for those with high tumor burden, i.e. stage T4 or N3 patients. Patients with stage T4 or N3 disease always have worse prognosis owing to the high incidence of distant metastasis or local failure, which may be due to the micrometastases that already exist during initial treatment [23, 24]. Xu et al. pointed out that for stage N3 NPC, previous conventional 2-cycle IC could not reach the required intensity of chemotherapy for metastatic lesions. Therefore, they introduced fluorouracil to the regimen of docetaxel plus cisplatin, and the IC increased to 4 cycles of [25]. In their study, the ORR was 100%, better than previous reports. However, the CR rate of nasopharyngeal lesions was lower, and 3-year PFS and OS rate were also lower than previous data, which might be due to the high proportion of patients with stage T4 tumor. This also suggests the limitation of increasing the intensity of chemotherapy alone. Oral mucositis may occur in 20–50% patients who receive fluorouracil, affecting the process of radiotherapy [26, 27]. We recruited a total of 26 stage IVa patients (45.6%, T4NanyM0 or TanyN3M0) in this study. After CCRT, both the nasopharyngeal lesions and lymph nodes regressed significantly, and 80% of nasopharyngeal lesions and 100% of lymph nodes achieved CR. These short-term data were relatively better than previously reported data [25], while the long-term efficacy needs further follow-up. Indeed, the addition of camrelizumab on the basis of IC and CCRT is more recommended for newly diagnosed locoregionally advanced NPC with bulky lesions, which is able to quickly active patients' antitumor response, cause rapid regression of tumor, and thus might ultimately enhance the patient's survival. However, further studies with expanded sample size and sub-analysis are still needed.

Most of the AEs in this trial were well-tolerated and manageable, and the combination regimen did not result in any unexpected grade 3 or 4 TRAEs. Most patients completed 2 cycles of induction therapy (98.2%) and 2 cycles of CCRT (83.6%). The majority of grade ≥ 3 TRAEs were related to chemotherapy, including grade 3–4 leukopenia and neutropenia. The irAEs were generally consistent with that reported for other anti-PD-1 antibodies, except RCCEP. The incidence of RCCEP in our study was 57.9%, similar with that in the CAPTAIN-1st study using camrelizumab plus gemcitabine and cisplatin to treat recurrent or metastatic NPC (58%) [28]. All the RCCEP events in our study were grade 1. During the follow-up of two patients, we observed some bleeding-prone lesions by nasopharyngoscopic about 8 months after CCRT, as shown in Additional file2: Fig.S4. The lesions disappeared on their own 3 months later by re-examining. The accompanied MRI results did not suggest any nasopharyngeal necrosis, and symptom was a little intermittent nasal bleeding. Because these lesions were not accompanied with obvious inflammation, ulceration, necrosis or massive hemorrhage in the nasopharynx, but seem to present similarly to the RCCEP on the skin surface, we suggest nasopharyngoscopy be carried out closely after CCRT.

Tumor regression grading (TRG) is used to evaluate the treatment efficacy in solid tumors based on images and histopathology, which is also an independent prognostic factor for survival [29]. In this study, 86.8% of the patients achieved pathological CR (pCR) of the nasopharyngeal lesions after 2 cycles of induction therapy, with

histological examination showing mucosal inflammation or squamous epithelial atypia after cytological examination. Correspondingly, most of them also showed complete tumor regression on imaging, suggesting a good response to the treatment. It was reported that IC plus camrelizumab resulted in a pCR rate of 37% and a major pathological response (MPR) rate of 74.1% in patients with locoregionally advanced head and neck cancer, and clinical to pathological downstaging rate was 100%, which greatly exceeded historical data and predicted a good outcome for patients [30]. In tumors such as esophageal cancer and gastric cancer, induction regimen including immunotherapy combined with chemotherapy have enabled patients to achieve good pathological responses and tumor regression, as well as further survival benefits [31, 32]. However, the TRG assessment is more commonly used in esophageal cancer, gastric cancer, and rectal cancer, which have poor reproducibility of measurement. Grading is more recommended by quantificationally assessing the proportion of residual tumor cells in the tumor bed after complete resection. Thus, the application of TRG has limitation in NPC. Nevertheless, the high pathological response rate in this study could still be adopted for the prediction of patient survival and the selection of beneficiary population.

The present study has some limitations. First, this was a single-arm trial and the conclusions need to be validated in a large randomized controlled trial in the same NPC patient population. Second, 2 cycles of three-weekly concurrent cisplatin with a total dose of 160 mg/m^2 during radiotherapy was not recommended by guidelines, except in cisplatin-intolerant patients. In future, we would compare 2 cycles of cisplatin (total dose: 160 mg/m^2) vs. 2–3 cycles of cisplatin (total dose: 200 mg/m^2). Third, the number of patients who underwent PD-L1 expression measurement was relatively small, and further validation is desirable. Fourth, longer follow-up is needed to assess the long-term survival benefits.

In conclusion, our findings suggest that in patients with locoregionally advanced NPC from non-endemic areas, induction camrelizumab combined with IC (docetaxel and cisplatin) and CCRT have promising antitumor activity with a manageable safety profile. Larger randomized controlled trials are warranted to validate our findings.

Conclusions

We represent the first prospective phase 2 clinical trial investigating the efficacy and safety of camrelizumab combined with IC and CCRT in patients with locoregionally advanced NPC from non-endemic regions of North China. We demonstrated that combining camrelizumab with IC followed by CCRT resulted in excellent local and distant metastasis control with a manageable safety profile. Longer follow up is needed to determine whether the short-term efficacy will translate into a benefit in overall survival.

Abbreviations

AE	Adverse event
CCRT	Concurrent chemoradiotherapy
CI	Confidence interval
CR	Complete response
CTV	Clinical target volume
CT	Computed tomography
DFS	Disease-free survival
DMFS	Distant metastasis-free survival
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
GTV	Gross target volume
IC	Induction chemotherapy
IQR	Interquartile ranges
LRFS	Locoregional recurrence-free survival
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-ligand 1
MRI	Magnetic resonance imaging
MPR	Major pathological response
NPC	Nasopharyngeal carcinoma
ORR	Objective response rate
OS	Overall survival
PR	Partial response
RCCEP	Reactive cutaneous capillary endothelial proliferation
RTOG	Radiation Therapy Oncology Group
TRAEs	Treatment-related adverse events
TRG	Tumor regression grading

Supplementary Information

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Additional file 1. Study Protocol.

Additional file 2. Table 1. Characteristics of patients who received or refused camrelizumab maintenance. Table 2. Characteristics of patients who received or refused biopsy. Figure S1-Tumor response to induction therapy. Figure S2-Representative images before and after induction therapy. Figure S3-Representative images of neck adverse event of a patient. Figure S4-Representative images of a patient who received nasopharyngoscopic re-examination after concurrent chemoradiotherapy.

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Authors' contributions

ZQ Wang and PG Wang had full access to research data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: PG Wang, Q Wang. Acquisition, analysis, or interpretation of data: ZQ Wang, Y Sun, QX Wang, YL Chai, J Sun, XM Zhang, Q Wang, W Wang. Drafting of the manuscript: ZQ Wang. Critical revision of the manuscript for important intellectual content: W Wang, PG Wang. Statistical analysis: QX Wang, YL Chai. Administrative, technical, or material support: QX Wang.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All procedures were approved by Chinese Ethics Committee of Registering Clinical Trials and the Medical Ethics Committee of Tianjin Medical University Cancer Institute & Hospital (20202011021305005 6). The protocol was registered at ClinicalTrials.gov (NCT04782765). Written informed consent was obtained from all participating patients before enrollment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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