Induction chemotherapy regimen of docetaxel plus cisplatin versus docetaxel, cisplatin plus fluorouracil followed by concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: Preliminary results of an open-label, noninferiority, multicentre, randomised, controlled phase 3 trial

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Summary

Background Induction chemotherapy regimens of docetaxel and cisplatin plus fluorouracil (TPF) are currently clinically used for patients with locoregionally advanced nasopharyngeal carcinoma (LA-NPC) but have well-known side effects, such as myelosuppression and diarrhea. A docetaxel plus cisplatin (TP) regimen was developed to decrease the toxic effects induced by fluorouracil. In this trial, we assessed whether the TP induction chemotherapy regimen was noninferior to the TPF regimen.

Methods We performed an open-label, noninferiority, phase 3, multicentre, randomised, controlled trial at six centres in China. Eligible patients with NPC (stage III-IVA (excluding T3-4N0), Karnofsky's Performance Scoring ≥70) were randomly assigned (1:1) to receive either TP (docetaxel (75 mg per square meter, d1, intravenous infusion) and cisplatin (75 mg per square meter of body-surface area, d1, intravenous infusion)) or TPF (docetaxel (60 mg per square meter, d1, intravenous infusion) plus cisplatin (60 mg per square meter, d1, intravenous infusion) and 5-fluorouracil (600 mg per square meter, d1-d5, intravenous 120-hour infusion)) administered every 3 weeks for 3 cycles followed by concurrent chemoradiotherapy. The primary endpoint was failure-free survival at 2 years. Secondary endpoints included overall survival, safety, and treatment compliance. The trial was stopped early because of strong evidence for noninferiority (margin was -10%) of TP in failure-free survival. Efficacy analyses were performed in both the intention-to-treat and per-protocol trial populations and we included the patients who started treatment in each group for the safety analysis. The study was registered with chictr.org.cn, ChiCTR1800016337.

Findings Between June 1, 2018 and October 31, 2021, we randomly assigned 361 patients to the TP (n = 181) or TPF (n = 180) induction chemotherapy group. The 2-year failure-free survival was 91·3% (95% CI 86·2-96·4) in the TP group and 82·4% (84·8-88·9) in the TPF group (P = 0·029). Patients in the TPF group had a higher frequency of grade 1 or 2 neutropenia (53 (30·0%) vs. 28 (15·7%); P = 0·0010), grade 1 or 2 diarrhea (20 (11·3%) vs. 9 (5·1%); P = 0·032), and grade 3 or 4 neutropenia (43 (24·3%) vs. 25 (14·0%); P = 0·014) in the induction chemotherapy period. There was no treatment-related death.

Interpretation The preliminary results revealed that TP induction chemotherapy regimen was found to be clearly non-inferior compared to the TPF regimen in failure-free survival, with a lower frequency of neutropenia, anaemia

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and diarrhoea. The more convenient and beneficial survival regimen of the TP regimen should be recommended in patients with LA-NPC.

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Keywords: Nasopharyngeal carcinoma; Docetaxel plus cisplatin (TP); Docetaxel, cisplatin plus fluorouracil (TPF); Survival; Toxicity

Research in context

Evidence before this study

We searched PubMed for relevant articles and the World Health Organization (WHO) International Clinical Trial Registry Platform for ongoing or completed trials from inception to January 11, 2022. The search terms included "nasopharyngeal carcinoma or cancer or neoplasm", "TP or TPF", "Induction chemotherapy (IC)", and "concurrent chemoradiotherapy (CCRT)". The search was limited to clinical trials but was not limited to studies written in English. However, neither retrospective nor prospective trial studies have directly compared the efficacy and safety of the docetaxel plus cisplatin (TP) regimen against docetaxel and the cisplatin plus fluorouracil (TPF) regimen in nasopharyngeal carcinoma treatment. Therefore, we designed a noninferiority trial to compare both regimens in patients with stage III–IVA NPC.

Added value of this study

To our knowledge, this is the first phase 3 study to assess the value of TP-based induction chemotherapy with TPF-based induction chemotherapy in nasopharyngeal carcinoma. Our findings show that TP-based induction chemotherapy followed by CCRT achieved better failure-free survival and resulted in lower hematologic and diarrhea harms. The results suggest that TP+CCRT is non-inferior compared to the TPF+CCRT in terms of failure-free survival.

Implications of all the available evidence

Our findings show that the TP induction chemotherapy regimen compared with the TPF regimen resulted in a non-inferior efficiency of failure-free survival. In addition, the TPF regimen resulted in remarkably higher rates of neutropenia, anemia and diarrhea than the TP regimen for patients with stage III–IVA NPC. This may offer evidence for clinicians. However, a longer follow-up is required to assess the long-term efficacy and toxicity of these two regimens.

Introduction

Nasopharyngeal carcinoma (NPC) has a distinct geographical distribution of occurrence worldwide and is endemic, especially in southern China, Southeast Asia, and North Africa, with an incidence of 50 cases per 100000 people per year.[1]

Of the 130,000 newly diagnosed cases reported worldwide in 2018, more than 70% were diagnosed with locoregionally advanced NPC (LA-NPC) at the initial presentation.[2] The results of the Intergroup 0099 randomised controlled trial established concurrent chemoradiotherapy as the standard treatment for locoregionally advanced (stage III-IVA) NPC.[3] Recently, several trials strongly supported induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT) as a new standard of care for LA-NPC, which brings a survival benefit. IC has many potential advantages, such as early relief of patient symptoms, better radiotherapy compliance with reduced targets, and elimination of tiny metastatic lesions which is the main failure pattern of LA-NPC.[4,5] In recent years, several large-scale multicentre randomised controlled trials from Guangzhou (China) have used docetaxel plus cisplatin (TP),[6] docetaxel, cisplatin and 5-fluorouracil (TPF),[7] cisplatin plus 5-fluorouracil (PF),[8] and gemcitabine plus cisplatin (GP)[9] as induction chemotherapy regimens, and the results revealed significantly improved survival in locoregionally advanced NPC with no marked increase in late adverse events. IC followed by CCRT is the mainstay treatment for patients with LA-NPC, as described in the Chinese Society of Clinical Oncology (CSCO) clinical guidelines[10] and the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology of head and neck cancers version 2.2022.[11]

Currently, TPF is clinically widely used (NCCN recommends evidence of category 1 for EBV-associated disease and category 2A for non-EBV-associated disease). However, the fact that TPF is accompanied by a longer treatment time and treatment-associated toxicities caused by 5-FU, such as myelosuppression and

diarrhea, should not be ignored and may indeed influence compliance with chemotherapy and radiotherapy. Therefore, finding another chemotherapy regimen with prolonged survival and acceptable toxicity is important. The TP regimen is recommended on the basis of category 2A evidence. A retrospective study[12] demonstrated that there were no differences in survival between the induction regimen of TPF and TP, and the patients in the TP regimen experienced fewer grade 3/4 toxicities of leukocytopenia, neutropenia, mucositis and diarrhea than the TPF regimen in patients with locally advanced squamous cell carcinoma of the head and neck. Until now, no randomised trials have directly compared the efficacy and safety of TP and TPF induction chemotherapy regimens for patients with LA-NPC. Thus, we performed a randomised, phase 3 trial to explore the noninferiority of TP compared with TPF in an induction chemotherapy regimen plus CCRT in patients with LA-NPC.

Methods

Study design and participants

The open-label, multicentre, noninferiority randomised, controlled trials in patients with nasopharyngeal carcinoma were designed in China. Patients were enrolled from 6 hospitals in China (Table S1 in the Supplementary Appendix). The institutional ethics review board at each participating centre approved the trial protocol. The trial was performed according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonization. Written informed consent was obtained from all the patients before enrollment. The protocol is available in the appendix. The study was registered with chictr.org.cn, number ChiCTR1800016337.

Eligible patients were aged between 18 and 65 years and had histologic confirmation of nasopharyngeal carcinoma without any previous treatments, including radiotherapy, chemotherapy, surgery, immunotherapy, anti-angiogenesis, targeted therapy or treatment with palliative intent; a clinical stage of III-IVA (excluding T3-4N0; according to the American Joint Committee on Cancer—Union for International Cancer Control 8th edition stage-classification system);[13] nondistant metastasis; a performance status as per a Karnofsky's Scoring of at least 70; adequate hematological, renal function and hepatic function. The key exclusion criteria were the following: a previously diagnosed malignancy (apart from carcinoma in situ of the nasopharyngeal and neck, or basal or squamous cell carcinoma of the skin); associated with other tumors; the presence of uncontrolled life-threatening illness; and pregnancy or lactation. Other exclusion criteria were any mental disorder or somatic comorbidities of clinical concern.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive either TP or TPF regimen induction chemotherapy. Random assignment was performed by a computer-generated random number code. Details of the random allocations were contained in sequentially numbered, opaque, sealed envelopes. The clinicians generated the random allocation sequence, enrolled participants, and assigned participants to interventions. Patients and clinicians were unmasked to treatment assignments. After informed consent was obtained from eligible patients, the investigators opened the envelopes sequentially and allocated patients to the corresponding interventions.

Procedures

The pretreatment assessment consisted of a complete physical examination, pathological examination, direct reoptic nasopharyngoscopy, nasopharyngeal and neck magnetic resonance imaging (MRI) (CT was indicated only in patients with contraindication to MRI), chest scan (CT), liver scan (abdominal sonography or CT), electrocardiography, bone scan, complete blood count with differential count, biochemical profile, and tumor biomarker.

All patients received induction chemotherapy followed by concurrent chemoradiotherapy. The patients assigned to the TP group received induction chemotherapy that consisted of docetaxel (75 mg per square meter, d1, intravenous infusion) and cisplatin (75 mg per square meter of body-surface area, d1, intravenous infusion). The TPF group had chemotherapy that consisted of docetaxel (60 mg per square meter, d1, intravenous infusion) plus cisplatin (60 mg per square meter, d1, intravenous infusion) and 5-fluorouracil (600 mg per square meter, d1-d5, intravenous 120-hour infusion) administered every 3 weeks for 3 cycles. The concurrent chemotherapy regimen consisted of cisplatin (80-100 mg per square meter, intravenous infusion) administered every 3 weeks for 2-3 cycles during radiotherapy. Details of the chemotherapy dose modifications and supportive measures are provided in the Supplementary Appendix.

Intensity-modulated radiotherapy (IMRT) was administered in both groups. The guidelines regarding radiotherapy are provided in the Supplementary Appendix.

Tumors were assessed with the use of nasopharyngoscopy and MRI of the nasopharyngeal and neck areas by a radiologist after the completion of induction chemotherapy and 12 weeks after the completion of chemoradiotherapy. Thereafter, follow-up was performed every 3 months during the first 2 years after radiotherapy, every 6 months during the third to fifth years, and annually thereafter. All endpoints were assessed or confirmed by the radiologist. Biopsy of suspected lesions was performed if deemed necessary to confirm

locoregional or distant disease progression. Salvage treatments, including reirradiation, chemotherapy, or surgery, were provided in cases of documented relapse or persistent disease, in accordance with standard practice.

Endpoints

The primary endpoint was failure-free survival, which was defined as the time from random assignment to documented local or regional relapse, distant metastasis, or death from cancer, whichever occurred first. The prespecified secondary endpoints included overall survival, which was defined as the time from random assignment to death from any cause or censored at the date of last follow-up, treatment response, treatment compliance, treatment complications and safety. Late radiotherapy-related toxic effects and quality of life will be presented in the long-term results of this study afterward. We used the Common Terminology Criteria for Adverse Events, version 5·0,[14] to grade acute toxic effects during treatment, and late toxic effects that were associated with radiotherapy were graded according to the Late Radiation Morbidity Scoring Scheme of the Radiation Therapy Oncology Group.[15]

Statistical analysis

The sample size was calculated by using the Power and Sample Size Program software (Version 15·0) and noninferiority log-rank tests. A phase 3, multicentre, randomised controlled trial at ten institutions in China reported that the 3-year failure-free survival was 80% (95% confidence intervals 75-85) in patients treated with induction chemotherapy plus concurrent chemoradiotherapy,[16] And the noninferiority margin was set as −10%, the selection of the noninferiority margin of 10% comes from a randomised phase 3 trial of nasopharyngeal carcinoma.[17] Besides, the preliminary clinical survival data among the group of our trial population have indicated us to choose 10% as the noninferiority margin for FFS within an affordable range. Thus, the 3-year survival in the TP group over 70% was thought to be noninferior to that in the TPF group. That was equal to the noninferiority margin of hazard ratios (HR) of 1·6. With 80% power and a one-sided type I error of 2·5%, 3 years and 5 years of follow-up were enrolled. We anticipated that 142 events would be required in 374 patients (187 per treatment group); therefore, we needed at least 416 patients (208 in each group) to allow for a 10% dropout rate.

This trial was under the supervision of an independent data monitoring committee. After reviewing the data in October 2021, the committee found that the TP group may bring better failure-free survival than TPF group. Therefore, we predefined the stopping rules and revised the protocol accordingly. Then an interim analysis was performed on October 24th, 2021. The current events were 43, with a proportion of 30·28% (43/142).

Efficacy analyses were performed in both the intention-to-treat and per-protocol trial populations (see the Supplementary Appendix). Kaplan-Meier curves were used to present time-to-event data, and the two treatment groups were compared by log-rank tests. The Cox proportional hazards model was used to calculate the hazard ratios (HR) and 95% confidence intervals (CI). The stopping rules were predefined as the 95% CI upper limit of HR less than 1.6 and the p-value for the noninferiority less than 0.00020, which was the threshold of noninferiority by O'Brien-Fleming boundary. The interaction analysis was conducted utilizing a test of treatment-by-covariate interaction based on the Cox proportional hazards model (17). Adjusted by age, sex, KPS score and TNM stage, multivariate Cox analysis was conducted to demonstrate the prognostic effect of the treatment group. For the safety analysis, we included the patients who started treatment in each group. Adverse events, treatment compliance, and categorical variables were compared by the chi-square test.

Analyses were performed with SPSS 22·0 and R 4·1·2. All tests were two-sided, and p values less than 0·05 were consequently significant, apart from other settings.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author YC had full access to all the data in the study and had final responsibility for the decision to submit for publication

Results

Patients and treatment

Between June 1, 2018 and October 31, 2021, across 6 sites, we randomly assigned 361 patients to the TP group (n = 181) or TPF group (n = 180) for induction chemotherapy plus chemoradiotherapy of patients with locally advanced (stage III-IVA) nasopharyngeal carcinoma for eligibility (Figure 1). The baseline demographic and clinical characteristics were presented in the two treatment groups (Table 1 and Appendix p1). Most patients were men (men: women = 3: 1), and the median age was 46 years old. Karnofsky's Performance Scoring of 90 to 100 was seen in most patients (85·6% and 86·1%). A total of 110 (60·8%) of 181 had stage III disease, and 71 (39·2%) of 181 had stage IVA disease in the TP group; 88 (48·9%) of 180 had stage III disease, and 92 (51·1%) had stage IVA disease in the TPF group.

In the TP group, 3 patients withdrew from the trial and did not receive TP induction chemotherapy, and 178 (98·3%) started protocol-defined induction

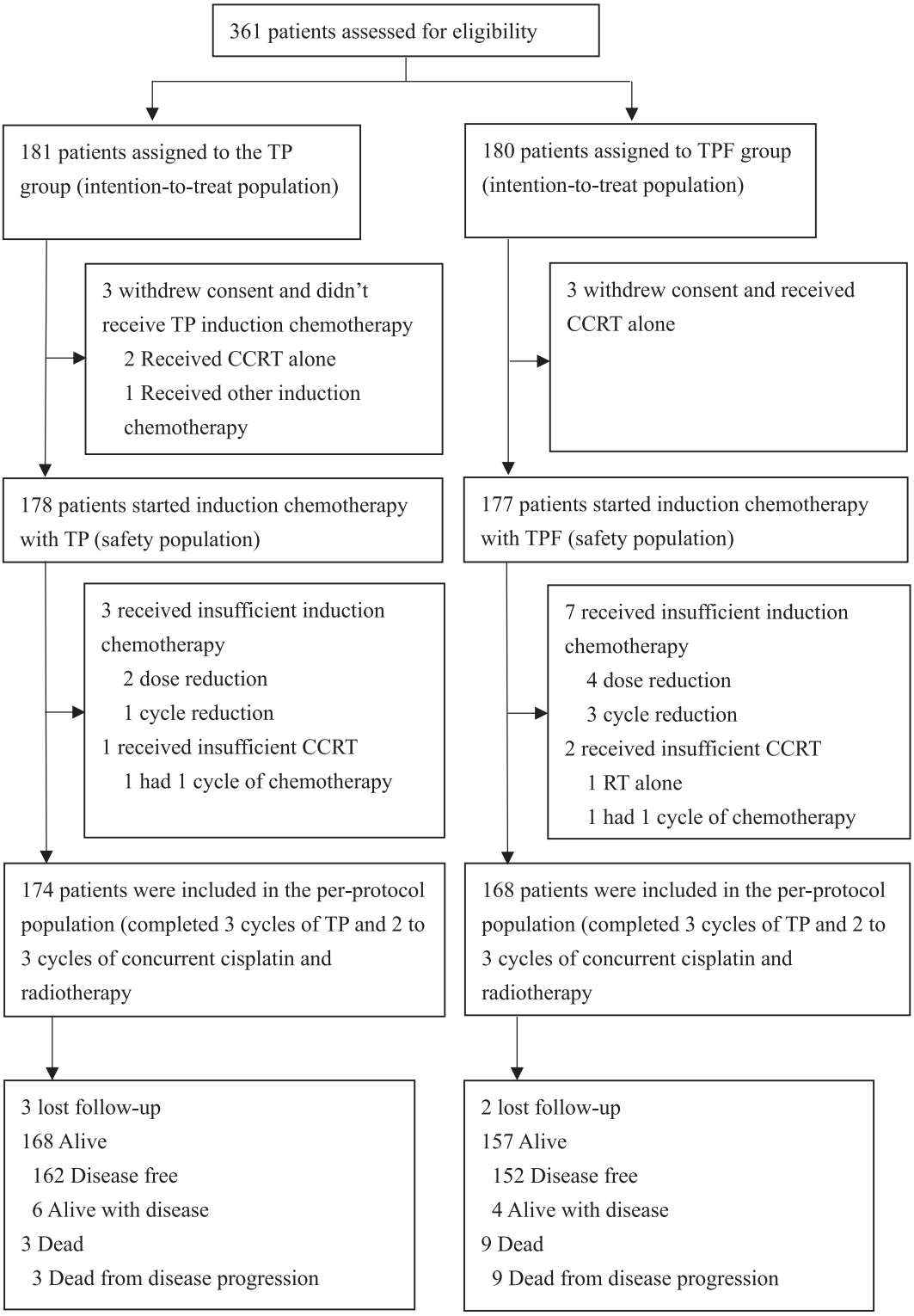

Figure 1. Flow chart of trial participants.

Variable	TP Group	TPF Group
Total	181 (100%)	180 (100%)
Median Age (years)	46 (20-65)	46 (19-65)
Sex		
Men	136 (75·1%)	137 (75·7%)
Women	45 (24·9%)	43 (24·3%)
KPS score		
90-100	155 (85·6%)	155 (86·1%)
70-80	26 (14·4%)	25 (13·9%)
Smoking		
Yes	81 (44·8%)	90 (50·0%)
No	100 (55·2%)	90 (50·0%)
Alcohol intake		
Yes	27 (14·9%)	26 (14·4%)
No	154 (85·1%)	154 (85·6%)
Histology		
WHO II	5 (2·8%)	7 (3·9%)
WHO III	176 (97·2%)	173 (96·1%)
T Category		
T1	7 (3·8%)	8 (4·5%)
T2	33 (18·2%)	38 (21·1%)
T3	101 (55·8%)	87 (48·3%)
T4	40 (22·2%)	47 (26·1%)
N Category		
N1	85 (47·0%)	67 (37·2%)
N2	59 (32·6%)	59 (32·8%)
N3	37 (20·4%)	54 (30·0%)
TNM Stage		
III	110 (60·8%)	88 (48·9%)
IVA	71 (39·2%)	92 (51·1%)
Pretreatment Epstein–Barr virus DNA test		
≤1500 copies/mL	92 (50·8%)	91 (50·6%)
>1500 copies/mL	76 (42·0%)	74 (41·1%)

***Table 1*: Baseline characteristics of all 361 patients in the intention-to-treat analysis.**

chemotherapy and were included in the safety population. Last, a total of 174 of the 178 patients (97·8%) completed 3 cycles of induction chemotherapy and 2 to 3 cycles of concurrent cisplatin and radiotherapy. In the TPF group, 3 patients who withdrew from the trial only received concurrent chemoradiotherapy, which induced 177 (98·3%) patients who started protocol-defined induction chemotherapy and were included in the safety population. Last, a total of 168 of the 177 patients (94·9%) completed 3 cycles of induction chemotherapy and concurrent radiotherapy (Figure 1).

Efficacy

The tumor responses were first evaluated 1 week after 3 cycles of induction chemotherapy. In the TP group, 2·8% of the patients (5 of 181) had a complete response, 150 (82·8%) had a partial response, and 26 (14·4%) remained stable. In the TPF group, 2·2% of the patients (4 of 180) had a complete response, 149 (82·8%) had a partial response, 26 (14·4%) remained stable, and 1 (0·6%) suffered progression. The tumor response rate was also evaluated 3 months after radiotherapy, details in Table 2.

At the last follow-up on January 11, 2022, the median follow-up was 25·1 months (range, 3·02 to 46·75). We recorded a total of 43 events of recurrence or death (16·1% of the patients in the overall trial population), including events in 15 of 181 patients (8·3%) in the TP group and in 28 of 180 (15·6%) in the TPF group (Table 2). The 2- and 3-year failure-free survival rates were 91·3% (95% CI 86·2-96·4) and 84.5% (83·3-92·5) in the TP group and 82·4% (84·8-88·9) and 78.1% (83·7-85·7) in the TPF group, respectively (hazard ratio (HR), 0·504; 95% CI, 0·269 to 0·943; $P = 0·029$) (Figure 2A).

We calculated that the upper limit of the 95% CI and P value of the noninferiority using the O'Brien-Fleming test were 0·94 and 0·00015, respectively, which were less than the predetermined level; thus, the noninferiority boundary was reached. We estimated that the current trial samples could have 100% power to detect a hazard ratio for failure-free survival of 0·5 using a postpower analysis, with a two-sided significance level of 0·050, so the trial stopped.

At the time of analysis, 3 of 181 patients (1·7%) in the TP group and 9 of 180 patients (5·0%) in the TPF group had died. Details regarding the cause of death are provided in the Supplementary Appendix. The 2-year overall survival was similar in the TP group and the TPF group 99·2% (95% CI 89·7-100·0) and 96·3% (88·2-99·4), respectively; HR = 0·309; 95% CI, 0·084 to 1·141; $P = 0·062$) (Figure 2B).

Similarly, in the per-protocol analysis, the 2-year failure-free survival was 91·9% (95% CI 86·4-96·8) vs. 82·7% (84·6-89·4) in the TP and TPF groups, respectively (HR = 0·470; 95% CI, 0·242 to 0·915; $P = 0·023$). The 2-year overall survival was similar in the TP and TPF groups 99·2% (95% CI 89·7-100·0) vs. 96·9% (88·4-99·8) (HR = 0·272; 95% CI, 0·056 to 1·310; $P = 0·082$) (Supplementary Appendix p2).

Subgroup analysis

We performed an interaction analysis to explore if the effect of the treatment varied for the following subgroups (age, sex, KPS score, T-category, N-category, and TNM stage). The subgroup analyses of failure-free survival revealed that there was no treatment interaction effect of age, sex, KPS score, or TNM stage. We have conducted the multivariate COX analysis for the FFS and found that the induction treatment group was an independent prognostic factor (TPF vs. TP; HR 0·527 [95% CI 0·279-0·994], $P = 0·048$) and reached the threshold of 95% CI upper limit for the noninferiority (Figure 3). There was no treatment interaction effect of

Variable	TP group *N*=181	TPF group *N*=180
Failure-free survival		
Recurrence, Distant metastasis or death from disease — no. (%)	15 (8·3%)	28 (15·6%)
Overall survival		
Death — no. (%)	3 (1·7%)	9 (5·0%)
Response to induction chemoradiotherapy		
Complete response — no./total no. (%)	5/181 (2·8%)	4/180 (2·2%)
Partial response — no./total no. (%)	150/181 (82·8%)	149/180 (82·8%)
Stable disease — no./total no. (%)	26/181 (14·4%)	26/180 (14·4%)
Progressive disease — no./total no. (%)	0/181 (0·0%)	1/180 (0·6%)
Response to whole treatment		
Complete response — no. (%)	173/181 (95·6%)	169/180 (93·9%)
Partial response — no. (%)	5/181 (2·8%)	8/180 (4·4%)
Progressive disease — no. (%)	0/181 (0·0%)	1/180 (0·6%)
Could not be assessed — no. (%)	3/181 (1·6%)	2/180 (1·1%)
Disease recurrence	15 (8·3)	28 (15·6)
Distant	13 (7·2)	21 (11·7)
Bone	6 (3·3)	8 (4·4)
Lung	2 (1·1)	5 (2·8)
Liver	3 (1·7)	2 (1·1)
Other	1 (0·6)	0 (0)
Multiple	1 (0·6)	6 (3·3)
Locoregional	5 (2·8)	9 (5·0)
Local alone	1 (0·6)	2 (1·1)
Regional alone	2 (1·1)	5 (2·8)
Local + regional	2 (1·1)	2 (1·1)
Distant+Locoregional	2 (1·1)	5 (2·8)
Death	3 (1·7)	9 (5·0)
Cancer-specific	3 (1·7)	9 (5·0)

***Table 2*: Survival, response to treatment and relapse sites in the two treatment groups.**

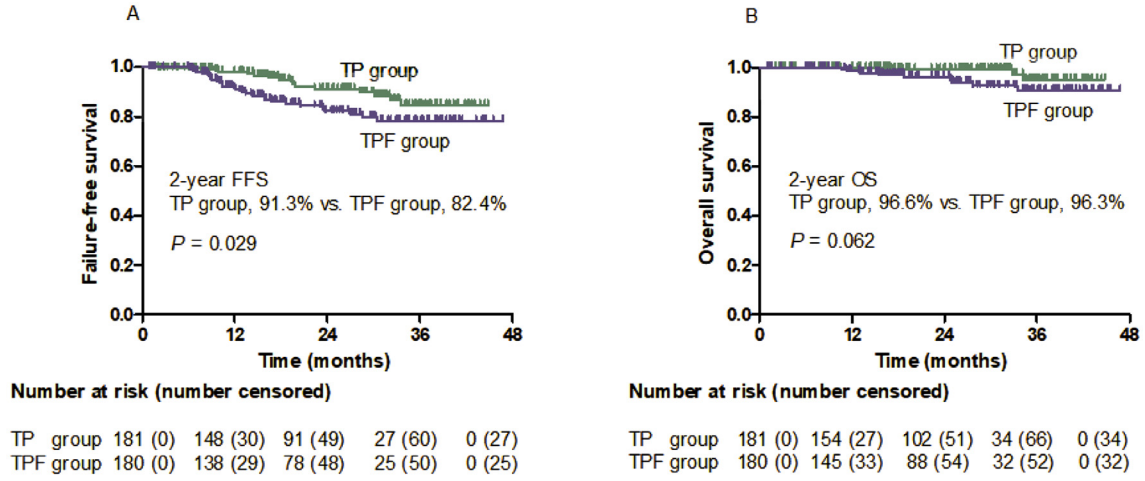

Figure 2. In the intention-to-treat analysis, survival outcome differences in the TP and TPF groups. Kaplan—Meier failure-free survival (A), overall survival (B).

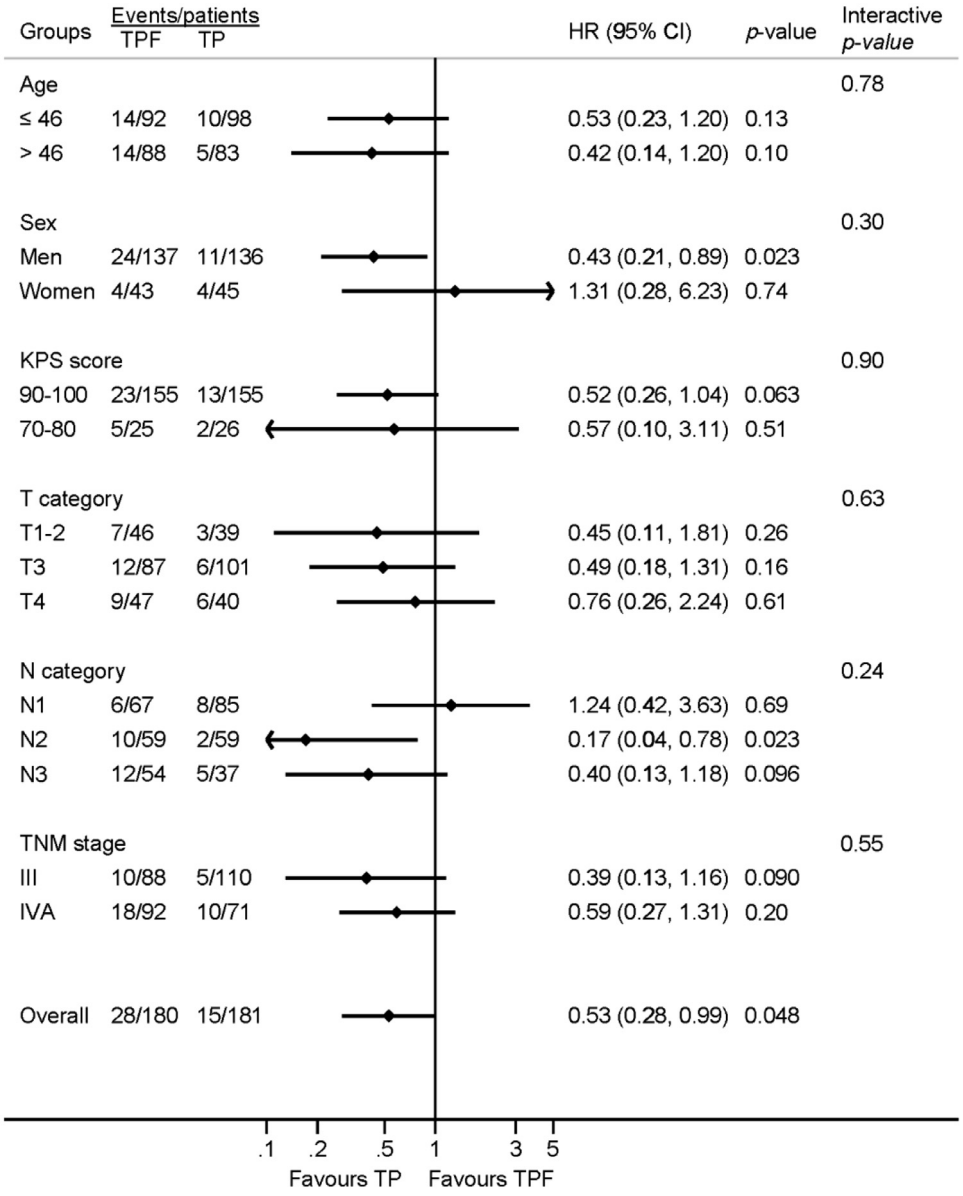

Figure 3. Effect of treatment on failure-free survival in subgroups of the intention-to-treat population defined according to prespecified factors and baseline characteristics. Overall treatment was using multi-variant cox models adjusted by age, sex, KPS score and TNM stage. The subgroup of each characteristic was also adjusted by the others when conducting multi-variant cox models. The interactive p values were produced by putting the interactive terms (treatment group * other group) into the multi-variant cox models. HR = hazard ratio, CI = confidence interval.

any of the above characteristics on overall survival (Supplementary Appendix p3).

Additionally, the patients with available EBV DNA concentrations were divided into two groups with a cut-off value of 1500 copies/mL, and there was no difference between the TP and TPF groups (P = 0·94; chi-square test) (Supplementary Appendix p4). And the subgroup analysis of the effects of EBV DNA on the FFS were exhibited in Supplementary Appendix p5, TP group expressed better FFS than TPF group in patients with EBV DNA over 1500 copies/mL (P = 0·0070) (Supplementary Appendix p5).

Treatment-related toxicities

The safety population included 178 patients in the TP group and 177 patients in the TPF group who were treated with induction chemotherapy and concurrent chemoradiotherapy (Figure 1). In the period of induction chemotherapy, we recorded a higher frequency of

grade 1 or 2 neutropenia (30·0% vs. 15·7%; $P = 0·0010$), grade 1 or 2 diarrhea (11·3% vs. 5·1%; $P = 0·032$) and grade 3 or 4 neutropenia (24·3% vs. 14·0%; $P = 0·014$) in the TPF group than in the TP group. Patients in the TPF group suffered a higher frequency of grade 1 or 2 anemia (71·2% vs. 59·0%; $P = 0·013$) and grade 3 or 4 neutropenia (7·9% vs. 2·8%; $P = 0·033$) than the TP group. The other adverse events, including nausea/vomiting, mucositis, hypokalemia, constipation, weight loss, fatigue, ototoxicity, hepatoxicity, nephrotoxicity and allergic reaction, did not differ between the two treatment groups (Table 3, Appendix p6).

Events	TP group (*n*=178) Grade 3-4 *n* (%)	TPF group (*n*=177) Grade 3-4 *n* (%)	*P* value
Adverse events during induction chemotherapy			
Hematological			
Neutropenia	25 (14·0)	43 (24·3)	0·014
Febrile neutropenia	2 (1·1)	8 (4·5)	0·053
Neutropenic infection	-	-	-
Anemia	5 (2·8)	5 (2·8)	0·99
Thrombocytopenia	2 (1·1)	4 (2·3)	0·41
Nonhematological			
Nausea/Vomiting	6 (3·4)	4 (2·3)	0·53
Hypokalemia	3 (1·7)	2 (1·1)	0·66
Diarrhea	3 (1·7)	7 (4·0)	0·20
Constipation	0 (0)	0 (0)	-
Weight loss	0 (0)	0 (0)	-
Fatigue	0 (0)	0 (0)	-
Hepatoxicity	2 (1·1)	2 (1·1)	1.00
Nephrotoxicity	0 (0)	0 (0)	-
Allergic reaction	0 (0)	0 (0)	-
Adverse events during concurrent chemotherapy			
Hematological			
Neutropenia	5 (2·8)	14 (7·9)	0·033
Febrile neutropenia	1 (0·6)	2 (1·1)	0·56
Neutropenic infection	0 (0)	0 (0)	-
Anemia	18 (10·1)	19 (10·7)	0·85
Thrombocytopenia	2 (1·1)	2 (1·1)	1.00
Nonhematological			
Nausea/Vomiting	7 (3·9)	2 (1·1)	0·093
Mucositis	13 (7·3)	7 (4·0)	0·17
Hypokalemia	0 (0)	2 (1·1)	0·061
Diarrhea	1 (0·6)	2 (1·1)	0·62
Constipation	0 (0)	0 (0)	-
Weight loss	0 (0)	0 (0)	-
Fatigue	0 (0)	0 (0)	-
Ototoxicity	0 (0)	0 (0)	-
Hepatoxicity	1 (0·6)	0 (0)	1·00
Nephrotoxicity	0 (0)	0 (0)	-
Allergic reaction	-	-	-

***Table 3*: Grade 3-4 adverse events during treatment in the safety population during induction chemotherapy and concurrent chemoradiotherapy.**

Abbreviations: This analysis was conducted in the safety population, which included only the patients who began receiving the trial treatment. As prespecified by the protocol, differences in adverse events were analyzed using the chi-square test. For adverse events that did not meet the requirement for analysis (absolute count was 1), Fisher's exact test was used. *P* values were calculated with the chi-square test.

Therapy compliance

Regarding the induction chemotherapy compliance, as seen in Table 4 and Appendix p7, overall, 177/178 (99·4%) patients in the TP group and 174/177 (98·3%) patients in the TPF group patients completed 3 cycles of induction chemotherapy. A total of 175 (98·3%) of the 178 patients received the complete TP regimen dose [docetaxel (75 mg per square meter of body-surface area, d1) and cisplatin (75 mg per square meter of body-surface area, d1)]. 170 (96·0%) of the 177 patients received the complete TPF regimen dose [docetaxel (60 mg per square meter, d1) plus cisplatin (60 mg per square meter, d1) and 5-fluorouracil (600 mg per square meter, d1-5)], and 10 patients received reduced doses and cycles owing to treatment-related toxicities or patient decline. For concurrent chemotherapy with cisplatin in the TP group, 1/178 (0·6%) patients had 1 cycle, 106/178 (59·6%) patients had 2 cycles, and 71/178 (39·8%) patients completed 3 cycles. In the TPF group, 1/177 (0·6%) patients had 0 cycles, 2/177 (1·1%) had 1 cycle, and 112/177 (63·3%) had 2 cycles.

For concurrent chemotherapy with cisplatin in the TP group, 71/178 (39·8%) patients completed 3 cycles, 106/178 (59·6%) completed 2 cycles and 1/178 (0·6%) completed 1 cycle. In the TPF group, 62/177 (35·0%) patients completed 3 cycles of concurrent cisplatin, 112/177 (63·3%) patients had 2 cycles, 2/177 (1·1%) had 1 cycle and 1/177 (0·6%) had 0 cycles. Overall, 160 (89·9%) patients received at least 200 mg/m^2, and 18 (10·1%) patients received 100–200 mg/m^2 of chemotherapy in the TP group. In the TPF group, 156 (88·1%) patients received at least 200 mg/m^2, and 18 (10·2%) patients received 100–200 mg/m^2 of chemotherapy. The treatment compliance did not differ between the groups ($P = 0·45$, unadjusted chi-square test).

With respect to radiotherapy, all the patients in the two groups completed the whole schedule radiation dose. The median GTVnx, GTVnd, CTV1 and CTV2 doses were 7000 cGy, 6400 cGy, 6000 cGy and 5400 cGy, respectively. The median fraction was 31. The median dose per fraction was 226 cGy. The median duration of radiotherapy was 45 days. The dose and duration of radiotherapy were well balanced between the treatment groups.

Discussion

Radiotherapy is the primary curative treatment modality for NPC because of the special complicated anatomical

Variable	TP group	TPF group
Safety population	178	177
Patients receiving induction chemotherapy no. (%)		
Patients completing induction chemotherapy 3 cycles no. (%)	177 (99·4%)	174 (98·3%)
Patients receiving sufficient dose of induction chemotherapy no. (%)	175 (98·3%)	170 (96·0%)
Patients receiving concurrent chemotherapy no. (%)		
Patients completing concurrent chemotherapy 2 cycles no. (%)	177 (99·4%)	175 (98·9%)
Patients receiving concurrent cisplatin 160 mg/m^2 no. (%)	177 (99·4%)	175 (98·9%)
Patients receiving RT no. (%)		
Patients completing RT no. (%)	178 (100%)	177 (100%)
Median (IQR) dose of GTVp (cGy)	7000 (6810-7006)	7000 (6810-7006)
Median (IQR) dose of GTVn (cGy)	6400 (6200-6600)	6400 (6200-6600)
Median (IQR) fractions	31 (30-31)	31 (30-31)
Median (IQR) dose per fraction (cGy)	226 (226-227)	226 (226-227)
Median (IQR) dose of CTV1 (cGy)	6000 (6000-6200)	6000 (6000-6200)
Median (IQR) dose of CTV2 (cGy)	5400 (5400-5580)	5400 (5400-5580)
Median (IQR) duration of RT (days)	45 (43-48)	45 (43-48)

***Table 4*: Compliance to induction chemotherapy and concurrent chemoradiotherapy.**
RT = radiotherapy; IQR = interquartile range; GTVp= gross tumor.
volume of the primary tumor; CTV1= high-risk clinical target volume; CTV2= low-risk clinical target volume.

location of NPC and its high sensitivity to radiation. After the application of IMRT and a combination of chemoradiation, the local control rate of locoregionally advanced NPC (LA-NPC) has increased. Distant metastasis has now become the main mode of treatment failure of NPC.[18] In recent years, a number of multicentre randomised controlled trials have identified the important role of induction chemotherapy (IC) plus concurrent chemoradiotherapy (CCRT). It can eliminate tumor micrometastases early and achieve tumor downstaging. As the standard therapy for LA-NPC, IC plus CCRT could significantly benefit the OS (5-year absolute benefit = 6%) and PFS (progression-free survival; 5-year absolute benefit = 6%) by mainly reducing the distant metastasis rate.[19] The commonly used IC regimens are TP (docetaxel, cisplatin), TPF (docetaxel, cisplatin), PF (cisplatin, fluorouracil), or GP (gemcitabine, cisplatin).

Which one has the best effect and is the least adverse? *Zhao* et al.[20] found that the TP regimen had significantly higher disease-free survival (DFS) and OS than the PF regimen, and no severe toxicities occurred. A small-sample multicentre noncomparative pilot study[21] of locally advanced squamous cell carcinoma of the head and neck revealed that compared with TPF, the 3-year PFS and OS rates were similar to TP. Another study[12] demonstrated that there were no differences in survival between the induction regimen of TPF and TP, and the patients in the TP regimen experienced fewer grade 3/4 toxicities of leukocytopenia, neutropenia, mucositis and diarrhea than those in the TPF regimen. The goals of treatment for NPC are to improve survival and reduce the complications caused by treatment. The choice of treatment regimen should be based on multiple factors, including the efficacy of the drug and patient selection. At present, TPF is a widely used clinical regimen for LA-NPC due to the survival benefits reported in several clinical trials.[19,22] As found above, the TP regimen resulted in similar survival to TPF and fewer complications. It is quite important to explore whether TP could replace the TPF regimen as induction chemotherapy for LA-NPC. There, prospective randomised trials that directly compared the two IC regimens were lacking. To our knowledge, this is the first randomised trial to reveal, in patients with locoregional stage III-IVA NPC, that the TP plus CCRT group achieved better failure-free survival than the TPF plus CCRT regimen and had fewer therapy-associated toxicities. The 2-year failure-free survival was 91·3% in the TP group, which was much higher than that reported in the TPF-based induction chemotherapy plus concurrent chemoradiotherapy group in a trial by *Sun* and colleagues (approximately 82%),[16] while it was similar to the result of 82·4% in our TPF group. The differences observed in the failure-free survival at 2 years could be explained by the fact that in our trial, 110 (60·8%) and 88 (48·9%) of the patients in the TP and TPF group had stage III tumors, respectively, while 129 (54%) of the patients had stage III tumors in the study by *Sun* and colleagues, indicating the more patients with the earlier stage in our cohort. Similarly, about 85% in the TPF group was observed in another phase 3 randomised controlled trial.[23] Additionally, the 2-year PFS was about 84% from a pooled analysis of four randomised trials, which was also similar to our result of 82.4% in this study.[19] Undoubtedly, there were studies that claimed a better 2-year FFS, the inconsistency in the 2-year FFS across these studies may be due to various characteristics of the enrolled population.

A big-data platform-based analysis[24] revealed that the induction TP regimen may result in similar survival to TPF for patients receiving a cumulative concurrent cisplatin dose over 200 mg/m², while TPF may be superior to TP and PF for patients receiving a cumulative cisplatin dose less than 200 mg/m², although grade 3–4 toxicities were more common but tolerable. Two other studies suggested selecting the IC regimen by adding the risk characteristics: *Xiong* et al.[25] revealed that the TPF regimen showed a higher 5-year distant metastasis-free survival for relatively advanced stage IVA and N2-3 patients, while for stage III and N0-1, TP might be enough. The nonkeratinizing subtype of NPC, which makes up the most cases in endemic areas, is mainly associated with Epstein–Barr virus (EBV) infection.[26] EBV DNA has been revealed to predict disease prognosis and even guide chemotherapy, and it should be adopted to complement the TNM classification in selecting high-risk patients with NPC.[27] *Liu* et al.[28] showed that TPF was associated with significantly better survival conditions in patients with stage IV or with stage IV and pre-EBV DNA with over 1500 copies. It may be conjectured from retrospective studies that induction chemotherapy with the TPF regimen resulted in better survival than TP in "high-risk" patients. In our subgroup analysis of male patients and patients with N2, TP prolonged FFS compared with TPF. However, there were no interactions with the other stratified indexes.

Regarding treatment-associated toxicity in our multicentre study, the patients in the TPF group expressed a higher frequency of hematological toxicities and diarrhea than those in the TP group, which was similar to other clinical trials.[12,16] During induction chemotherapy in this study, 25 (14%) of the 178 patients in the TP group and 43 (24·3%) of the 177 patients in the TPF group had grade 3 or 4 neutropenia, which was resolvable. The incidences of neutropenia in this study were lower than the rates of 72·7%-76·9% reported in a previous study,[22,29] probably attributed to the lower dose intensity of the TPF regimen used in this study. The dose of TPF in this study was 20% lower than that of the conventional regimen (docetaxel 60 mg/m² on day 1, cisplatin 60 mg/m² on day 1, fluorouracil 600 mg/m² per day on days 1–5), which was proposed in 2010[30] and was identified in a recent study.[16] The TP-based chemotherapy regimen was of good compliance due to the fewer toxicities, which again identifies its advantage.

According to the above, the TP-based induction chemotherapy regimen could be regarded as a better choice for longer survival, good compliance and fewer side effects. The excellent results have eliminated the suspicion of selecting induction chemotherapy. That is why we terminated the study ahead of schedule. However, several limitations existed in this study. First, there was no formal stopping rule established for the trial before it began and this was only added based on a review of preliminary data shortly before the trial was stopped. Second, we hadn't considered the influence of TNM stage, and we didn't make the stratification before enrollment. Although the multivariate COX analysis for the FFS found that the induction treatment group was an independent prognostic factor, which leads to the conclusion that the survival efficacy in TP group was non-inferior to that in TPF group although the TNM stage was different between the two groups. Thus, we reported the preliminary results and we will make the follow-up afterwards and observe the survival trends between the two groups. Third, Epstein–Barr virus analysis in the plasma was not listed as a prognostic factor or stratified index in our study, and EBV DNA testing was not performed in all the included patients. Additionally, the EBV DNA quantitative assays were performed at different centres' laboratories, which could add to the heterogeneity. Last, we only reported the 2-year survival results and acute toxicities in this study, and the evaluation of overall survival and therapeutic-associated long-term adverse events may need a longer follow-up time. Otherwise, a study of double-blind centres from all around the world is urgently needed to identify the results in the future.

In conclusion, our findings show that the TP induction chemotherapy regimen expressed a non-inferior efficiency of failure-free survival and less advanced hematological toxicities than the TPF regimen in patients with LA-NPC. TP is an alternative doublet treatment strategy. The results of this trial could strengthen and widen the choice of induction chemotherapy regimen offered to patients with NPC.

Contributors

YC and ZWP were responsible for study conception and design, supervision of the project, quality assessment, review, and approval of the manuscript. YW, CTW, SSH, LB and FK contributed to the design of the clinical trial, writing of the protocol, recruitment and treatment of patients, data and trial management. YW, CTW, SSH, and LB contributed to the data analysis and interpretation, and writing and final approval of the report. SYW and YYY were involved in the design of the clinical trial, recruitment and treatment of patients, data and trial management, and review of the report. LC, QQ, WX and MYZ participated in the recruitment and treatment of patients, data and trial management, and the report preparation. ZWP, ZYZ, YLL and WJB were responsible for the statistical analysis and interpretation, and the toxicity and data review. YW and CTW contributed to patient accrual and writing or review of the completed report. SSH was involved in trial management and toxicity review. All authors had full access to all the data in the study and had full responsibility for the decision to submit for publication.

Data sharing statement

The data that support the findings of this study are available from the corresponding author on reasonable request. De-identified participant data will be made available after approval from the corresponding author and Sun Yat-sen University First Affiliated Hospital. After publication of study findings, the data will be available for others to request. The research team will provide an email address for communication once the data are approved to be shared with others. The proposal with detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability to request for our data. The corresponding author and Sun Yat-sen University First Affiliated Hospital have the right to decide whether to share the data or not on the basis of these materials. Additional materials might also be required during the process of evaluation. The study protocol is available in the appendix.

Declaration of interests

All authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101625.

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