Original Article

Retrospective Analysis to Assess the Feasibility of Escalated Dose of Nimotuzumab in Patients with Locally Advanced Head and Neck Cancer

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Abstract

Introduction: Head and neck cancer (HNC) has large worldwide prevalence and accounts for almost 5% among all types of cancers. Nimotuzumab is a humanized anti-epidermal growth factor receptor monoclonal antibody that has shown promising results in patients with HNC. The present retrospective case study aimed at investigating the response rate and adverse events (AEs) of a high dose of nimotuzumab in patients with HNC who are ineligible for platinum-based chemotherapy. **Materials and Methods:** Patients with locally advanced HNC who refused chemotherapy or were ineligible for platinum-based chemotherapy were analyzed in the study. Patients were given nimotuzumab along with radiotherapy (RT). The duration of each treatment cycle was 6 weeks. About 200 mg nimotuzumab was administered, twice weekly for 6 weeks. The patients who received at least one treatment cycle of targeted therapy and accompanied regular follow-ups were assessed for response rate measurements. **Results:** A total of six patients were enrolled in the study. A response rate of 100% was observed in the patients who completed the treatment. Complete and partial response was 60% and 40%, respectively, in HNC patients at the end of treatment. Three patients were reported with Grade II mucositis. No Grade III or IV AEs were observed in the patients. **Conclusion:** High dose of nimotuzumab along with RT enhanced response rate in patients with HNC who are ineligible for platinum-based chemotherapy without producing any additional toxicity.

Keywords: *Anti-epidermal growth factor receptor, epidermal growth factor receptor, head and neck cancer, nimotuzumab*

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Introduction

Globally, head and neck cancer (HNC) constitutes approximately 5% of all the cancers and ranks sixth among all types of cancer.[1] The incidence of HNC is higher in South Asians and Americans with a 2-fold higher risk in blacks as compared with the whites.[2] This might be due to risk factors such as alcohol consumption, tobacco exposure, and infection with human papillomavirus.[3] Other factors responsible include ionizing radiation, sulfuric acid mists, mustard gas, and diesel exhausts.[4] Annually, the HNC accounts for more than 500,000 cases worldwide.[5] It has been reported that the ratio of HNC is significantly higher in men as compared to women.[6] According to GLOBOCAN 2012 report, HNC is the fifth most common cancer in women. In India, it accounts for 30%–33% of the overall diagnosed cancer.[7,8]

In general, the treatment approach for patients with HNC consists of a combination of surgery, chemotherapy, and radiotherapy (RT).[9] In the past decades, induction chemotherapy (cisplatin plus fluorouracil) followed by RT changed the therapeutic strategy for patients with HNC.[10,11] The current therapy for locally advanced HNC generally constitutes concurrent chemoradiotherapy or RT alone.[12] Various guidelines recommend RT followed by chemotherapy with concurrent cisplatin for patients with HNC. However, toxicities associated with this dosage regimen are well known.[13-15] In addition, old age, comorbidity, poor

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performance score, and organ dysfunctions make patients more vulnerable to toxicities due to platinum-based chemotherapy and make them ineligible for platinum-based chemotherapy.[16] These patients have less treatment options available and often better served with best palliative or supportive care only. Targeted therapies can have even greater role in such patient.

The inhibition of epidermal growth factor receptor (EGFR) and other members of the receptor family is an important target for treatment in HNC as it is overexpressed in >90% of patients with HNC and is found to be associated with a poor prognosis.[17] Currently, two types of anti-EGFR are available; tyrosine kinase inhibitors (TKIs) (small molecules) and monoclonal antibodies (MAbs). TKIs have failed to show beneficial effect in patients with HNC in multiple clinical trials, and MAbs are the only effective anti-EGFR therapy.

Nimotuzumab (BIOMAb EGFR®) is a humanized anti-EGFR MAb that binds to the extracellular domain of the EGFR with suboptimal affinity and high specificity. This results in the blockade of receptor-dependent signal transduction pathways and provides antitumor effects.[18] Different studies have reported that nimotuzumab targets the EGFR effectively, with minimum adverse events (AEs) in patients with HNC.[2,19] The clinical profile that leads to antitumor activity of nimotuzumab in the absence of severe toxicities is explained on the basis of bivalent binding to EGFR, an intrinsic property of nimotuzumab. The bivalent binding leads to a stable attachment to the cellular surface that leads nimotuzumab to selectively bind to the cells that express moderate to high EGFR expression levels.[20] This could be the reason why nimotuzumab in clinical trials did not report rash even in a single patient.[21] On the other hand, incidence of rash was very high with cetuximab which binds to EGFR monovalently and bivalently which means it acts on normal cell as well as high EGFR expressing tumor cells.[20,14]

Dose-escalation studies of nimotuzumab have reported minimal or comparable toxicity to standard doses while improving the efficacy. In two dose-escalation Phase I trials, nimotuzumab administered at a weekly dose of 400 or 800 mg resulted in minor Grade III/IV acute toxicity.[22,23] Wang *et al*. also reported that a high dose of nimotuzumab showed limited toxicity and improved survival in patients with esophageal squamous cell carcinoma.[24] In patients with HNC, the recommended dose of nimotuzumab is 200 mg weekly for 6 weeks. However, there is a lack of studies showing response rate and safety of high dose of nimotuzumab (400 mg) in patients with HNC, especially in the patients with large bulky tumors. The purpose of the present study was to retrospectively investigate the response rate and safety of a high dose of nimotuzumab in Indian patients with HNC.

Materials and Methods

Study design

The current retrospective study was conducted to evaluate the response rate and tolerability in patients with HNC treated with 200 mg twice weekly dose of nimotuzumab who refused chemotherapy or were ineligible for platinum-based chemotherapy, enrolled from December 2014 to May 2015. The study was approved by the Institutional Review Board.

Patient population and treatment plan

Patients with a locally advanced squamous cell carcinoma of HNC, confirmed histologically and radiologically using computed tomography (CT) or magnetic resonance imaging (MRI), were enrolled in the study. Patients either refused chemotherapy or were ineligible for platinum-based chemotherapy. Patients with an active infection, pregnancy and lactation, uncontrollable diabetes or hypertension, and other primary malignancy were excluded from the study. Nimotuzumab and RT were administered on an inpatient basis. Each treatment cycle lasted for 6 weeks. Nimotuzumab was administered in a dose of 200 mg twice weekly intravenously (400 mg/week) for 6 weeks.

Evaluation of tumor response and adverse events

Response was assessed just before the treatment and after completion of treatment as per the RECIST 1.1 criteria using CT/MRI scans. All sites with measurable lesions were followed for response. The National Cancer Institute Common Toxicity Criteria (Version 4.0) were used to grade AEs.

Results

Study patients

A total of six patients (five men and one woman) with locally advanced squamous cell HNC were retrospectively enrolled for the study. Patients either refused to receive chemotherapy or were ineligible for platinum-based chemotherapy due to poor renal function. The age range of these patients was 51–64 year. Four patients had either one or more risk factors for HNC such as alcohol consumption, smoking, and tobacco chewing, and one patient enrolled in the study was diagnosed with comorbidities such as diabetes mellitus and hypertension.

Treatment response

One patient did not complete the recommended treatment and could not be evaluated for tumor response. Out of 5 evaluable patients, 60% (3) of patients had complete response at primary and 40% (2) had partial response at primary. Three patients had nodal disease at the time of diagnosis and 33.33% (1) of patient had complete response at node and 66.66% (2) of patients had partial response at node [Table 1]. No patient had stable disease or progressive disease, and response rate of 100% was observed in the evaluable patients.

Toxicity

The dose of nimotuzumab administered was 200 mg twice weekly. The median cumulative dose of study drug was 2400 mg. The cumulative dose ranged from 200 mg to 7600 mg during this phase. The median duration of exposure to nimotuzumab was 42 days.

The RT dose used in the study was 2–2.2 Gy per fraction daily for 5 days a week for a total of 60.8–70 Gy over 6 weeks. The median cumulative dose was 60 Gy and the median duration of exposure to RT was 42 days.

AEs were reported as per the Common Terminology Criteria for AEs Version 4.0. Nimotuzumab was observed to be safe with no additional AEs (hypersensitivity, allergic reaction,

Table 1: Demographic details and response of treatment in patients

Age (years)/gender	TNM stage	Tumor site	Treatment received	Treatment response	Adverse events
60/male	TxN3M0	Buccal mucosa	RT (70 Gy in 35 fractions) + nimotuzumab 200 mg twice weekly × 6 cycles	P-CR, N-PR	
62/male	T3N1M0	Supraglottic larynx	RT (70 Gy in 35 fractions) + nimotuzumab 200 mg twice weekly × 6 cycles	P-CR, N-CR	Mucositis Grade II
64/male	T4N0M0	Maxilla, primary site - hard palate	RT (60.8 Gy in 27 fractions) + nimotuzumab 200 mg twice weekly × 6 cycles	PR	
55/male	T2N3M0	Oropharynx	Incomplete RT+nimotuzumab 200 mg twice weekly × 2 cycles	Nonevaluable	
60/female	T3N2M0	Tongue	RT (70 Gy in 35 fractions) + nimotuzumab200 mg twice weekly × 6 cycles	P-PR, N-PR	Mucositis Grade II
51/male	T3N0M0	Left upper alveolus	RT (60 Gy in 30 fractions) + nimotuzumab 200 mg twice weekly × 6 cycles	CR	Mucositis Grade II

CR: Complete response, PR: Partial response, TNM: Tumor nodes metastases, RT: Radiotherapy, P: Primary site, N: Nodal site

and skin changes) were reported during the study period only Grade II mucositis was observed in three patients. No Grade III/IV AEs were observed in the patients during and after the treatment.

Discussion

Currently, the treatment of patients with locally advanced HNC who are ineligible for platinum-based chemotherapy is based on three treatment options, RT alone, RT plus cetuximab, and RT plus nimotuzumab. RT alone has shown poor response as compared to other options.[14,25] RT plus cetuximab though shows survival benefits over RT alone. However, Bonner *et al*. in subgroup analysis of Phase III trial reported that RT plus cetuximab was ineffective in patients with T4 tumor, patients without neck lymph nodes, non-US patients and patients receiving once a day RT, patients with Karnofsky Performance Status <90, and patients aged more than 65 years. The majority of the patients in clinical practice who are ineligible for platinum-based chemotherapy fall in either of these categories which means that cetuximab will not be effective in many of these patients.[13] In clinical trials as well as in individual studies, nimotuzumab plus RT has shown beneficial effects in terms of improved response rate and survival in these set of patients with minimal toxicities.[26,27]

The recommended dose of nimotuzumab in HNC is 200 mg/week with six cycles without maintenance. However, it has been observed that high dose of nimotuzumab has been found to be more effective in various other indications such as Carcinoma rectum, esophagus, and pancreas.[24] Authors also believe that the low dose of nimotuzumab (200 mg/week) is less effective for the treatment of patients with HNC, especially in those with a large bulky tumors (tumor stage T3/T4) and those patients who cannot be administered platinum-based chemotherapy. Thus, in the present study, a higher dose of nimotuzumab (200 mg/twice weekly for 6 weeks) was administered with RT to the patients. A 100% response rate was observed in patients who completed the treatment with no Grade III/IV AEs.

Various other studies have examined the efficacy of higher dose of nimotuzumab in different cancers. Jin *et al*. reported that the addition of nimotuzumab to chemoradiotherapy in rectal cancer at a dose of 400 mg for six cycles significantly increased efficacy. The author observed Grade I or II (radiation dermatitis, nausea/vomiting, leukocytopenia, diarrhea, and proctitis) and Grade III (leukocytopenia) toxicities in patients.[28] Strumberg *et al*. in a randomized controlled trial compared 400 mg weekly nimotuzumab plus gemcitabine versus gemcitabine alone in patients with advanced pancreatic cancer and showed that 400 mg weekly dose of nimotuzumab is safe, well-tolerated, and these patients had significantly better 1-year survival.[29]

Similarly, Wang *et al*. in retrospective analysis of 66 patients of esophageal cancer compared patient given high dose of nimotuzumab against low dose. The high-dose group showed no increased incidence of toxicities compared to the low-dose group, and multivariate analyses showed that the high-dose group had better survival than the low-dose group.[24]

In the present study, 100% response rate in patients who completed the treatment with high dose of nimotuzumab is phenomenal considering the fact that these patients could not receive chemotherapy and had large bulky tumors. In addition, twice weekly dose of nimotuzumab did now increase the toxicity burden. Only Grade II mucositis was observed in three patients, and no Grade III/IV AEs were observed which showed higher dose of nimotuzumab is well tolerated. Thus, results of the high dose of nimotuzumab in patients with HNC are similar to the earlier studies conducted in various other indications.

Conclusion

A high dose of nimotuzumab along with RT is feasible, and it improved response rate in patients with locally advanced HNC who cannot be treated with platinum-based chemotherapy without producing additional toxicity. However, this study is limited by a small sample size, and a large randomized controlled trial can determine the best and appropriate doses of nimotuzumab in patients with HNC.

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Conflicts of interest

There are no conflicts of interest.

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