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Long-Term Use of Nimotuzumab in Combination With Intensity-Modulated Radiotherapy and Chemotherapy in the Treatment of Locoregionally Advanced Nasopharyngeal Carcinoma: Experience of a Single Institution

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In this retrospective review of a single institution's experience, the efficacy and safety of the long-term use of nimotuzumab in combination with intensity-modulated radiotherapy (IMRT) and chemotherapy in the treatment of locally advanced nasopharyngeal carcinoma (NPC) were studied. Between August 2008 and March 2014, 39 newly diagnosed patients with stages III–IV NPC were treated with IMRT, chemotherapy, and nimotuzumab. Twenty patients were diagnosed with stage III (51.3%), 14 with stage IVA (35.9%), and 5 with stage IVB (12.8%) disease. All patients received at least one cycle of cisplatin-based induction chemotherapy followed by IMRT and more than nine cycles of nimotuzumab at 200 mg/week. Acute and late radiation-related toxicities were graded according to the Acute and Late Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group. Accumulated survival was calculated according to the Kaplan–Meier method. The log-rank test was used to compare survival differences. With a median follow-up of 46 months (range, 22–86 months), the estimated 3-year local recurrence-free, regional recurrence-free, distant metastasis-free, progression failure-free, and overall survival rates were 92.1%, 89.7%, 82.5%, 77.6%, and 86.8%, respectively. Univariate analysis showed that clinical stage and the cycle of induction chemotherapy were related with prognosis. The median cycle for the addition of nimotuzumab was 12 weeks. Grade 3 radiation-induced mucositis was observed in 15.8% of the treated patients. No skin rash or infusion reaction was observed, which is distinctly different from what was reported in patients treated with nimotuzumab. The major toxicities observed were grades I–II mucositis and leukocytopenia. Long-term use of nimotuzumab plus IMRT showed promising outcomes in terms of locoregional control and survival, without increasing the incidence of radiation-related toxicities in patients.

Key words: Nasopharyngeal carcinoma (NPC); Intensity-modulated radiotherapy (IMRT); Nimotuzumab; Prognosis

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a common malignancy with remarkably distinctive ethnic and geographic distribution. It is endemic to Southern China[1] and Hong Kong[2], with an annual incidence rate of 20–30 per 100,000. Radiotherapy is the preferred modality of treatment because the anatomical location is an obstacle for surgery, and the tumors are radiosensitive. Because of the increased risk of distant metastasis, a combined modality treatment is administered in locally advanced disease. According to meta-analyses of randomized studies, the combination of radiotherapy and chemotherapy reduces the risk of mortality by 18% and increases 5-year survival by 4%–6%[3,4]. Chemoradiotherapy (CRT) is the standard treatment for locoregionally advanced (LA) NPC, and this combined modality approach is associated with a survival benefit[5]. However, with respect to the intensity-modulated radiotherapy (IMRT) era, the benefit of CRT is still uncertain. Therefore, it is important for clinicians to investigate new agents that could enhance the efficacy of IMRT and chemotherapy.

It has been shown that overexpression of epidermal growth factor receptor (EGFR) is observed in several different solid tumors, including gliomas, sarcomas, and

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head and neck cancers[6]. Moreover, high EGFR expression has been associated with a poor prognosis[7–10]. Several inhibitors of EGFR (e.g., cetuximab, panitumumab, erlotinib, and gefitinib) have shown favorable results in clinical trials[11–14]. Cetuximab is the most commonly used anti-EGFR antibody, combined with radiotherapy (RT), and this combination regimen has been shown to improve survival in patients with LA head and neck squamous cell carcinoma (HNSCC)[15]. In NPC, cetuximab with concurrent CRT is tolerable and has shown promising clinical efficacy for NPC patients[16]. However, the relatively high rate of mucositis and acne-like skin rash has limited its clinical application[16–18].

Nimotuzumab is a monoclonal antibody that targets the external cell surface domain of EGFR and leads to the inhibition of downstream EGFR signaling[19]. In preclinical studies, nimotuzumab demonstrated remarkably antiproliferative, proapoptotic, and antiangiogenic activity[20]. Nimotuzumab displayed a longer half-life and a more elevated area under the curve than cetuximab at the same dosage[21]. In addition, nimotuzumab improved the quality of life as it rarely caused severe dermatological toxicity, which is one of the most common adverse events associated with cetuximab and panitumumab[22].

Nimotuzumab safety and efficacy results have been formally reported in several phases I and II/III clinical studies involving patients with advanced NPC and head and neck cancers. In these trials, nimotuzumab was administered by intravenous infusion at doses of 100 or 200 mg. The published clinical trial results with nimotuzumab in these indications are summarized in Table 1.

In the phase II randomized, open-label, multicenter trial for patients with locally advanced nasopharyngeal squamous cell carcinomas from seven centers in China, nimotuzumab combined with RT showed efficacy benefits in terms of response, overall survival (OS) rate, and quality of life. The addition of nimotuzumab to RT did not exacerbate toxicity typically associated with RT during the study[23]. Therefore, the combination therapy has been approved for the treatment of NPC in China since 2008 and was included within the Chinese National NCCN guidelines as a recommended targeted therapy for this indication in 2009 (Clinical Practice Guidelines in Oncology–Chinese version, 2010 first edition). The recommended dosage and schedule by the medication guides for nimotuzumab is 200 mg weekly for 6 to 8 weeks for patients with NPC.

The safety and efficacy of nimotuzumab, as a radiosensitizer, administered along with CRT or RT in patients with inoperable, locally advanced HNSCC was studied by assessing response rates and long-term survival. At 5-year follow-up, when the OS of patients receiving CRT + nimotuzumab and RT + nimotuzumab ($n = 46$) was compared to that of patients who did not receive nimotuzumab ($n = 46$), the former demonstrated a significantly improved survival [49.38 vs. 16.36 months; hazard ratio (HR) = 0.52, 95% confidence interval (CI) = 0.30, 0.89; $p = 0.012$] with a 48% reduction in death[6]. These results strongly suggest that nimotuzumab contributes to improving locoregional control and helps prolong survival when used along with RT or CRT.

While nimotuzumab in combination with RT has marketing approval for the treatment of advanced NPC[23] and, in recognition of the constant need to develop novel concurrent therapies to improve outcomes of NPC OS, to optimize the treatment approach with the exceptional safety profile that has been previously reported for nimotuzumab[6,20–24], additional studies are exploring the combination of the recommended nimotuzumab dose with different modalities of RT and with concurrent chemotherapy[25,26]. In clinical practice, the current treatment strategies include the prolonged use of nimotuzumab,

Table 1. Published Clinical Trials With Nimotuzumab in Nasopharyngeal Carcinoma (NPC) and Head and Neck Cancer Patients

Indication	Study Design	Clinical Results
Advanced NPC[23]	Nimotuzumab + RTP versus RTP; 137 patients, 6 doses, 100 mg weekly	CRR: 90.63 % versus 51.52% ($p < 0.05$)
Advanced HNSCC[20]	Nimotuzumab + RTP; 24 patients, 6 doses, 200 mg weekly	MST: 45.2 months
Advanced HNSCC[24]	Nimotuzumab + RTP versus placebo + RTP; 106 patients, 6 doses, 200 mg weekly	CRR: 59.5% versus 34.2% ($p = 0.038$)
Advanced HNSCC[6]	Nimotuzumab + RTP/CTP versus RTP/CTP; 46 patients, 6 doses, 200 mg weekly	RR (at 24 weeks): 100% versus 70% ($p = 0.02$) OS rate (60 months): 57% versus 26% ($p = 0.03$)
	Nimotuzumab + RTP versus RTP; 46 patients, 6 doses, 200 mg weekly	RR (at 24 weeks): 76% versus 40% ($p = 0.023$) OS rate (60 months): 39% versus 26% ($p > 0.05$)

RTP, radiotherapy; CTP, chemotherapy; CRR, complete response rate; RR, response rate; MST, median survival time; OS, overall survival; HNSCC, head and neck squamous cell carcinoma.

beyond the recommended six cycles weekly, for NPC patients with high-risk factors (e.g., large tumor volume, etc.), despite the fact that the definition of long-term use remains unclear. The feasibility, safety, and clinical benefits of prolonged administration of nimotuzumab in a pediatric population with central nervous system tumors have been demonstrated by Cabanas et al.[27]. In this study, patients received 12 weekly doses of nimotuzumab as induction therapy combined with RT, chemotherapy, or alone. We conceived the prolonged use of nimotuzumab as the extension of drug administration beyond the recommended dose. Therefore, we retrospectively studied the safety and preliminary results of the long-term use of nimotuzumab in combination with IMRT and chemotherapy in LA NPC patients.

MATERIALS AND METHODS

Patients and Pretreatment

Between November 2008 and December 2013, 39 patients (median age 48 years; range 24–68 years) with histology-proven nonmetastatic NPC were treated in Zhejiang Cancer Hospital, and their cases and follow-up details were evaluated retrospectively. All patients with stage III or stage IV NPC were treated with nimotuzumab plus definitive IMRT and chemotherapy. These patients had a pretreatment evaluation including complete history, physical examination, hematology and biochemistry profiles, chest radiographs, sonography of the abdomen, bone scan, and magnetic response imaging of the nasopharynx and nasopharyngoscope. All patients were staged according to the 2010 AJCC staging system. Tumor histology according to the World Health Organization (WHO) classification[28] was type I (3), type II (34), and type III (2). The clinical characteristics of the patients are presented in Table 2.

Delineation for Tumor Volume

All patients were immobilized in a supine position with thermoplastic masks. Computed tomography scans with intravenous contrast (2.5-mm slices from the head to 2 cm below the sternoclavicular joints) were performed for planning. Target volumes were delineated according to the recommendations of the International Commission on Radiation Units and Measurements CTV delineation protocol for head and neck malignancies[29,30]. Gross tumor volume (GTV) refers to the extent of the tumor found in the clinical and imaging examinations. The extent of the primary tumor, including metastatic retropharyngeal lymph nodes, is defined as GTVnx, and the metastatic lymph node of the neck is defined as GTVnd.

The CTV was defined individually according to the GTV, and the potential regions at risk surrounding the

Table 2. Baseline Clinical Characteristics of Patients

Characteristics	No. of Patients (%)
Sex	
Male	29 (74.4)
Female	10 (25.6)
Age (years)	
≥60	17 (43.6)
<60	22 (56.4)
Histology (WHO type)	
I	3 (7.7)
II	34 (87.2)
III	2 (5.1)
Blood group	
A	16 (41.0)
AB	3 (7.7%
B	9 (23.1)
O	11 (28.2)
Tumor response	
Complete response	34 (87.2)
Partial response	5 (12.8)
The cycle of target	
≥12	19 (48.7)
<12	20 (51.3)
The time of target	
Induction	8 (20.5)
Induction + concurrent	29 (74.4)
Concurrent + adjuvant	2 (5.1)
Chemotherapy regimen	
TPF	20 (51.3)
TP	5 (12.8)
GP	1 (2.6)
FP	13 (33.3)
The cycle of IC	
1–2	8 (25.8)
3–4	31 (74.2)
Adjuvant chemotherapy	
Yes	5 (6.8)
No	34 (93.2)
T stage	
4	2
T2	4 (10.3)
T3	19 (48.7)
T4	16 (41.0)
N stage	
N0	3 (7.7)
N1	13 (33.3)
N2	18 (46.2)
N3	5 (12.8)
Clinical stage	
III	20 (51.3)
IVa	14 (35.9)
IVb	5 (6.8)

nasopharyngeal cavity. The CTV for GTVnx included CTVnx for the high-risk CTV and CTV1 when invasion was present. The CTVnx was defined as GTVnx plus a 7-mm margin that encompassed the nasopharyngeal mucosa plus 5-mm submucosal volume. For CTV1, the anatomic regions that were potentially involved were the entire nasopharyngeal cavity, the anterior one third to two thirds of the clivus (when invasion is present, the whole clivus should be covered), the skull base, the pterygoid plates, the parapharyngeal space, the inferior sphenoid sinus (the entire sphenoid sinus should be covered for stage T3 and T4 NPC), the posterior one quarter to one third of the nasal cavity, and the maxillary sinus. High-risk nodes included level Ib nodes in patients with metastatic lymph nodes in level IIa and any lymph nodes in drainage pathways containing metastatic lymph nodes. Low-risk areas for prophylactic neck irradiation areas were referred to as CTV2. These low-risk areas included levels IV and Vb without metastatic cervical lymph nodes.

The PTV was constructed automatically based on each volume with an additional 3-mm margin in three dimensions to account for setup variability. None of the PTVs, including PGTVnx, PTVnx, PTV1, and PTV2, were delineated outside of the skin surface. Critical normal structures including the brainstem, spinal cord, parotid glands, optic nerves, chiasm, lens, eyeballs, temporal lobes, temporomandibular joints, mandible, and hypophysis were contoured and set as organs at risk (OAR) during optimization.

Intensity-Modulated Radiotherapy Planning

Treatment was performed with a simultaneous integrated boost technique using 6 MV photons. The prescribed radiation dose was 69 or 72 Gy to PGTVnx, 66–69 Gy to PGTVnd, 63–66 Gy to PTVnx, 60–63 Gy to PTV1, and 51–54 Gy to PTV2, delivered in 30 or 33 fractions. Radiation was delivered once daily, five fractions per week, over 6–6.5 weeks. The volume of the PTV encompassed by less than 95% of the prescription dose should not exceed 1%. More than 110% of the prescription dose was not allowed in or out of the PTV. The dose to OAR was limited on the basis of the RTOG 0225 protocol.

Target Treatment

Nimotuzumab was added to the standard-of-care treatment, which varied by physician with multiple induction regimen, concurrent systemic agent during RT, and adjuvant chemotherapy.

Nimotuzumab was administered concomitantly with induction chemotherapy and/or IMRT at a dose of 200 mg weekly, which was diluted in 250 ml of saline to obtain a 200-mg suspension and intravenously infused over 1 h. All patients received a total of 9–18 cycles of nimotuzumab during treatment.

Chemotherapy

According to the standard clinical practice for chemotherapy, all patients met the following criteria: ECOG performance status ≤2, WBC count ≥4,000 cells/μl, and platelet count >10,000/μl.

All patients were given one to four cycles of platinum-based induction chemotherapy, and 6.8% of the patients had one to two cycles of adjuvant chemotherapy. The most common induction regimens of adjuvant chemotherapy included TPF (docetaxel 60 mg/m^2/day on day 1, cisplatin 25 mg/m^2/day on days 1–3, and 5-fluorouracil 500 mg/m^2/day on days 1–3), TP (docetaxel 60 mg/m^2/day on day 1, cisplatin 25 mg/m^2/day on days 1–3), GP (gemcitabine 1,000 mg/m^2/day on days 1 and 8, cisplatin 25 mg/m^2/day on days 1–3), and FP (cisplatin 25 mg/m^2/day on days 1–3, and 5-fluorouracil 500 mg/m^2/day on days 1–3). In the concurrent CRT, two courses of chemotherapy were planned with cisplatin (80 mg/m^2) for 3 days. The following adjuvant chemotherapy was planned to be administered at a time 3 weeks after IMRT.

Patient Evaluation

The assessment of tumor response was performed on three separate occasions: after the completion of induction chemotherapy, at the end of IMRT, and 3 months after radiation, which was based on the MRI and nasopharynx fiberscope according to the Response Evaluation Criteria for Solid Tumors criteria. The adverse effects of systemic chemotherapy were assessed using the National Cancer Institute Common Toxicity Criteria (NCI CTCAE, version 3.0), whereas RT-induced toxicities were scored according to the Acute and Late Radiation Morbidity Scoring Criteria of RTOG.

All subjects underwent weekly examinations for treatment response and toxicities during radiation therapy. After the completion of therapy, patients were followed every 3 months for the first 2 years, every 6 months from 3 to 5 years, and then annually thereafter. Each follow-up visit included careful examination of the nasopharynx and neck nodes by the attending physician. An MRI scan of the nasopharynx, a nasopharynx fiberscope, a chest computed tomography radiograph, and an ultrasound of the abdomen were performed 3 months after the completion of RT and every 6–12 months thereafter. Additional examinations were performed when indicated to evaluate local relapse or distant metastasis.

Statistical Analysis

Survival curves were performed using the Kaplan–Meier product-limit methods. Comparison of the curves was performed using the log-rank test. Multivariate analysis to identify significant prognostic factors was accomplished using Cox regression models. HRs and 95% CIs were calculated for each prognostic factor to identify those

with statistical significance. IBM SPSS statistics version 19.0 software was used for all data analysis. Statistical significance was indicated at $p<0.05$. Survival time was calculated from the date of diagnosis to the most recent follow-up or to the date of relapse (vent free, local recurrence free, or distant metastasis free) or death (OS). After recurrence or metastasis, patients were given appropriated salvage therapy as determined by their physicians.

The main purpose of this investigation was to evaluate the efficacy and safety of the long-term use of nimotuzumab in combination with IMRT and chemotherapy in the treatment of locally advanced NPC. The estimated OS, progression failure-free survival (PFS), local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and distant metastasis-free survival (DMFS) were calculated by the Kaplan–Meier method. Univariate analysis was performed with a log-rank test.

RESULTS

Response of Disease

The overall response rates (ORRs) were 100% [complete remission (CR) = 87.2%] and 100% (CR = 89.7%), respectively (Table 3), for lesions of nasopharynx and cervical lymph nodes 3 months after completion of radiation therapy. The residual tumor gradually disappeared or became less obvious in the following 6–9 months.

Local Control and Survival Rates

The median follow-up period was 46 months (range, 22–86). The estimated 3-year LRFS, RRFS, DMFS, PFS, and OS rates were 92.1%, 89.7%, 82.5%, 77.6%, and 86.8%, respectively (Fig. 1). The 3-year LRFS rate for patients with one to two cycles of induction chemotherapy was 75% versus 96.8% for patients with three to four cycles of induction chemotherapy ($p=0.049$) (Fig. 2). The 3-year DMFS rate was 100% for stage III and 63.2% for stage IV ($p=0.006$), respectively (Fig. 3).

Altogether, seven patients experienced treatment failure: one patient had evidence of local recurrence only; one had locoregional recurrence; five patients developed ≥1 distant metastasis, two of whom died because of disease progression; and one patient had both regional and distant failure and was still alive. The specific details of these patients are presented in Table 4.

Table 3. Response to Treatment

Response	Local [*n* (%)]	Regional [*n* (%)]
Complete response (CR)	34 (87.2)	35 (89.7)
Partial response (PR)	5 (12.8)	4 (10.3)
Stable disease (SD)	0 (0)	0 (0)
Progression disease (PD)	0 (0)	0 (0)
Objective response (CR + PR)	39 (100)	39 (100)

Prognostic Factors

The values of potential prognostic factors including age, gender, clinical stage, T stage, N stage, WHO histology, chemotherapy, the number of cycles of nimotuzumab used, and tumor response at 3 months after completion of RT were evaluated. Univariate analysis showed that the number of cycles of induction chemotherapy used was a significant prognostic factor for LRFS and clinical stage for DMFS, favoring those with three to four cycles of induction chemotherapy and stage III (Table 5). We attributed that to the relatively small sample size and short follow-up time.

Safety and Toxicity

The most common treatment-related acute adverse effects included hematologic and nonhematologic toxicity (Table 6). In the induction chemotherapy, hematologic toxicity and gastrointestinal reactions commonly occurred. Hematologic toxicity was reported as grade 3 and worse in severity in 20 patients (51.3%). Five of these patients developed neutropenic fever, which was tolerated without delaying the chemotherapy and interrupting RT by G-CSF treatment. The gastrointestinal toxicities were mild or moderate, and patients recovered rapidly with or without symptomatic medication. During the concurrent phase, hematologic toxicity was reported as grade 3 and worse in severity in nine patients (23.1%). Two patients developed neutropenic fever. The grade 3 radiation-relative oral mucositis was reported in six patients (15.4%). No grade 3 dermatitis was observed within the RT field. No acneiform eruptions were observed in these patients.

The long-term complications included xerostomia, dental caries, deafness, trismus, radiation encephalopathy, and neck fibrosis. Xerostomia was the most common side effect, and the degree of xerostomia appeared to decrease with time. At the time of analysis, most patients developed mild to moderate xerostomia, and only five patients (12.8%) were observed to have severe xerostomia. Two patients (5.1%) developed temporal lobe necrosis, diagnosed by MRI examination at follow-up. Three cases were found to have a second primary tumor, including thyroid, colon, and breast cancers, and these secondary malignancies were treated by surgical resection. No severe trismus, hearing impairment, or neck fibrosis was found because of the short follow-up period.

DISCUSSION

Since 1998, Al-Sarraf et al. confirmed that, compared with RT alone, combined RT and chemotherapy in the treatment of locally advanced NPC significantly improved local control and OS rates[5]. Concurrent CRT has been considered to be the standard treatment for locally advanced NPC. However, in the IMRT era, concurrent CRT has been controversial. Several studies of IMRT

combined with chemotherapy for locally advanced NPC have reported the 3-year survival rate to be high, in the range of 84%–93%[31–33]. Concurrent chemotherapy significantly increased the incidence of grade 3 toxicity and worse mucositis with an incidence rate of 41%–78%[34–37], so the severe oral mucositis limited the application of concurrent chemotherapy. At present, some investigators have focused on the TPF neoadjuvant chemotherapy for LA NPC[32–34]. Sun et al.[37] demonstrated that the addition of TPF induction chemotherapy to concurrent CRT significantly improved failure-free survival in LA NPC with an acceptable safety profile, and the 3-year failure-free survival was 80% (95% CI = 75–85) in the induction chemotherapy plus concurrent CRT group and 72% (66–78) in the concurrent CRT-alone group (HR = 0.68, 95% CI = 0.48–0.97; $p = 0{\cdot}034$). However, long-term follow-up is required to determine long-term efficacy and side effect profile. Therefore, it is necessary to introduce new agents into the comprehensive treatment regimen for locally advanced NPC. In this study, we evaluated the safety and efficacy of the long-term use of nimotuzumab in combination with IMRT and chemotherapy in the treatment of locally advanced NPC.

With further research of the molecular mechanism of tumorigenesis and tumor development, the incorporation of molecular targeted therapy in patients with NPC has become an active area of clinical research. EGFR overexpression has been detected in 94% of patients with NPC[9]. Cetuximab is the most common anti-EGFR monoclonal antibody used, and it has a good curative effect in the treatment of NPC with a 2-year PFS of 86.5%–89.3% and a 3-year OS of 90.9%[16]. However, severe oral mucositis and the classic acneiform rash associated with anti-EGFR therapy have limited its use in NPC. To minimize cetuximab-related toxicities, there has been continued interest in developing novel EGFR-targeted agents.

Nimotuzumab is a humanized immunoglobulin G1 (IgG1) isotype monoclonal antibody with a unique safety profile and associated with a low incidence of skin toxicity. This agent has been approved for the treatment of NPC and HNSCC[6,23]. The advantage of this anti-EGFR antibody is that the affinity constant for EGFR is much lower than that of cetuximab, allowing for high tumor uptake and low normal tissue uptake[38]. Nimotuzumab requires bivalent binding for stable attachment, which renders the agent to selectively bind to tumors with moderate to high EGFR levels. When EGFR expression is low in the normal tissues, cetuximab still has the high ability to bind because of its higher affinity constant[38]. All of these factors indicated that nimotuzumab plus RT could be a viable therapeutic option in patients with LA NPC. Our previous preclinical studies confirmed that nimotuzumab is sensitive to RT in the NPC cell line CNE-2 in vitro and can reduce cancer cell proliferation, induce cell

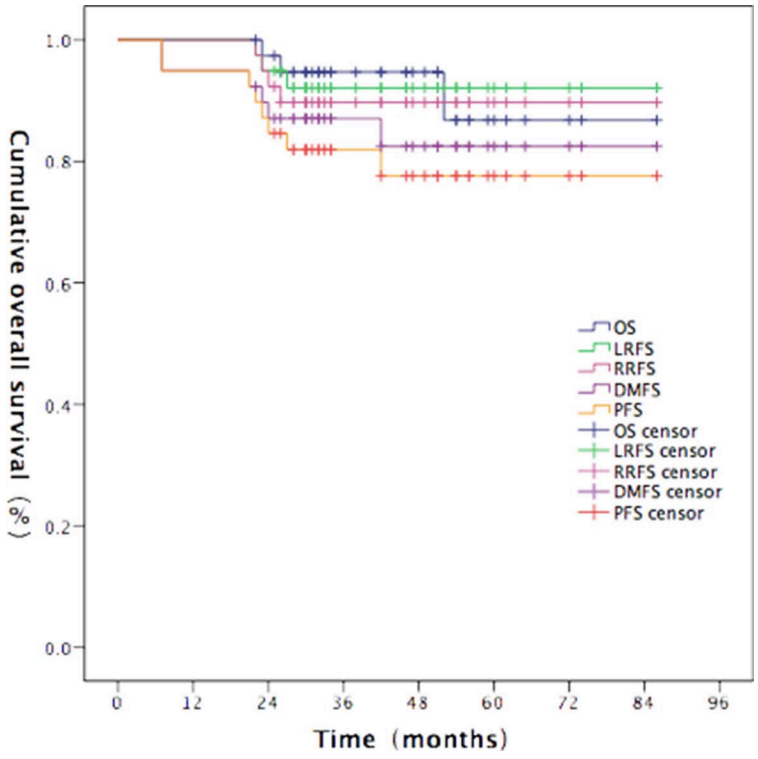

Figure 1. Kaplan–Meier survival curves of local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), progression failure-free survival (PFS), and overall survival (OS).

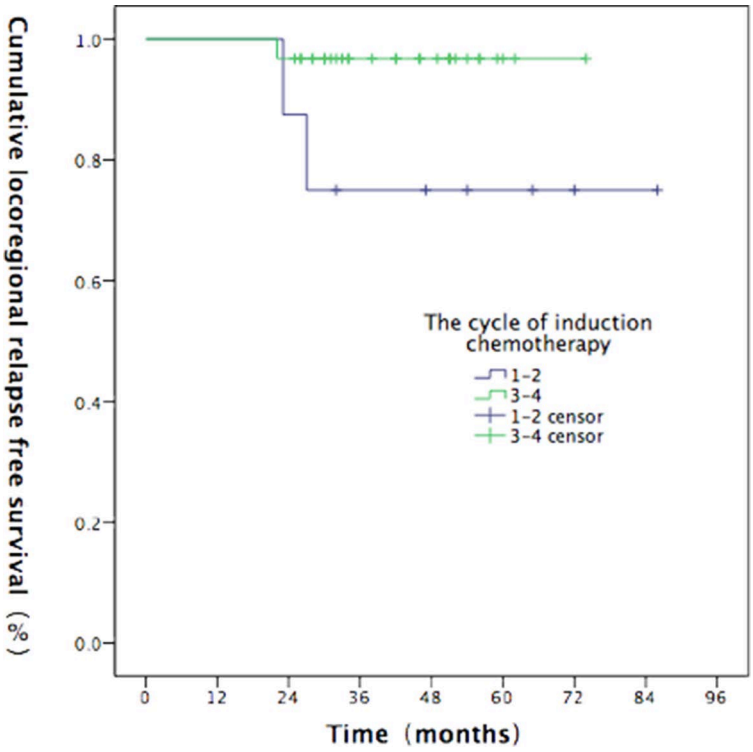

Figure 2. Kaplan–Meier survival curves of LRFS for induction chemotherapy.

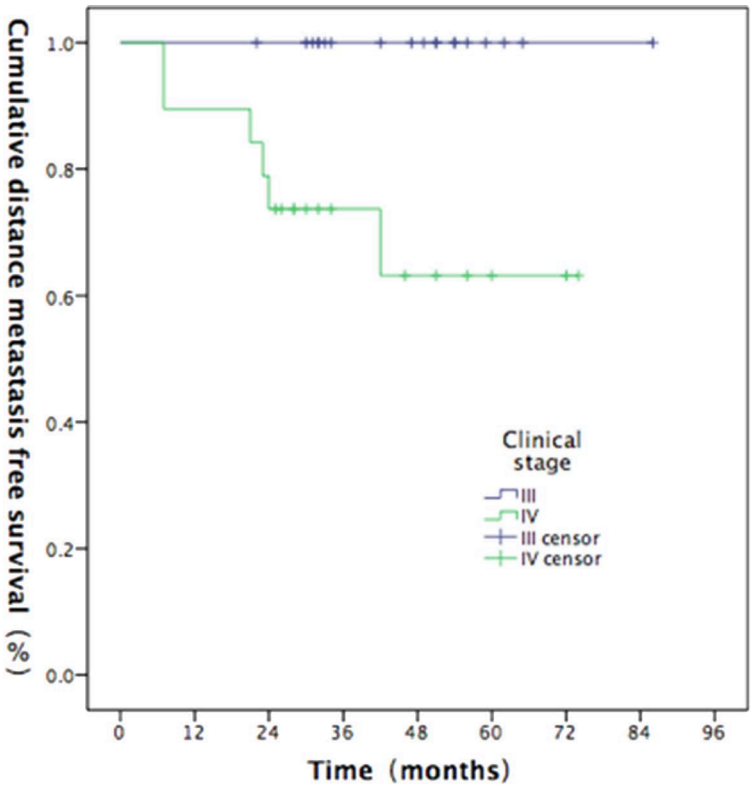

Figure 3. Kaplan–Meier survival curves of DMFS for clinical stage.

Table 4. Site and Incidence of Treatment Failure

Sites	No. of Patients ($n=7$)
Local only	1
Local and regional	1
Locoregional and distant	1
Distant only	4
Lung only	2
Bone only	1
Lung, liver, and bone	1

apoptosis, and cause alterations in cell cycle distribution[39]. In a phase II study of nimotuzumab plus RT for stages III–IVb NPC, the nimotuzumab group was superior to the placebo group, resulting in a significantly higher CR rate (90.63% vs. 51.52%, respectively, $p=0.02$) and a higher 3-year OS rate (84.29% vs. 77.61%, respectively, $p<0.05$) without increasing radiation-related adverse events[23]. Similar results were observed in a retrospective study where nimotuzumab was combined with concurrent CRT in the treatment of LA NPC[25,26].

In our previous study of gemcitabine/cisplatin induction chemotherapy before concurrent chemotherapy and IMRT, the outcome was improved for LA NPC[40]. At a median follow-up of 48 months (10–59 months), 4-year LRFS was 86.9%, RRFS was 90.6%, DMFS was 79.8%, PFS was 77.0%, and OS was 81.9%. This study showed encouraging clinical activity, even when more patients were diagnosed as stage IV, and with a median follow-up of 46 months (range, 22–86 months), the estimated 3-year local recurrence-free, regional recurrence-free, distant metastasis-free, progression failure-free, and OS

Table 5. Impact of Prognostic Factors on Treatment Results by Univariate Analysis

Variable	3-Year OS	3-Year LRFS	3-Year RRFS	3-Year DMFS	3-Year PFS
Sex					
Male	82.4%	89.2%	86.1%	95.0%	70.1%
Female	100.0%	100.0%	100.0%	100.0%	100.0%
p Value	0.3	0.29	0.225	0.133	0.078
Age (years)					
≥60	94.1%	94.1%	94.1%	82.4%	74.4%
<60	84.7%	90.7%	86.4%	82.4%	82.4%
p Value	0.89	0.731	0.453	0.702	0.805
T stage					
T1–2	50.0%	50.0%	50.0%	66.7%	50.0%
T3–4	94.2%	94.2%	94.3%	83.7%	80.8%
p Value	0.211	0.14	0.15	0.508	0.109
N stage					
N0–1	93.8%	93.8%	93.8%	93.8%	93.8%
N2–3	95.2%	86.7%	87.0%	73.2%	65.5%
p Value	0.766	0.776	0.5	0.165	0.066
Clinic stage					
III	100.0%	90.0%	95.0%	100.0%	90.0%
IV	71.3%	94.7%	83.9%	63.2%	63.2%
p Value	0.061	0.62	0.284	0.006	0.077
Response					
CR	96.7%	90.1%	93.5%	84.6%	78.4%
PR	65.6%	100.0%	75.0%	75.0%	75.0%
p Value	0.1	0.376	0.15	0.404	0.707
No. of Ni cycles					
≥12	94.4%	94.7%	89.5%	82.9%	78.3%
<12	83.1%	89.7%	90.0%	80.0%	74.7%
p Value	0.718	0.618	0.969	0.462	0.517
No. of ICT cycles					
1–2	87.5%	75.0%	87.5%	87.5%	75.0%
3–4	84.5%	96.8%	90.2%	80.8%	83.9%
p Value	0.723	0.049	0.808	0.748	0.846
Ad CT					
Yes	75.0%	80.0%	91.2%	82.3%	76.7%
No	93.8%	91.1%	80.0%	80.0%	80.0%
p Value	0.557	0.493	0.461	0.901	0.872

Ni, nimotuzumab; ICT, induction chemotherapy; Ad CT, adjuvant chemotherapy

Table 6. Toxicity of Nimotuzumab Plus Radiotherapy and Chemotherapy

	During Induction Chemotherapy					During Concurrent Chemotherapy				
Adverse Events	0	1	2	3	4	0	1	2	3	4
White blood cells	9	4	11	14	0	6	6	18	8	1
Leukocytopenia	8	3	8	8	12	6	14	15	4	0
Anemia	31	5	2	1	0	19	8	11	1	0
Thrombocytopenia	25	8	4	2	0	23	5	8	3	0
Liver function	24	12	2	1	0	23	5	8	3	0
Renal function	37	2	0	0	0	38	1	0	0	0
Mucositis	33	5	1	0	0	0	7	26	6	0
Dermatitis	39	0	0	0	0	0	34	5	0	0
Diarrhea	32	7	0	0	0	37	2	0	0	0
Nausea/vomiting	28	8	2	1	0	30	9	0	0	0

rates were 92.1%, 89.7%, 82.5%, 77.6%, and 86.8%, respectively.

In the majority of the clinical studies conducted to date, nimotuzumab has been used for 6–8 weeks. However, the optimal administration frequency of nimotuzumab has yet to be identified.

This study retrospectively analyzed the safety of long-course nimotuzumab treatment in patients with LA NPC. The results showed that the administration of 9–18 cycles (median 12) of nimotuzumab combined with IMRT and chemotherapy is safe and well tolerated. This approach was associated with a relatively low rate of RT-related acute skin and mucosal side effects. In our study, grade 3 radiation-induced mucositis accounted for 15.8% of treated people, and no grade 4 mucositis was observed. Of note, no skin rash or infusion reactions were observed.

In conclusion, our study showed that a long course of nimotuzumab administration with IMRT and chemotherapy was safe and well tolerated. This combination regimen is a promising treatment option for LA NPC, especially in NPC patients with high-risk features receiving long-term nimotuzumab plus induction chemotherapy followed by CCRT. Because of the limitations of the varying induction regimens, the small number of cases, and bias in patient selection, our results should be considered as preliminary. Well-designed, randomized, controlled clinical trials are therefore needed to further validate these findings.

According to the EGFR levels, some clinical data of randomized trials directly comparing IMRT plus a long course of nimotuzumab with IMRT plus a conventional course of nimotuzumab are needed to confirm the optimal administration frequency of nimotuzumab.

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