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Nimotuzumab plus induction chemotherapy followed by radiotherapy/concurrent chemoradiotherapy plus nimotuzumab for locally advanced nasopharyngeal carcinoma: protocol of a multicentre, open-label, single-arm, prospective phase II trial

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ABSTRACT

Epidermal growth factor receptor (EGFR) is a therapeutic target in nasopharyngeal carcinoma (NPC). The optimal combined modality of optimal combined modality of anti-EGFR monoclonal antibodies, induction chemotherapy (ICT), concurrent chemotherapy and radiotherapy for NPC remains poorly defined. None of previous studies have developed subsequent treatment strategies on the basis of stratification according to the efficacy following ICT plus anti-EGFR mAbs. This study aims to increase treatment intensity for patients with poor efficacy of ICT and reduce treatment toxicity for patients with favourable efficacy of ICT by assessing whether the efficacy of this treatment regimen is non-inferior to ICT plus concurrent chemoradiotherapy (historic controls).

Introduction

Methods and analysis Pathology-confirmed WHO type II/III NPC patients at clinical stage III–IVA (eighth American Joint Committee on Cancer/Union for International Cancer Control staging system) will be included in the study. They will receive ICT plus nimotuzumab (NTZ), followed by radiotherapy plus NTZ or concurrent chemoradiotherapy plus NTZ (stratified based on the efficacy of ICT plus NTZ). The primary endpoint is 3-year failure-free survival rate; while the secondary endpoints are 3-year overall survival rate, distant metastasis-free survival rate and locoregional recurrence-free survival rate, and short-term remission rate of tumour and treatment toxicity.

Ethics and dissemination The study protocol has been approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University. Our findings will be disseminated in a peer-reviewed journal. Implementation strategies are in place to ensure privacy and confidentiality of participants.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a prospective multicentre study.
⇒ This is the first study to stratify nasopharyngeal carcinoma patients according to the efficacy following induction chemotherapy plus antiepidermal growth factor receptor (EGFR) mAbs.
⇒ Nimotuzumab, an anti-EGFR mAbs with mild toxicity and favourable tolerability is used in this study.
⇒ This is a single-arm study that lacks of control group, so it is difficult to evaluate the final results affirmatively.

Trial registration number ChiCTR2000041139.

INTRODUCTION

Nasopharyngeal carcinoma (NPC), arising from nasopharyngeal epithelium, is highly prevalent in Southeast Asia and southern China.[1] Radiotherapy remains the radical treatment for NPC. Early-stage cases generally possess a favourable prognosis with radiotherapy alone, in which 5-year survival rate exceeds 90%.[2–4] However, since the anatomical location of nasopharynx is concealed and NPC is characterised by a wide range of clinical manifestations, more than 70% of patients present with a locally advanced (LA) stage at diagnosis.[5] The 5-year overall survival (OS) rate is only 67%–77%.[6] Currently, radiotherapy plus concurrent chemotherapy is

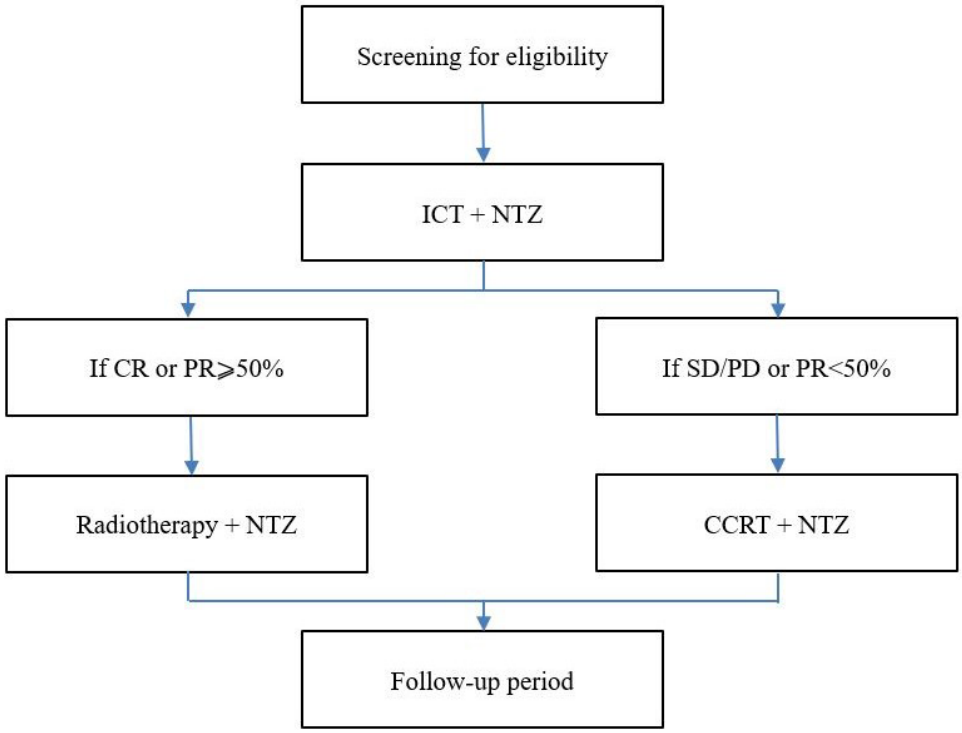

Figure 1 Flow chart of the study design. CCRT, concurrent chemoradiotherapy; CR, complete remission; ICT, Induction chemotherapy; NTZ, nimotuzumab; PD, progressive disease; PR, partial remission; SD, stable disease.

affirmed as the first-line treatment of LA-NPC. Concurrent chemoradiotherapy (CCRT) could increase the sensitivity of radiotherapy and reduce distant metastases, which in turn may improve tumour remission rate, reduce the local recurrence rate and increase disease-free survival (DFS) rate.[7] Chemoradiotherapy-based treatment is regarded as the standard treatment for LA-NPC. However, how to search for low-toxicity, highly effective agents and more preferable combination modalities of radiotherapy and chemotherapy still needs to be further pursued.

Epidermal growth factor receptor (EGFR) is expressed in 90% of NPC[8 9] and overexpression of EGFR is implicated in poor prognosis.[10] EGFR activation facilitates the proliferation, invasion and metastasis of tumour cells, inhibits apoptosis and induces resistance to chemotherapy and radiotherapy.[11–14] EGFR has been taken as a therapeutic target in NPC. Binding of anti-EGFR monoclonal antibodies (anti-EGFR mAbs) to the extracellular domain of EGFR restrains activation of downstream signalling pathways, thus serving a crucial role in antitumour effect. Several commercialised anti-EGFR mAbs such as cetuximab (CTX) or nimotuzumab (NTZ) combined with radiotherapy demonstrates similar efficacy to platinum-based CCRT.[15 16] Whether anti-EGFR mAbs combined with CCRT is superior to CCRT alone is not consistent in previous literatures. You *et al* and Xia *et al* have reported CTX or NTZ combined with CCRT exhibits superior efficacy than CCRT alone.[17 18] However, Li *et al* have reported the effectiveness of anti-EGFR mAbs combined with CCRT is comparable to that of CCRT alone.[19] We speculate the reason is no stratified subgroup analyses have been performed in the above studies.

Induction chemotherapy (ICT) can increase the compliance of patients with LA-NPC, with low rates of distant metastases and high rates of failure-free survival (FFS) and OS.[20–22] Anti-EGFR mAbs combined with ICT may further decrease the rate of distant metastasis and improve OS. Peng *et al* retrospectively analysed the data of 596 NPC patients. Patients were randomly assigned to two groups in a ratio of 1:3: ICT plus anti-EGFR mAbs (CTX or NTZ) group and ICT group. Subsequently, both groups were treated for combined radiotherapy or CCRT. In both groups, 3-year DFS rates were 84.3% vs 75.2%

Table 1 The dose level of chemotherapeutic drugs

Dose level	Gemcitabine dose (ICT)	Nedaplatin dose (ICT)	Nedaplatin dose (CCRT)
0 (starting dose)	1000 mg/m^2	75 mg/m^2	80 mg/m^2
−1	800 mg/m^2	75×80% mg/m^2	80×80% mg/m^2
−2	600 mg/m^2	75×60% mg/m^2	80×60% mg/m^2

CCRT, concurrent chemoradiotherapy; ICT, induction chemotherapy.

Table 2 Dose modifications according to haematological toxicity

Dose modification	ICT		CCRT
	Gemcitabine	Nedaplatin	Nedaplatin
Dose level −1	1. Neutrophil ≤0.5×10^9 /L. 2. Febrile neutropenia. 3. Agranulocytosis-derived infection. 4. Platelet <50×10^9 /L 5. Chemotherapy toxicity results in course extension for greater than a week.	1. Neutrophil ≤0.5×10^9 /L. 2. Febrile neutropenia. 3. Agranulocytosis-derived infection. 4. Platelet <25×10^9 /L. 5. Chemotherapy toxicity results in course extension for greater than a week.	Neutrophil of (0.5–1.0)×10^9 /L and/or platelet of (50–75)×10^9 /L.
Dose level −2	A second occurrence.	A second occurrence.	Neutrophil <0.5×10^9 /L or febrile neutropenia or Agranulocytosis-derived infection and/or platelet of (25–50)×10^9 /L.

Values in the table is compared with the lowest values of test results.
CCRT, concurrent chemoradiotherapy; ICT, induction chemotherapy.

(p= 0.059), while 3-year OS rates were 94.0% vs 87.9% (p=0.053). Multivariate analysis revealed that ICT plus anti-EGFR mAbs was an independent prognostic factor for DFS (HR 1.497; 95% CI 1.016 to 2.206; p=0.041) and OS (HR 1.984; 95% CI 1.023 to 3.848; p=0.043).[23] In previous studies, subsequent treatment strategies were not stratified following the efficacy following ICT plus anti-EGFR mAbs. The optimally combined modality of ICT plus anti-EGFR mAbs, chemotherapy and radiotherapy remains poorly defined. This study is designed to stratify patients according to the efficacy following ICT plus anti-EGFR mAbs to further explore the optimally combined modality of ICT plus anti-EGFR mAbs, chemotherapy and radiotherapy. If patients achieve complete remission or tumour regression is greater than 50% then NTZ–radiotherapy combination will be administered, whereas if patients achieve stable disease or progressive disease or tumour regression is observed <50% of the patients then NTZ–CCRT combination will be followed.

METHODS AND ANALYSIS

Study objectives

The primary endpoint is FFS rate and the secondary endpoints include OS, distant metastasis-free survival (DMFS) and locoregional recurrence-free survival (LRRFS), and short-term remission rates of tumour and treatment toxicity. The therapeutic effect will be evaluated using FFS and OS. FFS refers to the time from initial therapy until to the date of locoregional failure, distant failure or death from any cause, which occurred first. OS is defined as the time lag between patient enrolment and death resulting from any cause. DMFS was defined as the time from diagnosis to distant metastasis. LRRFS was defined as the time from initial therapy until the occurrence of a locoregional recurrence or death by cancer.

Study design

This study is designed as a multicentre, open-label, single-arm, prospective phase II trial in individuals who will be treated with ICT plus NTZ, followed by choice of radiotherapy with NTZ or CCRT with NTZ according to the efficacy (figure 1). The study will be performed at six tertiary grade A hospitals in Jiangxi province, China. We aim at increasing treatment intensity for patients with poor efficacy of ICT and reducing treatment toxicity for patients with favourable efficacy of ICT by assessing whether the efficacy of this treatment regimen is non-inferior to ICT plus CCRT (historic controls).

Inclusion criteria

1. Pathology-confirmed WHO type II / III NPC patients.
2. Age ≥18 years old and ≤70 years old.
3. Patients at clinical stage III–IVA (Union for International Cancer Control/American Joint Committee on Cancer eighth Edition, except T3-4N0).
4. Patients receiving intensity-modulated radiotherapy (IMRT).
5. Eastern Cooperative Oncology Group performance status of 0–1.
6. Haematological examination: white cell count (WCC) ≥4×10^9 /L, neutrophil ≥2×10^9 /L /L, haemoglobin ≥90 g/L, platelet ≥100×10^9 /L.
7. Liver function: alanine aminotransferase, aspartate aminotransferase ≤1.5 × ULN, alkaline phosphatase (ALP) ≤2.5 × ULN, bilirubin ≤1.5 × ULN.
8. Renal function: creatinine ≥60 mL/min.
9. Patients with informed consent.

Exclusion criteria

1. WHO pathological classification of patients with keratinising squamous cell carcinoma or basal cell carcinoma.
2. Age <18 years old and >70 years old.
3. Palliative treatment.

Table 3 Dose modifications according to non-haematological toxicity

Non-haematological toxicity	Coping strategy
Anaphylaxis	In case of serious allergic reaction associated with gemcitabine and/or nedaplatin, the ICT will be terminated.
Gastrointestinal toxicity	In patients with gastrointestinal toxicity, no dose modification is necessary during ICT and CCRT.
Kidney toxicity	Nedaplatin will be reduced to dose level −1 if creatinine clearance is 40–60 mL/min. Chemotherapy will be discontinued when creatinine clearance is ≤40 mL/min.
Liver toxicity	Gemcitabine will be reduced to dose level −1 if ALT/AST is (2.5–5.0) × ULN and/or ALP is (2.5–5.0) × ULN. If bilirubin >2.5 × ULN, or AST/ALT>2.5 × ULN and/or ALP >2.5 × ULN, the cessation of chemotherapy will be required. HBV carriers should receive antiviral therapy under the guidance of specialties before chemotherapy.
Neurotoxicity	In case of neurological grade 2 toxicity, nedaplatin will be reduced to dose level −1. Subjects will be withdrawn from the clinical trial if they develop grade 3 or 4 neurotoxicity.
Ototoxicity	If patients exhibit ototoxicity profiles, a hearing screening will be necessary. Participants with grade 3 or 4 ototoxicity will be dropped out of the trial.

CTCAEv3.0 will be used to evaluate acute toxicity.
ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CCRT, concurrent chemoradiotherapy; HBV, Hepatitis B virus; ICT, induction chemotherapy; ULN, Upper limits of normal.

4. Patients with history of any malignant tumours (except for cutaneous basal cell carcinoma, cutaneous squamous cell carcinoma and cervical carcinoma in situ).
5. Pregnant women and lactating females (A pregnancy test for the female subjects of reproductive age will be taken into account and patients will be requested to use effective contraception).
6. Patients with previous radiotherapy history (except for non-melanoma skin cancer outside the planned target area).
7. Patients who have received chemotherapy or surgery for primary tumour or lymph node (except for diagnostic surgery).
8. Any patients with serious comorbid diseases that may bring risks to the trial or affect the trial compliance, such as unstable heart disease, kidney disease, chronic hepatitis, diabetes mellitus with poor blood glucose control (fasting blood glucose >1.5 × ULN) and mood disorders requiring treatment.
9. Patients with allergic history of platinum compounds.

Preparation for treatment

All subjects will undergo head and neck CT and/or MRI during the 2 weeks prior to enrolment. Laboratory data included blood routine, blood coagulability, electrolyte, liver and kidney function and Epstein-Barr virus, and baseline examination results will be obtained within 2 weeks prior to enrolment.

Treatment regimen

Radiotherapy

All patients were immobilised in the supine position with a thermoplastic mask. After administration of intravenous contrast material, 3 mm CT slices were acquired from the head to the level 2 cm below the sternoclavicular joint. Target volumes were delineated according to the International Commission on Radiation Units and Measurements Reports 50 and 62. The primary nasopharyngeal gross tumour volume (GTVnx) and the involved cervical lymph nodes were determined from the imaging, clinical and endoscopic finding. The enlarged retropharyngeal nodes were outlined, together with primary GTV, as the GTVnx on the IMRT plans. The first clinical tumour volume (CTV1) was defined as the GTVnx plus a margin of 5–10 mm for potential microscopic spread, including the entire nasopharynx mucosa plus a 5 mm submucosal volume. The second CTV (CTV2) was defined by adding a margin of 5–10 mm to CTV1 (when CTV2 was adjacent to critical organs such as brain stem and spinal cord, the margin was reduced to 3–5 mm) and included the retropharyngeal lymphnodal regions, clivus, skull base, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus and posterior edge of the nasal cavity and maxillary sinuses and the level of the lymph node located at bilateral levels II-V. Elective-level IB irradiation was decided by the attending physician. Planning target volumes (PTVs) for all gross tumour volumes and CTVs have generated automatically after delineation of tumour targets according to the immobilisation and localisation uncertain ties. A simultaneous integrated boost method was used. The prescribed dose was 66–70 Gy to the PTV of the GTVnx, 60 Gy to the PTV of CTV1 (ie, high-risk regions), 54–56 Gy to the PTV of CTV2 (ie, low-risk regions), and 64-70 Gy to the PTV of the GTVnd for the metastatic cervical lymph nodes in 30–33 fractions. For the GTV and CTV, the target volumes that received more than 95% of the prescribed dose were used to reflect the target coverage. The dose received by each critical organ was limited to tolerance according to the Radiation Therapy Oncology Group(RTOG) 0225 protocol.[24]

Chemotherapy

All chemotherapy schemes will be platinum-based, including ICT and concurrent chemotherapy.

Table 4 Table of events: ICT

	Enrolment	Pre-treatment	Treatment period				Follow-up period
Assessment	**Outpatient**	**Screening**	**Each week**	**Every 2 weeks**	**Every 3 weeks**	**At the end of treatment**	**Each time point***
Eligibility screen	X						
Informed consent	X						
GP					X†		
NTZ					X		
Baseline examination		X					
General physical examination‡						X	X
Specialist oncology examination§						X	X
Nasopharynx fiberscope				X			
Whole-blood cell counts			X			X	X
Blood biochemical						X	X
Blood routine		X					
Blood coagulability		X					
Electrolyte		X					
Epstein-Barr virus		X					
Liver and kidney function		X			X¶		
Head and neck CT or MRI		X				X	X
Chest X-ray						X	X
Abdominal B-ultrasonography						X	X
Quality of life						X	X

*The patients will be reviewed every 3 months within the first 2 years after the end of treatment, and at 6 months intervals thereafter. If the blood routine and Epstein-Barr virus examinations are normal at the last evaluation, they can be omitted.
†GP regimen: gemcitabine 1000 mg/m^2/day on days 1 and 8, nedaplatin 25 mg/m^2/day on the first 3 days.
‡Including Karnofsky score and weight.
§Including indirect nasopharyngoscopy and a clinical evaluation of neck lymph nodes.
¶Assessed prior to each chemotherapy.
ICT, induction chemotherapy; NTZ, nimotuzumab.

1. Chemotherapy regimens: The subjects will receive GP (gemcitabine 1000 mg/m^2/day on days 1 and 8, nedaplatin 25 mg/m^2/day on the first 3 days) as ICT regimen, which will repeat every 3 weeks for three cycles. The concurrent chemotherapy regimen will be administered as follows: nedaplatin, 80 mg/m^2, divided into 3 days, repeated 3 weeks for two cycles.
2. The timing of chemotherapy: Adequate doses of chemotherapy will be administered only if neutrophil is ≥2×10^9 /L (or WCC ≥4×10^9 /L, absolute neutrophil count not available) and platelet is ≥100×10^9 /L. When patients are clinically appropriate without fever, the number of neutrophils could adjust to (1.5–1.9)×10^9 /L. The time point of chemotherapy can be advanced or postponed by 1 day on the basis of the regimen. However, chemotherapy could not be earlier than the initiation of radiotherapy during the first CCRT cycle.
3. Dose modifications: Dosages will be adjusted depending on the toxicity observed during the previous treatment course. The prescribed dose level is outlined in table 1, and the dose modifications regimens on the basis of haematological and non-haematological toxicities are demonstrated in tables 2 and 3.

Targeted therapy

NTZ will be administered at a dose of 200 mg per time when used in combination with ICT, which will repeat every 3 weeks for three cycles. When coadministered with radiotherapy or CCRT, the usage of NTZ will be as follows: 200 mg per time, begun 1 week before radiotherapy, repeated every week for seven cycles. Vital signs will be closely monitored before and within 1 hour after administration of each dose, and throughout drug administration sessions. The weekly dose of NTZ should be administered strictly following the trial design during the course of the study. The drip rate must be maintained at a slow state once the drip rate is decelerated due to hypersensitivity. If there is another hypersensitivity after slowing down the drip rate, the infusion should be stopped and therapy permanently terminated. If grade 3 or 4 hypersensitivity (according to CTCAE V.3.0) occurs, the NTZ should be discontinued and chemotherapy and radiotherapy

Table 5 Table of events: continuing with radiotherapy plus NTZ

	Treatment period			Follow-up period
Assessment	**Each week**	**Every 2 weeks**	**At the end of treatment**	**Each time point***
Radiotherapy	X†			
NTZ	X‡			
General physical examination§	X		X	X
Specialist oncology examination¶	X		X	X
Nasopharynx fiberscope		X		
Whole-blood cell counts	X		X	X
Blood biochemical			X	X
Head and neck CT or MRI			X	X
Chest X-ray			X	X
Abdominal B-ultrasonography			X	X
Quality of life			X	X

*The patients will be reviewed every 3 months within the first 2 years after the end of radiotherapy, and at 6 month intervals thereafter. If the blood routine and Epstein-Barr virus examinations are normal at the last evaluation, they can be omitted.
†Five times per week.
‡Begun at 1 week before radiotherapy.
§Includes Karnofsky score and weight.
¶Including indirect nasopharyngoscopy and a clinical evaluation of neck lymph nodes.
NTZ, nimotuzumab.

should be continued concurrently. In the event of grade 1 or 2 fever, the drip rate will be reduced to 50%. If patients develop grade 3 or 4 fever without remission even after the administration of the antipyretic analgesic, NTZ will be discontinued. If patients present grade 3 or 4 rash, the drip rate of NTZ will be reduced by 50%. Topical medication of hydrocortisone ointment/erythromycin ointment will be given to patients and will be evaluated after 2 weeks. If symptoms are not relieved, patients will be treated with oral loratadine. Rational use of antibiotics will be considered in the event of coinfection. In case of non-remission following treatment as mentioned above, patients will be withdrawn from NTZ.

Table 6 Table of events: continuing with CCRT plus NTZ

	Treatment period				Follow-up period
Assessment	**Each week**	**Every 2 weeks**	**Every 3 weeks**	**At the end of treatment**	**Each time point***
Radiotherapy	X†				
Nedaplatin			X		
NTZ	X‡				
General physical examination§	X			X	X
Specialist oncology examination¶	X			X	X
Nasopharynx fiberscope		X			
Whole-blood cell counts	X			X	X
Blood biochemical				X	X
Head and neck CT or MRI				X	X
Chest X-ray				X	X
Abdominal B-ultrasonography				X	X
Quality of life				X	X

*The patients will be reviewed every 3 months within the first 2 years after the end of radiotherapy, and at 6 months intervals thereafter. If the blood routine and Epstein-Barr virus examinations are normal at the last evaluation, they can be omitted.
†Five times per week.
‡Begun at 1 week before radiotherapy.
§Includes Karnofsky score and weight.
¶Including indirect nasopharyngoscopy and a clinical evaluation of neck lymph nodes.
CCRT, concurrent chemoradiotherapy; NTZ, nimotuzumab.

Other therapy

If there is still residual neck nodal disease after 3 months of sufficient radiotherapy, patients could be performed local resection or cervical lymph node dissection. Subjects are discouraged from conducting node biopsy before treatment. Nutritional adjustment according to changes in body weight could be given weekly by a dietitian during the treatment. In the event of grade 4 acute skin and mucosal reactions (using the RTOG criteria), treatment will be suspended until toxicity is returned to grade 3 or lower.

Follow-up

The follow-up period is specified as the time from the enrolment to the last follow-up. Details regarding the check-up items can be found in tables 4–6. CTCAE V.3.0 will be used to evaluate acute toxicity, and late toxicity will be scored according to the RTOG/EORTC classification. Short-term outcomes will be assessed according to the RECIST V.1.1 guidelines. Long-term efficacy will be evaluated based on the sites and timing of recurrence and distant metastasis, the cause and date of death and survival rate.

Sample size and statistical design

The primary objective was to determine 3-year FFS for NTZ plus ICT, followed by radiotherapy/CCRT plus NTZ for locally NPC compared with the same end point for NPC patients receiving ICT, followed by CCRT on previously reported studies.[21 22 25] In these refs, it has been reported that patients undergoing ICT plus CCRT expected FFS of 80%–85.3% at 3 years and 3-year FFS among patients treated with CCRT was 72%–76.5%. A sample of 68 patients provided 80% power to detect a difference between the 3-year FFS and the non-inferiority margin of 13% for the historical controls while accepting a one-sided type I error of 0.025. We further assumed that 10% of the patients would be lost to follow-up or would prematurely discontinue the trial. This yielded a final sample of 76.

A 3-year and 5-year follow-up plan has been set up. Kaplan-Meier analysis will be used to evaluate FFS, OS, DMFS and LRRFS at the third year and fifth year. The incidence of acute and late adverse reactions will be made public in tabular format following adverse events observed in participants.

Recruitment

Patients will be recruited from December 2020 and December 2022. The implementation time is from January 2021 to December 2025.

Quality control and assurance

To determine whether the study is being conducted in accordance with the protocol and Good clinical practice (GCP), the GCP Audit Department of the Second Affiliated Hospital of Nanchang University performs a GCP audit and formulates an appropriate procedure.

Data collection and management

Enrolment, interventions and assessments will be according to the schedules presented in tables 4–6. The treatment scheme should be jointly confirmed by the study physician and physiotherapist, and verified by the treating centre before the first treatment. All original data will be recorded in case report forms, and case record forms will be established using EpiData software (V.3.1, EpiData Association, Odense, Denmark).

Patient and public involvement statement

Patients or the public were not involved in the design, recruitment and reporting of the study.

DISCUSSION

A meta-analysis suggested that the addition of anti-EGFR mAbs to standard therapy can improve OS, DFS and LRFS in NPC comparing with standard therapy alone with a tolerable degree of toxicity.[26] NTZ is one of the few anti-EGFR mAbs that have been approved for cancer therapies. It shows an intermediate affinity against the EGFR, different from panitumumab and CTX, which reduces binding of normal cells that have lower EGFR density and consequently exhibits milder toxicities. In addition to inducing antibody-dependent cellular cytotoxicity depending on natural killer cell, NTZ is able to reverse one EGFR-mediated mechanism of immune escape by restoring HLA-I expression on tumour cells.[27]

Zhu *et al* and Zhao *et al* have reported that NTZ plus chemotherapy demonstrated potential efficacy, and exhibited good tolerability without increasing treatment-related toxicity.[28 29] These findings prompt us to investigate combined modalities of NTZ and other treatments with higher efficacy and lower toxicity. To our knowledge, no study has developed subsequent treatment strategies according to the efficacy of ICT plus NTZ. This study attempts to establish a patient-individualised therapy including NTZ, which aims to provide a new idea for the optimal combined modality of ICT plus anti-EGFR mAbs, chemotherapy and radiotherapy.

The single-arm design makes it hard to distinguish differences among studies when compared with historical data, hindering an accurate interpretation of survival results. However, we focus on improving efficacy and quality of life of LA-NPC in this study. If this idea is confirmed in the phase II trial, it could open new avenues for the refinement of therapeutic approaches for NPC.

ETHICS AND DISSEMINATION

The study protocol has been approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University. Our findings will be disseminated in a peer-reviewed journal. Implementation strategies are in place to ensure privacy and confidentiality of participants.

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Contributors LZ conceived the study and revised the manuscript. J-JY drafted the manuscript and will analyse the clinical data. J-WD participated in the design of the subject and will analyse the clinical data. J-WL, R-HH, DG, J-LH, K-BZ, YL, Y-HD, J-WW, J-LZ, Z-BL, W-HY, S-FA, G-HZ, Z-LZ and RZ were involved in the design of the subject and will carry out the clinical implementation of the trial.

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Competing interests None declared.

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