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ORIGINAL ARTICLE

An open-label, single-arm phase II clinical study of induction chemotherapy and sequential Nimotuzumab combined with concurrent chemoradiotherapy in N3M0 stage nasopharyngeal carcinoma

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Summary

Purpose: *The purpose of this study was to analyze the efficacy and safety of induction chemotherapy and sequential Nimotuzumab combined with concurrent chemoradiotherapy in N3M0 stage nasopharyngeal carcinoma (NPC).*

Methods: *This study included 45 N3 stage NPC patients treated with induction chemotherapy, sequential Nimotuzumab plus concurrent chemoradiotherapy. The intensity modulated radiation therapy (IMRT) doses for planning target volume (PTV) were 70-72 Gy for gross disease in the nasopharynx, and 66-70 Gy for positive lymph nodes. The doses for high risk and low risk regions PTV were 60-62 Gy and 54-56 Gy in 31-33 fractions. Induction chemotherapy consisted of 3 cycles of docetaxel (75 mg/m², day 1) plus lobaplatin (30 mg/m², day 1). Concurrent with radiotherapy, patients received chemotherapy consisting of lobaplatin 50 mg/m², day 1. Targeted drug therapy given on the first time of IMRT consisted of Nimotuzumab (200mg, iv weekly for 7 courses). Cycle repetition of chemotherapy was every 21 days.*

Results: *The efficacy of 3 cycles of induction chemotherapy before the start of concurrent chemoradiotherapy was 100%, and the overall efficacy after the end of chemoradiotherapy was also 100%. Three-year overall survival (OS), distant metastasis-free survival (DMFS), locoregional control (LRC) and progression-free survival (PFS) rates were 85.6, 81.9, 97.8 and 79.5%, respectively. The main adverse reactions were hematologic toxicity, particularly neutropenia (100%), anemia (88.9%) and thrombocytopenia (68.9%). Patients developed a relatively low degree of mucositis and vasculitis. Chronic toxicity was mainly grade I-II radiation-induced xerostomia (18 cases). There were 11 cases of hearing loss and 4 cases of neck skin fibrosis. No cases of treatment-related death and radiation-induced cranial nerve damage or trismus were observed.*

Conclusion: *In N3 stage NPC, induction chemotherapy and sequential Nimotuzumab plus concurrent chemoradiotherapy yielded an excellent survival benefit, and the toxicities were tolerable. Distant metastasis was the main cause of treatment failure.*

Key words: *chemotherapy, docetaxel, intensity modulated radiotherapy, lobaplatin, nasopharyngeal carcinoma, nimotuzumab*

Introduction

Nasopharyngeal carcinoma (NPC) is the most common head and neck cancer in Southeastern Asia. In 2013 its incidence was 2.5:1 in males and females, with a mortality rate of 2.71:1 [1]. The primary tumor volume and N stage are the most important prognosis factors affecting the local control rate and DMFS rate, respectively. Currently, distant metastasis is the main reason for treatment failure,

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and the ratio of distant metastasis to locoregional failure is 9 to 1 [2]. Therefore, to increase the efficacy of NPC, could basically be achieved by reducing the incidence of distant metastases. The 5-year DMFS of N3M0 stage NPC is 50-70% [3].

Induction chemotherapy theoretically has the advantages of reducing the tumor volume, shrinking the radiotherapy target volume, improving radiotherapy efficacy and reducing the side effects. In the past, induction chemotherapy regimen for NPC mainly consisted of cisplatin combined with 5-fluorouracil (PF). Subsequent studies showed that induction chemotherapy with paclitaxel plus cisplatin combined with fluorouracil (TPF) was better than traditional PF in terms of PFS and OS [4,5]. However, due to the physical body construction in China (Chinese people are slightly thinner than European and American populations) the majority of patients often can not tolerate the induction chemotherapy with TPF. Docetaxel combined with lobaplatin has achieved a satisfactory clinical efficacy in primary, recurrent or metastatic NPC [6,7].

Nimotuzumab is a humanized monoclonal antibody that is obtained by replacing a murine complementary-determining regions with a human framework. Irradiation combined with Nimotuzumab has shown clinical efficacy in improving locoregional control and OS in NPC and significantly reducing the incidence of mucositis and dermatitis. So it was loaded in "NCCN Clinical Practice Guidelines (Chinese Version) in March 2009 [8].

In the present study, we retrospectively analyzed the long-term outcomes and toxicity in N3M0 stage NPC patients who received three cycles of induction chemotherapy and sequential Nimotuzumab combined with concurrent chemoradiotherapy. The aim of the study was to investigate whether N3M0 stage NPC treatment could be optimized by appropriate administration of induction chemotherapy and targeted drug therapy.

Methods

Patients

We analyzed data from 45 patients with N3M0 stage NPC who were treated in our department between November 2013 and February 2015. These patients had histologically confirmed non-keratinizing carcinoma without distant metastasis. Written informed consent was obtained by all patients. Karnofsky performance status (KPS) ≥80, clinical and laboratory examinations included magnetic resonance imaging (MRI) of the head and neck region, Epstein Barr virus (EBV) DNA, neck ultrasound, positron emission tomography/computed tomography (PET/CT) and whole-body bone imaging.

Table 1. Clinical characteristics of NPC patients

Characteristic	*Patients (n)*	*% of Patients*
Age (yr)		
Median	52	
Range	21-69	
Sex		
Male	32	71.1
Female	13	28.9
Non-keratinizing		
Undifferentiated type	39	86.7
Differentiated type	6	13.3
T stage		
1	5	11.1
2	16	35.6
3	17	37.8
4	7	15.5
N stage		
3a	4	8.9
3b	41	91.1
EB DNA		
≥5.0E+2 copies/ml	35	77.8
<5.0E+2 copies/ml	10	22.2

The NPC patients were classified according to the 8th Edition of American Joint Committee on Cancer (AJCC) TNM classification. The clinical characteristics of the patients included in this study are shown in Table 1.

Radiation therapy

IMRT was delivered by using a simultaneous-integrated boost (SIB) technique. The gross tumor volume (GTV) included the nasopharynx gross tumor volume (GTVnx) and positive neck lymph nodes (GTVnd) as measured by MRI. The high-risk clinical tumor volume (CTV1) included the entire nasopharyngeal mucosa, retropharyngeal lymph nodes, skull base, parapharyngeal space, pterygopalatine fossa, sphenoid sinus, posterior third of nasal cavity and maxillary sinus. The low-risk clinical tumor volume (CTV2) included those without lymph node metastasis in the cervical lymph drainage area. The planning target volume (PTV) was created based on GTVnx and each CTV with an additional 3mm margin, and GTV with an additional 4-5mm margin. The prescribed doses were PTV 70-72 Gy for gross disease in the nasopharynx, 66-70 Gy for positive lymph nodes in 31-33 fractions, the prescribed doses for high risk and low risk region PTV were 60-62 Gy and 54-56 Gy in 31-33 fractions, respectively.

Chemotherapy and targeted drug therapy

The induction chemotherapy program consisted of three cycles of docetaxel (75 mg/m^2, day 1) plus lobaplatin (30 mg/m^2, day 1). Concurrent with radiotherapy, patients received chemotherapy consisting of lobaplatin 50 mg/m^2, day 1. Targeted drug therapy consisted of Nimotuzumab (200mg iv, weekly for 7 courses). The time

of each Nimotuzumab infusion was not less than 1.5 hrs. Cycle repetition of chemotherapy was every 21 days. If there was grade IV hematologic toxicity, chemotherapy dose was decreased to 80% of the initial. Throughout the whole course of chemotherapy, liver and renal function tests and routine blood and serum tests were performed.

Follow-up

Each patient was scheduled for follow-up visits every three months for the first three years, and annually thereafter. Each follow-up included chest X-ray, neck ultrasound and endoscopy. Chest and abdominal CT, MRI of the head and neck and ECT were performed every six months. Toxicities were observed and scored according to the Toxicity Criteria of the Radiation Therapy Oncology Group (RTOG). Efficacy was determined using the RECIST evaluation criteria.

Statistics

Data were processed using SPSS 21.0 software. The following endpoints were assessed: overall survival (OS), distant metastasis-free survival (DMFS), local-regional control (LRC) and progression-free survival (PFS). Alll the endpoints were defined as the intervall from the date of treatment initiation to the date of failure or last follow-up. The Kaplan-Meier method was used to estimate the rates of OS, DMFS, LRC and PFS and the Log rank test was applied to compare the differences. The relevant factors were screened by chi-square test. P values <0.05 were considered statistically significant.

Results

Short-term effect of chemoradiotherapy

The primary taget of this trial was the cervical lymph nodes. After induction chemotherapy, 5 patients achieved CR and 40 PR. The total short-term efficacy of induction chemotherapy was 100.0% (Table 2). Three months after IMRT, the total chemoradiotherapy efficiency was 100.0% with 35 CR and 10 PR (Table 2). We attempted to observe the potential relationship between related factors and lymph nodes to achieve CR, by assessing lymph node size, extracapsular extension, lymph node fusion , liquefaction necrosis, palpation texture and ultrasound estimation of blood supply. Only the CR rates in the groups with diameter > 3cm and MRI-assessed liquefaction necrosis in lymph nodes were inferior to those < 3cm and no liquefaction necrosis ($p<0.05$).

Toxicities

All 45 patients completed three courses of induction chemotherapy, received Nimotuzumab ×7 courses and had at least one cycle of concurrent chemoradiotherapy. Seven patients were unable to undergo chemotherapy for 21 days due to toxic side effects, thus prolonging the time required, or had

Table 2. Treatment's clinical efficiency

Efficiency	*CR* *n (%)*	*PR* *n (%)*	*NC* *n (%)*	*PD* *n (%)*
Short-term effect of IC	5 (11.1)	40 (88.9)	0 (0)	0 (0)
Short-term effect of CRT	35 (77.8)	10 (22.2)	0 (0)	0 (0)

IC: induction chemotherapy, CRT: chemoradiotherapy

Table 3. Acute toxicities during chemoradiotherapy

Toxicities	*Grade*			
	I *n (%)*	*II* *n (%)*	*III* *n (%)*	*IV* *n (%)*
Dermatitis	22 (48.9)	7 (15.6)	0 (0)	0 (0)
Mucositis	29 (64.4)	16 (35.6)	0 (0)	0 (0)
Xerostomia	29 (64.4)	8 (17.8)	0 (0)	0 (0)
Neutropenia	11 (24.4)	18 (40.0)	15 (33.3)	1 (2.2)
Anemia	31 (68.9)	9 (20.0)	0 (0)	0 (0)
Thrombocytopenia	10 (22.2)	13 (28.9)	6 (13.3)	2 (4.4)
Nausea/vomiting	8 (17.8)	2 (4.4)	0 (0)	0 (0)
Liver dysfunction	3 (6.7)	0 (0)	0 (0)	0 (0)
Fever	5 (11.1)	0 (0)	0 (0)	0 (0)
Neurotoxicity	1 (2.2)	0 (0)	0 (0)	0 (0)
Fatigue	11 (24.4)	0 (0)	0 (0)	0 (0)
Hypotension	2 (4.4)	0 (0)	0 (0)	0 (0)

interruption of chemotherapy due to myelosuppression. The main adverse reactions were hematologic toxicity, particularly neutropenia (100%), anemia (88.9%) and thrombocytopenia (68.9%). Patients developed a relatively low grade mucositis and vasculitis. Acute toxicities experienced by patients are summarized in Table 3. Chronic toxicities were mainly grade I-II radiation-induced xerostomia (18 cases). There were 11 cases of hearing loss and 4 cases of neck skin fibrosis. No cases of treatment-related death and radiation-induced cranial nerve damage or trismus were observed.

Patterns of failure

Patients were monitored for 14-51 months, with a median follow-up duration of 38 months. There were 7 treatment-related deaths, attributable to adverse drug reactions, including IIA

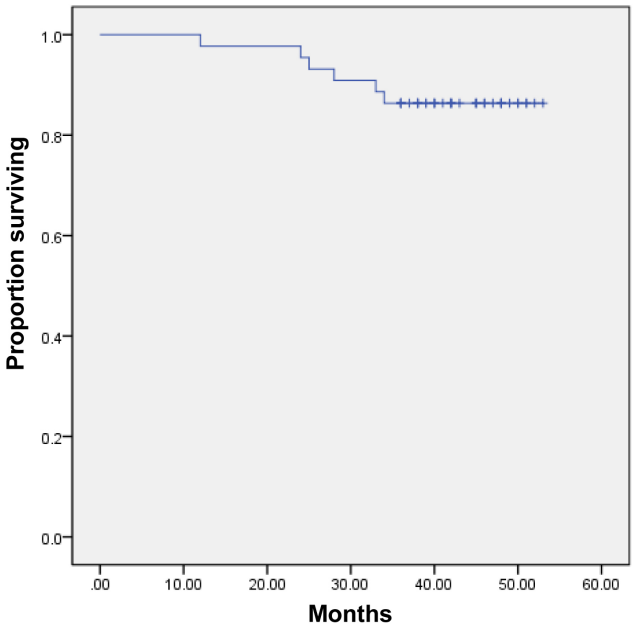

Figure 1. Kaplan-Meier estimate of OS in N3 stage NPC patients treated with nimotuzumab combined with chemoradiotherapy.

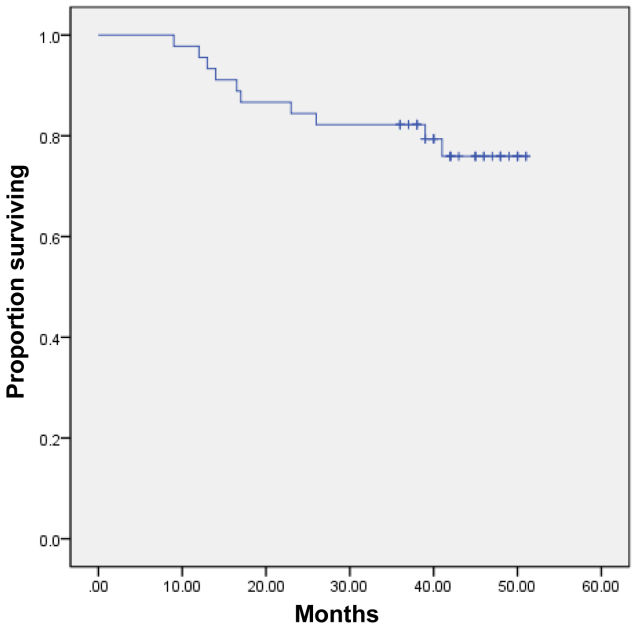

Figure 2. Kaplan-Meier estimate of distant-metastasis-free survival in N3 stage NPC patients treated with nimotuzumab combined with chemoradiotherapy.

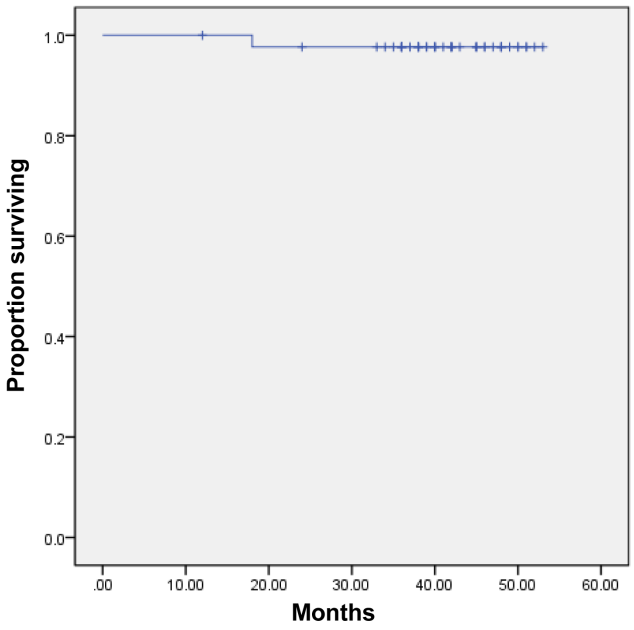

Figure 3. Kaplan-Meier estimate of locoregional control in N3 stage NPC patients treated with nimotuzumab combined with chemoradiotherapy.

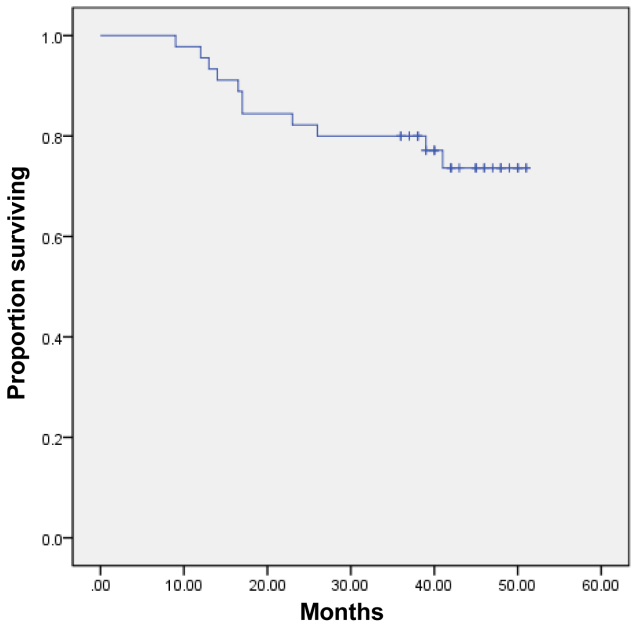

Figure 4. Kaplan-Meier estimate of progression-free survival in N3 stage NPC patients treated with nimotuzumab combined with chemoradiotherapy.

region lymph node recurrence with parotid gland metastasis (1 case), and distant metastasis (6 cases). The recurrent patient died 4 months after re-IMRT. Until now, the overall failure rate was 22.2% (10 patients). Distant metastasis was the main cause of failure. The median distant metastasis time was 17 months (range 9-41).

Survival analysis

The 3-year OS, DMFS, LRC and PFS rates were 85.6, 81.9, 97.8 and 79.5%, respectively (Figures 1-4). We divided the tumor regression rate into fast-fading lymph nodes group (reaching PR before the second cycle of induction chemotherapy) and general fading lymph nodes group (all the remaining), and discovered no differences in the DMFS and efficiency between the two groups (all $p>0.05$). There was also no difference in the DMFS between T1+T2 groups vs T3+T4 groups ($p>0.05$).

Discussion

With the wide use of IMRT, clinical, local and regional control rates of NPC have been significantly improved. However the 2-year OS rate is 15.0-34.4% and the median OS is 9.0-15.6 months in metastatic NPC patients [9]. Although a variety of therapeutic methods has been tried, the effect is not satisfactory. The monoclonal antibody of immune check point PD-1 has proved that the objective response rate of treatment was 25.9% in a phase Ib study of recurrent or metastatic NPC [10]. The immunodetection point PD-L1 positive expression rate was 25% in head and neck squamous cell carcinoma (HNSCC) [11]. Lots of phase 3 clinical studies of PD-1 monoclonal antibody have been proved to achieve negative results in HNSCC [12]. These results suggest that therapy may still return to chemotherapy to improve the efficacy of N3M0 stage NPC.

Induction chemotherapy has achieved improved LRC and DMFS [13,14]. Induction chemotherapy with 4-6 cycles is not recommended, mainly for the following reasons: First, the Chinese people's physique is thin; second, the surviving tumor cells will become more resistance after 4 cycles of chemotherapy; third, concurrent chemoradiotherapy is difficult to complete; and fourth, oral mucositis, anemia and nutritional status will be more severe.

Targeted drug therapy is a new therapeutic approach for NPC, mainly including epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR), two intervention targets. Overexpression of EGFR is a feature of NPC, and 68%-89% of high EGFR expression was associated with a targeted therapy [15,16]. Nimotuzumab is the first monoclonal antibody targeting EGFR, and the total effective rate was more than 90% in locally advanced NPC by chemoradiotherapy plus Nimotuzumab. With i.v. injection of 50, 100, 200 and 400 mg, the elimination half-life of Nimotuzumab was 62.92, 82.60, 302.95 and 304.52 hrs [17,18]. Administration of 200 mg weekly can make stable blood drug concentration. Docetaxel is a fat-soluble anticancer drug that shows efficient antitumor activity in head and neck tumors. It stabilizes microtubules and prevents the disassembly of micro-tubules during mitosis, thereby leading to catastrophic cell death. Platinum and its derivatives are DNA alkylators that cause cell death by inducing collapse of DNA replication process [9].

In this study, the short-term effect of induction chemotherapy and chemoradiotherapy was 100.0%. The efficacy and survival rates observed in this study were better compared with the results of our previous study [7]. In the era of conventional radiotherapy, we observed that while the tumor regression was faster in NPC patients, a part of patients often were more prone to distant metastasis. Possibly this suggests that these tumor cells of the faster regression were more aggressive. We divided the tumor regression rate into fast-fading lymph nodes group (reaching PR before the second cycle of induction chemotherapy) and general responding lymph node group (all the remaining), and found no differences in the DMFS and efficacy between the two groups (all $p>0.05$). The 3-year OS, DMFS, LRC and PFS rates were 85.6%, 81.9%, 97.8% and 79.5%, respectively. The most commonly observed toxicities were moderate neutropenia, followed by anemia and thrombocytopenia. Because thrombocytopenia is more difficult to deal with and the increase of platelet count is relatively slow, it is recommended to prophylactically use interleukin 11 and recombinant human thrombopoietin injection. The incidence and extent of mucositis are tolerable and late adverse reactions are acceptable. Nimotuzumab can make NPC patients get lighter reactions and better nutritional status, so the incidence of mucositis becomes low and myelosuppression is easily corrected. This trial also enrolled a pregnant patient with T4N3M0 stage with chemoradiotherapy beginning after the birth of the child and we found that this woman had a very good tolerance, and chemoradiotherapy toxicities were mild including appetite, bone marrow suppression and mucositis. We considered this might be related to the higher levels of progestins. According to long-term observation, her tumor did not recur. Our results on treatment failure indicate that distant metastasis was the major factor affecting treatment outcome.

In summary, induction chemotherapy with sequential nimotuzumab combined with concurrent chemoradiotherapy in any T, N3M0 stage NPC was feasible and resulted in a better LRC and DFMS rates. The side effects of treatment were acceptable. In the future, a larger number of randomized controlled trials should be conducted to further confirm the efficacy of this therapeutic approach.

Conflict of interests

The authors declare no conflict of interests.

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