

Phase II study of induction chemotherapy followed by concurrent chemoradiotherapy with raltitrexed and cisplatin in locally advanced nasopharyngeal carcinoma

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Abstract

Objective: For locally advanced nasopharyngeal carcinoma (LA-NPC) patients, high incidences of distant metastases and severe treatment related toxicities are the main obstacles needed to be overcome. Raltitrexed, a specific thymidylate synthase inhibitor with a convenient administration schedule, has an acceptable and manageable toxicity, and possesses radio-sensitizing properties. To investigate the efficacy and safety of raltitrexed and cisplatin induction chemotherapy and concurrent chemoradiotherapy (IC+CCRT) in patients with LA-NPC, a phase II clinical study was conducted.

Methods: Sixty eligible patients with LA-NPC were enrolled into this study. A raltitrexed-cisplatin combination was used as part of an IC+CCRT regimen. Raltitrexed-cisplatin IC was given once every 3 weeks (q3w) for two cycles, followed by raltitrexed-cisplatin based CCRT q3w for two cycles. Intensity-modulated radiotherapy (IMRT) was given for all enrolled patients.

Results: All patients were included in survival analysis according to the intent-to-treat principle. The objective response rate (ORR) 3 months after treatment was 98%. The 2-year overall survival (OS) rate was 92%. The median relapse-free survival (RFS) time was 30.5 [95% confidence interval (95% CI), 28.4–32.3] months. The 2-year RFS rate was 85%. The 2-year local failure-free survival (LFFS) rate was 97% and the 2-year distant metastasis-free survival (DMFS) rate was 88%. Acute toxicities were mostly grade 2 and 3 reactions in bone marrow suppression, gastrointestinal side effect and oropharyngeal mucositis. Only two patients occurred grade 4 acute toxicities, one was bone marrow suppression and the other was dermatitis radiation.

Conclusions: The combination of raltitrexed and cisplatin has a comparable efficacy to those in standard first-line therapy.

Keywords: Nasopharyngeal carcinoma; raltitrexed; cisplatin; induction chemotherapy; concurrent chemoradiotherapy

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Introduction

Nasopharyngeal carcinoma (NPC) is one of the common malignant tumors of the head and neck in Southeast Asia

with an annual incidence rate of approximately about 15/100,000–50/100,000 (1). The incidence of NPC in China ranks first in head and neck malignant tumors with a mortality rate of 1.74/100,000, which seriously threatens

people's health and lives (2). The histological types of NPC are mostly non-keratinized carcinomas (>90%) with a low degree of differentiation and a high degree of malignancy, these tumors typically result in local invasive growth and are prone to distant metastasis (3). The symptoms and signs of early NPC are usually not obvious; most patients present with a mass on the neck or one of the cranial nerves. As a result, about 70% of patients are diagnosed with locally advanced nasopharyngeal carcinoma (LA-NPC) (4,5). Improving prognosis in patients with LA-NPC is one of the main objectives of this study.

Recent research has reported that the combination radiotherapy has become the mainstream treatment for locally advanced NPC (6). Combined with radiotherapy, chemotherapy can be used to reduce tumors size, increase radio-sensitivity, and reduce micro-metastases, thereby reducing distant metastasis and improving overall survival (OS). The concept that a comprehensive treatment of radiotherapy coupled with chemotherapy can improve the prognosis of LA-NPC has achieved clinical consensus, however the optimum combination of radiotherapy combined with chemotherapy has not been clarified (7,8). A considerable number of studies have shown that induction chemotherapy (IC) has a beneficial effect on survival in the radiotherapy comprehensive treatment mode (9,10). Patients with adjuvant chemotherapy often find that the treatment is difficult to tolerate and frequently results in incomplete treatment (6,11). Concurrent chemoradiotherapy (CCRT) has shown significant survival benefit in the treatment of LA-NPC (12). Therefore, IC+CCRT may be a treatment method to further improve clinical efficacy. Hui *et al.* (10) showed that the IC+CCRT group had a 9-year OS of 34%, which was significantly higher than that of the CCRT group (68%) ($P=0.012$). However, Fountzilias *et al.* (13) found that the IC+CCRT group did not further improve the efficiency and OS rate compared with the CCRT group. Chua *et al.* (14) combined the Asia-Oceania Clinical Oncology Association (AOCOA) with the Guangzhou trial [Ma *et al.*, 2001 (15)] to show that the local failure rate and distant location of IC for 5 years decreased by 18% and 13%, respectively, but did not improve the 5-year OS rate. Therefore, the clinical efficacy of IC+CCRT for NPC needs to be validated by further research. At present, regimen of platinum-based antineoplastic drugs is the most commonly used chemotherapy for NPC. Cisplatin combined with fluorouracil (PF) is also considered as one of the most appropriate chemotherapy for NPC (16). However, its

clinical efficiency has always been maintained at 40%–60%, and is often accompanied by more serious gastrointestinal reactions, nephrotoxicity and oral mucosal reactions during treatment which limit its use in CCRT (16,17). Therefore, it is imperative to find safer and more effective chemotherapy drugs.

Raltitrexed is an analog of quinazoline folate whose function is to specifically binds to thymidine synthase (TS) and inhibits its action (18). TS is a key enzyme in the synthesis of thymidine triphosphate (TTP), which in turn is an essential nucleotide for DNA synthesis (19). Inhibition of TS can lead to DNA fragmentation and cell apoptosis (20). As a result, raltitrexed is effective in treating solid tumors such as colorectal cancer, malignant pleural mesothelioma, gastric cancer, pancreatic cancer, head and neck cancer, and non-small cell lung cancer (21).

Teicher *et al.* (22) studied the combined effects of raltitrexed and radiotherapy and found that for human colon cancer cells and human head and neck squamous cell carcinoma, raltitrexed had a sensitizing effect on radiotherapy, and this sensitization was stronger than 5-fluorouracil. A dose-climbing trial of raltitrexed with standard radiotherapy for advanced head and neck cancer has been performed, which included 17 patients with locally advanced head and neck cancer. Within this study it was suggested that raltitrexed was an effective drug for the treatment of patients who were not suitable for cisplatin combined with chemoradiotherapy, and that it warranted further study (23). A multicenter, phase II clinical study evaluated the efficacy and safety of raltitrexed carboplatin in the treatment of relapsed or metastatic head and neck squamous cell carcinoma and found that raltitrexed combined with carboplatin was safe and effective in the treatment of recurrent and metastatic head and neck squamous cell carcinoma (24). As raltitrexed had been studied as a radiosensitizer in rectal cancer and had few short-term effects (23), the aim of this study was to determine the efficacy and safety of IC+CCRT with raltitrexed and cisplatin in LA-NPC.

Materials and methods

Patients

Patients with LA-NPC were enrolled based on their eligibility of the following criteria: 1) having a pathologically confirmed undifferentiated NPC; 2) a performance status of 0–1 according to the Eastern Cooperative Oncology Group (ECOG) scale; 3) no

previous radiotherapy, chemotherapy or targeted drug therapy; 4) furthermore, routine blood examination standards need to meet the following criteria: hemoglobin ≥ 90 g/L (no blood transfusion within 14 d); absolute neutrophil count (ANC) $\geq 2.0 \times 10^9/L$; platelet $\geq 100 \times 10^9/L$; 5) blood biochemical examinations must meet the following criteria: bilirubin < 1.25 times the upper limit of normal (ULN); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $< 2.5 \times ULN$; serum Cr $\leq 1.5 \times ULN$; and 6) finally informed written consent.

Patients were not eligible for this study when they met any of these following criteria: 1) previously or currently diagnosed with a malignant tumor that was not an undifferentiated NPC, with the exception of cured skin basal cell carcinoma and cervical carcinoma; 2) patients who have had a distant metastasis at the time of diagnosis; 3) pregnant or breastfeeding females; 4) those who have a psychiatric history of drug abuse and cannot effectively treat ongoing mental disorders; 5) previous chemotherapy using raltitrexed or cisplatin; or 6) participated in other clinical trials of anti-tumor drugs within 4 weeks of their participation.

Therapy

Raltitrexed-cisplatin IC (raltitrexed, 2.5 mg/m², IV in 15 min, d 1; cisplatin, 25 mg/m², IV, d 1–3. Cycled every 21 d for 2 cycles) was given every 3 weeks (q3w) for two cycles, followed by raltitrexed-cisplatin based CCRT q3w for two cycles. Intensity-modulated radiotherapy (IMRT) was given for all enrolled patients. The primary outcome measure was objective response rate (ORR) and secondary outcome measures were OS and relapse-free survival (RFS).

Ethics

This study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki. All patients were required to provide informed written consent as approved by the local institutional review board before initiation of any study procedures. The research within this study was followed and approved by the Ethics Committee of the Hubei Cancer Hospital. The clinical trial registration number is NCT02562599 and date of registration was 29/09/2015.

Statistical analysis

The primary goal of this study was to use intent-to-treat

analysis to estimate the ORR of patients enrolled in this trial. Objective responses were reported as relative rates with 95% confidence limit (95% CL). The duration of response was calculated from the first recording of response to the date of progression; the time to progression was calculated from the date of the first cycle of therapy to the date of progression; and OS from the start of chemotherapy to death or last known follow-up. A univariate analysis of survival data according to the Kaplan-Meier product-limit estimate was performed. Comparisons in survival distribution were made by log-rank testing. All data was analyzed using IBM SPSS Statistics (Version 22; IBM Corp., New York, USA).

Results

Patients and treatment

A total of 60 patients with LA-NPC were enrolled from July 2015 to March 2017. Of them, 52 patients completed the trial, their characteristics are shown in *Table 1*. Among the 60 patients, 35 (58%) patients were males and 25 (42%) were females, with a median age of 50 (22–66) years. Thirty cases were in stage III and 30 cases were in stage IVA–B, according to the seventh edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) tumor-node-metastasis classification. Among these 60 patients, one patient missed his follow-up after 1 cycles of chemotherapy, one patient missed his follow-up after 2 cycles of chemotherapy, two patients did not receive CCRT according to the protocol after 2 cycles of chemotherapy (1 radiotherapy alone, 1 radiotherapy combined with cisplatin monotherapy), and four patients requested to withdraw from clinical trials after 2 cycles of chemotherapy. Overall, in this study, 52 patients completed 2 cycles of induction chemotherapy plus 2 cycles of CCRT.

Efficacy

We demonstrated the efficacy, as shown in *Table 2*, of ORR after IC and concurrent chemoradiotherapy and 3 months after concurrent chemoradiotherapy group as 48%, 97% and 98%, respectively. The disease control rate (DCR) after IC, after concurrent chemoradiotherapy and 3 months after concurrent chemoradiotherapy group were all 100%. The follow-up information is shown in *Table 3*. The 2-year OS rate in the IC+CCRT group was 92%. The median RFS time in IC+CCRT group was 30.5 (95% CI, 28.4–32.3) months. The 2-year RFS rate in IC+CCRT

Table 1 Baseline characteristics (N=60)

Characteristics	n (%)
Sex	
Male	35 (58)
Female	25 (42)
Age (year)	
Median age	50 (22–66)
Average age	49
ECOG	0–1
Clinical stage (AJCC 7th)	
III	30 (50)
IV	30 (50)
T	
1	0 (0)
2	11 (18)
3	27 (45)
4	22 (37)
N	
0	2 (3)
1	13 (22)
2	37 (62)
3	8 (13)

ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer.

group was 85%. The 2-year local failure-free survival (LFFS) rate in IC+CCRT group was 97%. The 2-year distant metastasis-free survival (DMFS) rate in IC+CCRT group was 88%.

Adverse events

Table 4 highlights the side effects recorded of this treatment plan. Grade 0–2 and 3 reactions in bone marrow suppression, gastrointestinal events and oropharyngeal mucositis were observed. Two patients acquired grade 4 acute toxicities, one was bone marrow suppression and the other was dermatitis radiation.

Table 2 Effectiveness analysis

Variables	After induction chemotherapy	After concurrent chemoradiotherapy	3 month after concurrent chemoradiotherapy
DCR (%)	100	100	100
ORR (%)	48	97	98

DCR, disease control rate; ORR, objective response rate.

Discussion

The efficacy of IC followed by CCRT in LA-NPC patient is controversial (10,13,25–31). Cisplatin and fluorouracil chemotherapy is the recommended regimen for NPC (6). A phase III clinical trial showed that cisplatin and fluorouracil IC followed by CCRT has higher 3-year DFS (82%) than CCRT alone (74%), however the 3-year OS does not statistically improve (88% vs. 89%, respectively) (27). We replaced fluorouracil with a less toxicity TS inhibitor, raltitrexed and treated LA-NPC patients with raltitrexed and cisplatin IC+CCRT. Our results showed the following: the 2-year OS rate in these patients was 92%, the 2-year RFS rate was 85%, the 2-year LFFS rate was 97%, and the 2-year DMFS rate in these patients was 88%. The most frequent acute toxicities in this study were grade 2 and 3 reactions and only two patients experienced grade 4 reactions. We have demonstrated that treatment with both raltitrexed and cisplatin has a comparable efficacy to those in standard first-line therapy of LA-NPC, which suggesting it is a potential choice for LA-NPC. The short-term ORR of the two-drug induction effect was lower than that of the three-drug docetaxel, cisplatin and 5-fluorouracil (TPF) and gemcitabine + cisplatin (GP) regimen, however, both our three-month and two-year follow-up was superior. Considering that this study aimed to look at the effectiveness of the combination of two drugs during simultaneous radiotherapy and chemotherapy, the effect intensity may be lower than that with TPF (32,33). Therefore, the two-drug joint scheme is still used in the synchronization stage, and the final 2-year OS is not inferior. In summary, the combination of raltitrexed with cisplatin IC combined with CCRT for LA-NPC is effective and is a safe regimen for LA-NPC.

The patients enrolled in this study had significantly advanced disease; 30 patients (50%) had stage IVA–B disease, and 30 patients (50%) had stage III disease. Previous studies confirmed the efficacy and feasibility of IC

Table 3 Follow-up information (N=52)

Variables	Value (%)
2-year OS rate	92
2-year RFS rate	85
2-year LFFS rate	97
2-year DMFS rate	88
Median RFS (month)	30.5 (95% CI, 28.4–32.3)

OS, overall survival; RFS, relapse-free survival; LFFS, local failure-free survival; DMFS, distant metastasis-free survival.

with cisplatin + 5-fluorouracil (FP) regimen in LA-NPC (34). As reported, the response rates achieved by a FP regimen were approximately 70%, and the median survival for all patients was 11 months (35-37). In this study, the response rate 3 months after treatment was over 90% and the 2-year survival rate was 92%. Moreover, the median RFS time was 30.5 (95% CI, 28.4–32.3) months. The current study demonstrated that LA-NPC was sensitive to a raltitrexed and cisplatin regimen and that IC treatment before CCRT was a feasible clinical strategy.

The grade 3–4 oropharyngeal mucositis or nausea that occurred during CCRT can lead to hypoalimentation and was a significant issue. Several studies have indicated that acute toxic effects during CCRT could decrease the patient’s tolerance to chemotherapy (28). It is suggested that giving a combination of drugs prior to CCRT may improve compliance and might result in some

improvements in systemic control. Further investigation into IC+CCRT as a curative modality for LA-NPC is warranted. In this study, we aimed to find out whether the drug raltitrexed could replace 5-fluorouracil in IC+CCRT regimens. Oral mucositis is an adverse reaction that restricts patients from completing radiotherapy. The occurrence rates of grade 0–2, grade 3 and grade 4 oral mucositis were 64%, 6% and 0%, respectively. The incidence of oral mucositis in this study is lower than that of FP regimen reported in the literature (38).

Raltitrexed, in combination of cisplatin had a high efficacy which was similar to the standard first-line therapy used against LA-NPC (39). In this study we found that the toxicity from a combination of drugs was tolerable even when it was applied with CCRT. In conclusion, the raltitrexed-cisplatin was an effective and safe regimen for LA-NPC. Although we have reported the OS results, further observations are needed to follow up the prognosis of patients and generate multi-year data to fully assess the survival rates of NPC and potentially long-term toxicity of raltitrexed-cisplatin IC+CCRT.

Conclusions

The results showed that the combination of raltitrexed with cisplatin-induced chemotherapy combined with CCRT for LA-NPC are encouraging and warrant further

Table 4 Incidence of major acute toxicities

Variables	Induction chemotherapy (n=60) (%)			Concurrent chemoradiotherapy (n=52) (%)		
	Grade 0–2	Grade 3	Grade 4	Grade 0–2	Grade 3	Grade 4
Leukocytes	42	3	2	58	25	0
Neutrophils	18	2	2	20	12	0
ALT/AST increased	18	0	0	10	0	0
Gastrointestinal reactions	62	7	0	77	2	0
Pharyngeal inflammation	3	0	0	62	0	0
Oral mucositis	0	0	0	64	6	0
Dermatitis radiation	0	0	0	69	2	2
Tinnitus/hearing impaired	3	0	0	6	0	0
Nausea	53	7	0	69	2	0
Vomit	43	7	0	39	2	0
Dry mouth	3	0	0	33	0	0
Anorexia	30	0	0	40	0	0
Dizziness/headache	5	0	0	6	0	0
Fatigue	32	2	0	42	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

investigation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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