

Concurrent chemoradiotherapy plus anlotinib vs. concurrent chemoradiotherapy alone in locally advanced nasopharyngeal carcinoma: An interim analysis of a multicenter randomized controlled trial

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Abstract. Despite the use of intensity-modulated radiation therapy (IMRT) and concurrent chemotherapy (CCRT), the treatment of locoregionally advanced nasopharyngeal carcinoma (LA-NPC) is not satisfactory. EGFR and VEGFR are highly expressed in 60-80% of patients with LA-NPC and this is associated with a poor prognosis, which suggests the potential effectiveness of an inhibitor targeting tumor angiogenesis for treating LA-NPC. The present study aimed to assess the safety and effectiveness of CCRT combined with anlotinib in patients with LA-NPC. The study involved patients with LA-NPC (stage III-IVA) from four institutions in Guangxi, China. Patients were randomized to receive CCRT + anlotinib (n=36) or CCRT alone (n=37). Acute toxicity and short-term efficacy were evaluated. The most common grade 3 or 4 adverse events were leucopenia [10 (27.7%) vs. 8 (21.6%)], neutropenia [6 (16.7%) vs. 5 (13.5%)] and mucositis [13 (36.1%) vs. 11 (29.7%)] in the CCRT + anlotinib vs. CCRT cohort but there were no significant differences between the two cohorts (P=0.54, P=0.70 and P=0.56, respectively). Two patients (5.6%) displayed grade 1/2 hemorrhage in the CCRT + anlotinib cohort. No patient displayed grade 3/4 hemorrhages or

adverse event-associated deaths in any cohort. Complete response rates in the CCRT + anlotinib arm at 1 week and 3 and 6 months post-radiotherapy were 60.0, 91.4, and 97.1%, respectively, compared with 40.5, 81.1 and 91.9% in the CCRT arm but there was no significant difference (P=0.10, P=0.35 and P=0.65, respectively). This interim analysis of the ongoing trial showed that administration of CCRT + anlotinib has acceptable toxicity profiles, good compliance and promising results in patients with LA-NPC. A larger study cohort and a longer follow-up period are needed to confirm therapeutic effectiveness and late toxicity.

Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common types of cancer in Southeast Asia and is particularly observed in Southern China, including Guangxi Zhuang Autonomous Region (1,2). NPC had an incidence of >20 cases per 100,000 individuals and a mortality risk of 6 cases per 100,000 individuals in Southern China between 2004 and 2005 (2). At initial diagnosis, >80% of patients present with locoregionally advanced NPC (LA-NPC) (3). Despite use of intensity-modulated radiation therapy (IMRT) and concurrent chemotherapy (CCRT), treatment of LA-NPC is not satisfactory, with a 5-year survival rate of 80% (4). The latest phase 3 trial suggests that application of gemcitabine combined with cisplatin induction therapy before chemoradiotherapy significantly extends recurrence-free and overall survival of patients with LA-NPC; however, 15.3% of patients develop local recurrence and 9.5% experience distant metastasis, which are primary reasons for treatment failure in these patients (5). The addition of targeted therapy to CCRT increases local control rate and decreases occurrence of distant metastasis (6,7).

Anlotinib is a small-molecule, multi-tyrosine kinase inhibitor targeting tumor angiogenesis and proliferation (8);

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it may inhibit vascular endothelial growth factor receptor (VEGFR), fibroblast and platelet-derived growth factor receptor, epidermal growth factor receptor (EGFR) and kinases (8,9). Anlotinib was approved by the National Medical Products Administration as a third-line treatment for advanced non-squamous non-small cell lung cancer without a driver gene and small cell lung cancer and as a second-line treatment for soft tissue sarcoma and locally advanced or metastatic medullary thyroid carcinoma (8,10-12).

EGFR and VEGFR are highly expressed in 60-80% of patients with LA-NPC and this is associated with poor prognosis (13,14). This suggests potential effectiveness of anlotinib against LA-NPC. An interim analysis of a phase 2 trial shows promising efficacy of anlotinib as a third-line or further treatment for advanced NPC (trial no. NCT03906058) (15). Nevertheless, the role of CCRT + anlotinib for LA-NPC is still uncertain. Therefore, the present study aimed to assess the effect of CCRT + anlotinib in patients with LA-NPC.

Materials and methods

Study design. To assess the safety and effectiveness of CCRT + anlotinib vs. CCRT alone in patients with LA-NPC (www.chictr.org.cn; Chinese Clinical Trial Registry identifier: ChiCTR1900022969), patients were recruited from four tertiary hospitals in Guangxi, China between July 1, 2019, and February 20, 2021. The four hospitals were Guiping People's Hospital, The First People's Hospital of Nanning, The People's Hospital of Guangxi Zhuang Autonomous Region and The First Affiliated Hospital of Guangxi Medical University. The present study was approved by the Ethics Committees of these four hospitals.

Participants. Eligible patients were aged 18-70 years with newly treated stage III-IVA NPC, as diagnosed according to the 8th Union for International Cancer Control and American Joint Committee on Cancer (16), with histologically confirmed non-keratinization. Other inclusion criteria included Karnofsky performance status (KPS) score ≥ 70 and adequate bone marrow (white blood cell count $>4.0 \times 10^9/l$; absolute neutrophil count $>2.0 \times 10^9/l$; hemoglobin >90 g/l; platelet count $>100 \times 10^9/l$), renal and hepatic function (creatinine clearance rate >60 ml/min; urinary protein $<2+$; serum total bilirubin $\leq 1.5 \times \text{ULN}$; aspartate aminotransferase $\leq 2.5 \times \text{ULN}$; alanine aminotransferase $\leq 2.5 \times \text{ULN}$; serum albumin >28 g/l). The exclusion criteria included previous malignancy, previous antitumor treatment of NPC, contraindication to magnetic resonance imaging (MRI), pregnancy or lactation, severe bleeding tendency or any severe coexisting disease. Patients aged ≥ 70 years were not included since elderly patients are generally less tolerant of adverse events (17). In addition to complete patient history and physical exam, routine pretreatment assessments also included hematology (key items include white blood cell count, absolute neutrophil count, hemoglobin and platelet count) and biochemistry analyses (key items include creatinine clearance rate, urinary protein, serum total bilirubin, aspartate aminotransferase, alanine aminotransferase, serum albumin and fasting blood glucose), as well as NP fiber-optic endoscopy, histopathological diagnosis, chest and abdomen computed tomography (CT) scan, nasopharynx

and neck enhanced MRI and skeletal scintigraphy. Written informed consent to participate was obtained from all patients included in the study.

Randomization and masking. Randomization was performed (via sealed envelopes) centrally at Guiping People's Hospital (Guiping, China). Patients were randomized to the CCRT + anlotinib or the CCRT alone cohort. The random allocation of the treatment was not concealed.

Treatment procedure. The present study compared CCRT plus anlotinib with CCRT alone. All patients received radical IMRT at a cumulative dose of ≥ 70 Gy to the primary tumor at 2.12-2.27 Gy/fraction with five daily fractions/week for 6-7 weeks, 66-70 Gy to associated areas of the neck, 60 Gy to high-risk subclinical areas and 54 Gy to low-risk subclinical areas. MRI fusion with treatment planning CT images was proposed to determine total tumor volume, including the primary tumor and metastatic lymph nodes. High-risk clinical target tumor volume was defined as the total nasopharynx tumor volume with a 5-10 mm margin (2-3 mm posteriorly if contiguous to the brainstem or spinal cord) encompassing the entire nasopharynx and high-risk areas of microscopic extension. Low-risk clinical target tumor volume was defined as high-risk clinical target tumor volume with 5-10 mm margin (2-3 mm posteriorly if contiguous to the brainstem or spinal cord) encompassing the low-risk areas of microscopic extension, including retropharyngeal nodal regions, skull base, clivus, sphenoid sinus, parapharyngeal space, pterygoid fossae, posterior third of the nasal cavity or maxillary sinuses including the pterygopalatine fossae and level II-V lymph node regions. The level IB nodal region was radiated in the case of any nodal involvement at this level. The ipsilateral level IB nodal region should be covered if there is gross involvement of the ipsilateral submandibular gland, anterior half of the nasal cavity, oral cavity or ipsilateral level IIA lymph nodes with extra-capsular extension or maximum nodal axial diameter >2 cm (18).

All patients received intravenous cisplatin (100 mg/m^2) on day 1 of every cycle of 3 weeks, with three cycles in total. Oral anlotinib (12 mg/day) was administered to patients in the CCRT + anlotinib cohort on days 1-14 of every cycle of 3 weeks, with three cycles in total. Both cisplatin and anlotinib were administered concurrently with radiotherapy.

Treatment response rates were evaluated using Response Evaluation Criteria in Solid Tumors (version 1.1) (19) through physical examination, nasopharyngoscopy and head and neck MRI at 1 week and 3 and 6 months post-radiotherapy. Patients were evaluated at least once every 3 months for 2 years post-radiotherapy and every 6 months thereafter. The nasopharynx and neck MRI, chest CT scan and abdominal sonography were conducted every 3 months for the first 2 years post-radiotherapy and every 6 months thereafter. Biopsy was conducted when tumor relapse was suspected. Acute toxic effects were assessed weekly during treatment and graded according to the Common Terminology Criteria for Adverse Events (version 5.0) (20).

Statistical analysis. Statistical analysis was performed using SPSS 26.0 software (IBM Corp.). All categorical variables are

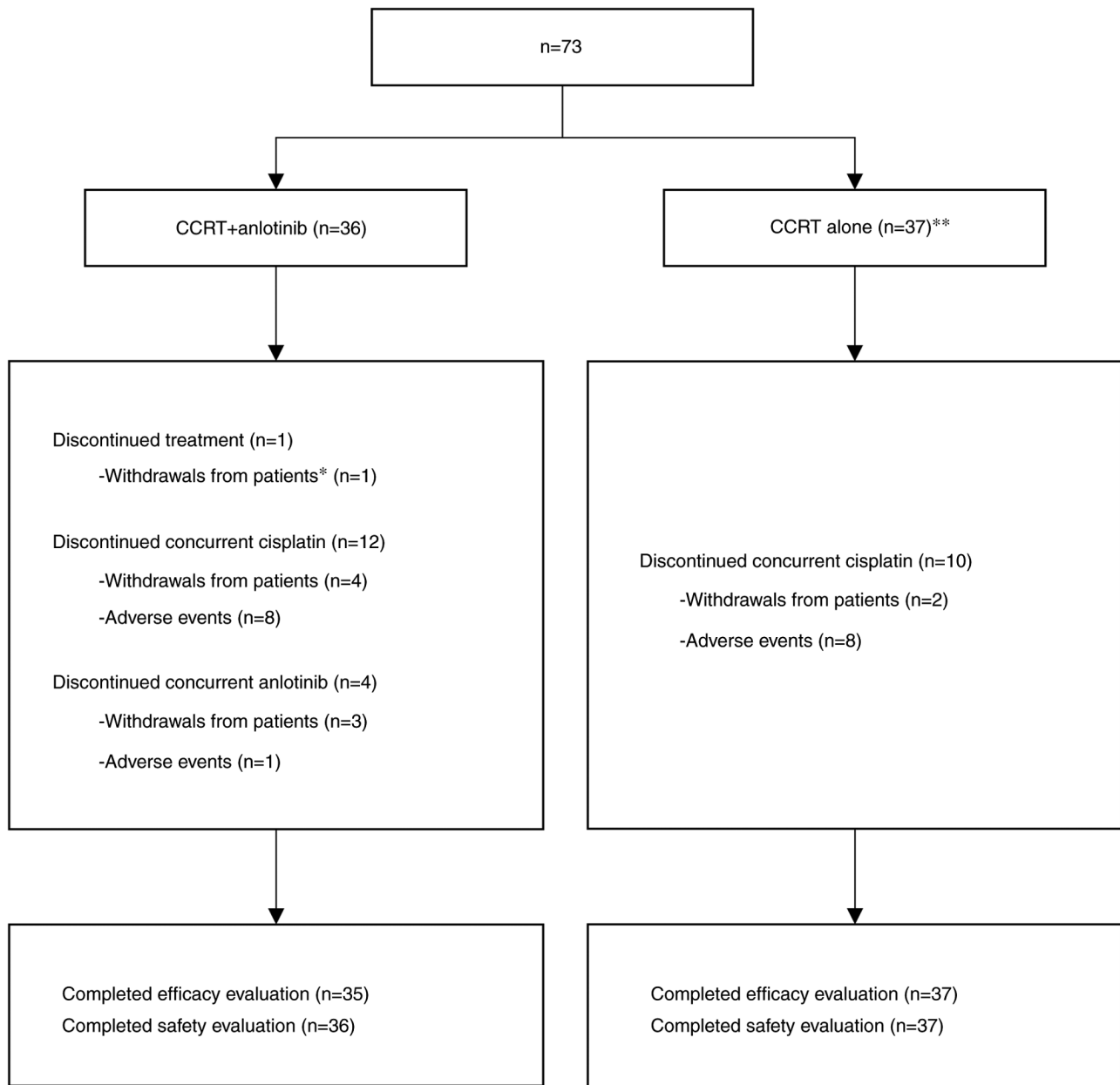


Figure 1. Study flowchart. *Lost to follow-up at 1 month post-randomization. **One patient received adjuvant chemotherapy by request. CCRT, concurrent radiotherapy.

reported as numbers with percentages. Continuous variables are expressed as median and range. P-values were calculated using χ^2 test or Fisher's exact test for categorical variables. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. From July 2019 to February 2021, 73 patients with LA-NPC randomly received CCRT + anlotinib (n=36) or CCRT alone (n=37) (Fig. 1). The baseline characteristics of patients were well balanced between the two treatment cohorts (Table I).

All patients in both treatment arms completed the scheduled dose of radiotherapy. However, one patient from the CCRT + anlotinib arm withdrew from treatment after 3 weeks.

In the CCRT + anlotinib cohort, 24 patients (66.7%) achieved three cisplatin treatment cycles as planned, but 12 (33.3%) did not achieve this therapy target. A total of eight patients and four patients reached two and one cycle, respectively; four patients were unwilling to continue chemotherapy and eight patients experienced adverse events. A total of 32 patients (88.9%) achieved three concurrent anlotinib treatment cycles; four patients (11.1%) did not achieve three anlotinib treatment cycles (three and one patient reached two cycles and one cycle, respectively; three patients were unwilling to continue anlotinib treatment and one patient had experienced adverse events). In the CCRT cohort, 27 patients (73.0%) achieved three concurrent cisplatin treatment cycles; ten patients (27.0%) did not reach the planned therapy target (nine and one patient reached two cycles and one cycle, respectively; two patients were unwilling to continue chemotherapy and

Table I. Baseline characteristics of patients.

Characteristic	CCRT + anlotinib (n=36)	CCRT alone (n=37)
Sex, n (%)		
Male	26 (72.2)	29 (78.4)
Female	10 (27.8)	8 (21.6)
Median age, years (range)	47 (22-69)	53 (28-70)
ECOG performance status, n (%)		
0	27 (75.7)	26 (70.3)
1	9 (24.3)	11 (29.7)
T stage, n (%)		
T1	4 (11.8)	2 (5.4)
T2	7 (20.6)	9 (24.3)
T3	15 (44.1)	14 (37.8)
T4	8 (23.5)	13 (35.1)
N stage, n (%)		
N0	1 (2.8)	0 (0.0)
N1	2 (5.6)	4 (10.8)
N2	24 (66.7)	31 (83.8)
N3	9 (25.0)	2 (5.4)
Clinical stage, n (%)		
III	19 (55.9)	23 (62.2)
IVA	16 (44.1)	14 (37.8)

CCRT, concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group.

eight experienced adverse events). Treatment procedures and outcomes are shown in Fig. 1.

Therapeutic effects. Treatment responses were evaluated for eligible patients (Table II). The complete response (CR) rate in the CCRT + anlotinib group 1 week post-radiotherapy was 81.1% compared 60.0% in the CCRT group. However, this difference was not significant ($P=0.10$). At 3 months post-radiotherapy, the CR rates in the CCRT + anlotinib cohort and in the CCRT cohort were 91.4 and 81.1%, respectively, without significant difference ($P=0.35$). CR rates increased to 97.1 and 91.9%, respectively, at 6-month follow-up; however, the difference was not significant ($P=0.65$). Furthermore, no significant differences were found between groups at 3 months post-radiotherapy for nasopharyngeal ($P=0.50$) and neck lymph node lesions ($P=0.77$).

With a median follow-up of 13.6 months (range 6.1-26.2 months), 2 (5.5%) and 4 (10.8%) of patients in the CCRT + anlotinib cohort and CCRT alone cohort, respectively, experienced tumor progression. In the CCRT + anlotinib cohort, one patient developed bone metastasis at 7.6 months and another developed liver metastasis 6 months after randomization. In the CCRT cohort, one patient experienced lung metastasis at 5.1 months, while two patients experienced liver metastasis and another patient developed bone metastasis at 10.7, 11.0 and 12.3 months, respectively, after randomization.

Adverse reactions. The acute toxicity during treatment is shown in Table III. Grade 3/4 mucositis and myelosuppression, particularly leucopenia, were the most common severe toxicities. In the CCRT + anlotinib cohort, the incidence of grade 3/4 mucositis and leucopenia were 36.1 and 27.7%, respectively, compared with incidence rates of 29.7 and 21.6% in the CCRT arm ($P=0.56$ and $P=0.54$, respectively). A total of five patients displayed grade 3 hypertension during treatment, one developed grade 3 hepatotoxicity due to a hepatitis B flare up, one reported grade 4 nephrotoxicity after three cycles of concurrent cisplatin and required short-term dialysis therapy and two reported hemorrhage (grade 1 or 2). No patient presented with grade 3/4 hemorrhage or adverse event-associated death.

Discussion

The present interim analysis reports on an ongoing multicenter randomized controlled trial comparing CCRT + anlotinib with CCRT alone in patients with LA-NPC. The primary objective was to define the toxicity and compliance of chemoradiotherapy + anlotinib in LA-NPC. The results revealed that concurrent administration of chemoradiation + anlotinib had acceptable toxicity profiles, good compliance and encouraging efficacy.

EGFR and VEGFR are highly expressed and associated with increased therapeutic tolerance and poor prognosis in patients with nasopharyngeal carcinoma (21-24). EGFR- and VEGFR-blocking drugs may offer a potential treatment for LA-NPC.

Studies have confirmed that anti-EGFR antibodies, such as cetuximab, nimotuzumab and endostar, plus CCRT for patients with LA-NPC is well tolerated and safe (25-27). To the best of our knowledge, however, most studies have shown no survival benefit (26,28,29). Xu *et al* (30) performed a contrasting study of induction chemotherapy followed by concomitant cisplatin-chemoradiotherapy (CRT) or cetuximab-radiotherapy (ERT). ERT was not superior to CRT. The three-year disease-free survival rates of CRT and ERT were 78.3 and 85.7%, respectively ($P=0.547$), and ERT was more likely to cause acute adverse events. In a phase 2 trial by Huang *et al* (7), chemoradiation + nimotuzumab was well-tolerated, grade 3/4 serious toxicity was observed in 14 of 23 (60.9%) patients, while grade 3/4 oral mucositis was recorded in 8 (34.8%) patients; CR rates of nasopharynx and regional nodal involvement were 91.3 and 95.5%, respectively; 2-year progression-free and overall survival reached 83.5 and 95.0%, respectively. However, the aforementioned study did not establish a control cohort. By contrast, a study by Kang *et al* (31) demonstrated that the efficacy of radiotherapy + endostar is comparable to radiotherapy + chemotherapy in LA-NPC but acute adverse reactions are milder.

Several retrospective studies have explored the effect of cetuximab or nimotuzumab in LA-NPC: Li *et al* (28) reported that patients with stage II-IV NPC receive no additional benefit from cetuximab + CCRT, with similar 3-year progression-free, local relapse-free, distant metastasis-free survival (DMFS) and overall survival but resulted in more severe acute mucositis and acneiform rash. Similar results were achieved in a retrospective study by You *et al* (32), where cetuximab/nimotuzumab + IMRT produced similar disease-free, locoregional recurrence-free and overall survival and DMFS compared with

Table II. Response to treatment.

A, All sites									
Best response	CCRT + anlotinib ^a (n=35)			CCRT alone (n=37)			P-value		
	1 week, n (%)	3 months, n (%)	6 months, n (%)	1 week, n (%)	3 months, n (%)	6 months, n (%)	1 week	3 months	6 months
CR	21 (60.0)	32 (91.4)	34 (97.1) ^b	15 (40.5)	30 (81.1)	34 (91.9) ^c	0.10 ^d	0.35 ^d	0.65 ^e
PR	14 (40.0)	3 (8.6)	0 (0.0)	16 (43.2)	6 (16.2)	2 (5.4)	-	-	-
SD	0 (0.0)	0 (0.0)	0 (0.0)	6 (16.2)	1 (2.7)	0 (0.0)	-	-	-
PD	0 (0.0)	0 (0.0)	1 (2.9) ^f	0 (0.0)	0 (0.0)	1 (2.7) ^g	-	-	-

B, Nasopharyngeal lesions									
Best response	CCRT + anlotinib ^a (n=35)			CCRT alone (n=37)			P-value		
	1 week, n (%)	3 months, n (%)	6 months, n (%)	1 week, n (%)	3 months, n (%)	6 months, n (%)	1 week	3 months	6 months
CR	22 (62.9)	32 (94.3)	34 (97.1)	20 (54.1)	32 (86.5)	36 (97.3)	0.64 ^d	0.50 ^e	1.00 ^e
PR	10 (28.6)	3 (8.6)	1 (2.9)	8 (21.6)	4 (10.8)	0 (0.0)	-	-	-
SD	3 (8.6)	0 (0.0)	0 (0.0)	9 (24.3)	1 (2.7)	1 (2.7)	-	-	-
PD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	-	-

C, Lymph node lesions									
Best response	CCRT + anlotinib ^a (n=35)			CCRT alone (n=37)			P-value		
	1 week, n (%)	3 months, n (%)	6 months, n (%)	1 week, n (%)	3 months, n (%)	6 months, n (%)	1 week	3 months	6 months
CR	23 (65.7)	32 (94.3)	35 (100.0)	20 (54.1)	32 (86.5)	36 (97.3)	0.31 ^d	0.77 ^e	1.00 ^e
PR	11 (31.4)	2 (5.7)	0 (0.0)	12 (32.4)	5 (13.5)	1 (2.7)	-	-	-
SD	1 (2.9)	0 (0.0)	0 (0.0)	5 (13.5)	0 (0.0)	0 (0.0)	-	-	-
PD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	-	-

CCRT, concurrent chemoradiotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. ^aOne patient (T3N0M0 III stage) was not assessed for a response to treatment as they had discontinued chemoradiotherapy + anlotinib after one cycle. ^bOne patient developed bone metastasis at 7.6 months after randomization (August 2021). ^cTwo patients developed liver metastasis and one patient developed bone metastasis at 10.7, 11.0 and 12.3 months, respectively, after randomization. ^dCalculated by χ^2 test. ^eCalculated by Fisher's exact test. ^fOne patient developed liver metastasis at 6 months after randomization. ^gOne patient developed lung metastasis at 5.1 months after randomization.

CCRT. Skin reaction and mucositis appeared more frequently in the cetuximab/nimotuzumab cohort.

The additional benefit of combined EGFR-blocking drugs + CCRT for LA-NPC treatment remains controversial. The aforementioned studies did not report positive results, which may be due to small sample size with low statistical power or EGFR-blocking drugs combined with radiotherapy instead of CCRT. For studies where EGFR-blocking drugs were combined with CCRT, the inclusion of low-risk stage II patients may be a possible cause of failure.

Cai *et al* (15) reported that the disease control rate of anlotinib as a third-line or further treatment for advanced NPC is 76.5% (trial no. NCT03906058). In the present study, anlotinib was combined with CCRT for stage III-IVA NPC. Only one

patient discontinued CCRT + anlotinib after one treatment cycle. A total of 66.7% of patients in the CCRT + anlotinib cohort achieved the planned three cycles of cisplatin treatment, compared with 73.0% of the CCRT cohort. The total dose of cisplatin in the CCRT alone cohort was similar to those in previous studies (28,30-32). The most common causes of interruption of concurrent cisplatin were grade 3/4 treatment toxicity and patient refusal. Anlotinib was also well-tolerated, with 91.7% of patients completing three cycles of concurrent anlotinib therapy. The present data revealed a slight increase in CR rate after anlotinib therapy, but this increase was not significant. These preliminary results suggested non-inferiority of CCRT + anlotinib compared with CCRT alone in terms of CR rates. Nevertheless, long-term follow-up

Table III. Acute adverse events.

Adverse event	CCRT + anlotinib (n=36)		CCRT alone (n=37)		P-value (grade 3/4)
	Grade 1/2, n (%)	Grade 3/4, n (%)	Grade 1/2, n (%)	Grade 3/4, n (%)	
Any	12 (33.3)	24 (66.7)	16 (43.2)	21 (56.8)	0.38 ^a
Hematological					
Leucopenia	23 (63.9)	10 (27.7)	25 (67.6)	8 (21.6)	0.54 ^a
Neutropenia	20 (55.6)	6 (16.7)	25 (67.6)	5 (13.5)	0.70 ^a
Neutropenic infection	0 (0.0)	1 (2.8)	0 (0.0)	1 (2.7)	1.00 ^b
Anemia	23 (63.9)	3 (8.3)	26 (70.3)	5 (13.5)	0.74 ^b
Thrombocytopenia	7 (19.4)	4 (11.1)	6 (16.2)	2 (5.4)	0.65 ^b
Non-hematological					
Hypertension	6 (16.7)	5 (13.9)	3 (8.1)	0 (0.0)	0.06 ^b
Hemorrhage	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	-
Dermatitis	29 (80.5)	3 (8.3)	25 (67.6)	3 (8.1)	1.00 ^b
Mucositis	21 (58.3)	13 (36.1)	24 (64.9)	11 (29.7)	0.56 ^a
Vomiting	17 (47.2)	4 (11.1)	19 (51.3)	5 (13.5)	1.00 ^b
Diarrhea	2 (5.6)	1 (2.8)	1 (2.7)	2 (5.4)	1.00 ^b
Hepatotoxicity	2 (5.6)	1 (2.8)	0 (0.0)	0 (0.0)	0.49 ^b
Nephrotoxicity	2 (5.6)	1 (2.8)	2 (5.4)	0 (0.0)	0.49 ^b

CCRT, concurrent chemoradiotherapy. ^aCalculated by χ^2 test. ^bCalculated by Fisher's exact test.

is required to determine the long-term effects of anlotinib on survival. The common acute adverse events during treatment were leucopenia, neutropenia, anemia, thrombocytopenia, dermatitis, mucositis and vomiting. The major grade 3/4 hematological events in the CCRT + anlotinib group were mucositis (36.1%), leucopenia (27.7%) and neutropenia (16.7%), which were manageable by using drugs for symptomatic treatment. Grade 3/4 hypertension was observed in 5 patients in the CCRT + anlotinib group, whereas no grade 3/4 hypertension occurred in the CCRT group. The incidence of grade 3/4 hypertension (13.9%) was consistent with that reported by ALTER 0303 Trial (13.6%), a phase 3 trial confirming the efficacy of anlotinib treatment for advanced non-small cell lung cancer (11). No patient presented with grade 3/4 hemorrhage or adverse event-related death. The incidences of grade 3/4 neutropenia, anemia and thrombocytopenia were higher than those in similar treatment cohorts reported in a previous study by Zhang *et al* (5) (13.5 vs. 10.5, 16.7 vs. 0.8, 5.4 vs. 1.3%, respectively), which may be due to a higher number of enrolled patients aged >45 years in the present study.

The present study has limitations. Firstly, the small sample size may lead to underpowered statistics and potential selection bias. Secondly, the present study only collected short-term follow-up data to assess therapy efficacy and acute toxicity. Hence, a follow-up period of ≥ 5 years is required to observe other treatment-associated events and evaluate the therapeutic impact and late toxic effects of CCRT + anlotinib in LA-NPC. Thirdly, some patients ceased treatment or were lost to follow-up. Furthermore, the latest phase 3 trial (5) suggests that induction chemotherapy with gemcitabine + cisplatin added to CCRT significantly improves recurrence-free and overall survival of patients with high-risk LA-NPC, which made induction

chemotherapy with gemcitabine + cisplatin followed by CCRT a standard treatment regimen for LA-NPC. The present study was initiated earlier than the publication of the phase 3 trial above, so induction chemotherapy with gemcitabine + cisplatin was not performed in this study. However, to the best of our knowledge, the present study is the first to assess the effectiveness and toxicity of CCRT + anlotinib in LA-NPC.

In conclusion, concurrent anlotinib has acceptable toxicity profiles, good compliance and encouraging efficacy with a favorable CR rate in patients with LA-NPC. However, further studies with larger cohorts, long-term follow-up and new induction regimens are required to confirm the clinical value of CCRT + anlotinib.

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Availability of data and materials

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

Authors' contributions

KC, GX, YL, PL, WG, ZL, WL, ZT, JC, XH and YX contributed to the study conception and design. KC, GX, YL, PL and WG analyzed data. KC and GX wrote the manuscript. All authors have read and approved the final manuscript. KC and YX confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was performed in line with the principles of the Declaration of Helsinki. Approval (no. 2019-001) was granted by the Ethics Committee of Guiping People's Hospital (Guiping, China), The First People's Hospital of Nanning (Nanning, China), The People's Hospital of Guangxi Zhuang Autonomous Region (Nanning, China) and The First Affiliated Hospital of Guangxi Medical University (Nanning, China). Written informed consent to participate was obtained from all participants included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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