

Nimotuzumab with Concurrent Chemoradiation in Inoperable Locally Advanced Squamous Cell Carcinoma of Head and Neck: An Indian Experience

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Abstract

Background: The prognosis of patients with Epidermal Growth Factor Receptor (EGFR) overexpression in inoperable Locally Advanced Squamous Cell Carcinoma of Head and Neck (LASCCHN) remains poor. Nimotuzumab is an Anti EGFR humanized monoclonal antibody approved for treatment of LASCCHN, with concurrent chemoradiation. **Objective:** To assess the efficacy and safety of nimotuzumab with concurrent chemoradiation in inoperable LASCCHN patients. **Methodology:** This is a single-centre, single arm, retrospective study evaluating 35 patients with histologically confirmed inoperable LASCCHN (stages III-IV). The patients were administered IV cisplatin 50 mg/m² and IV nimotuzumab 200 mg for 6 - 7 weeks, along with radiotherapy of 6600 - 7000 cGy over 35 fractions. Patients were evaluated over response evaluation criteria in solid tumors (RECIST) criteria 12 weeks after the last cycle of chemotherapy. They were also followed up for overall survival and relapse free survival. **Results:** The median duration of follow-up was 20 months. The most common site of cancer was oropharynx (68.6%). One patient was lost to follow up. Objective Response Rate (ORR) was observed in 97% of the patients with 17 patients (48.6%) achieving complete response (CR) and 17 patients (48.6%) achieving partial response (PR). The median overall survival was 22.7 months (95% CI: 21.30, 34.27). The median relapse free survival was 16.7 months (95% CI: 9.80, 24.50). Nimotuzumab was safe and well tolerated with few mild, self-limiting adverse events. **Conclusion:** Nimotuzumab with chemoradiation is a safe and efficacious option in patients

with LASCCHN. Larger studies are needed to verify the same.

Keywords

Epidermal Growth Factor Receptor, Chemoradiation, Locally Advanced Squamous Cell Carcinoma of Head and Neck, Humanised Monoclonal Antibody, Nimotuzumab

1. Introduction

Globally, head and neck cancers (HNC) account for about 5% of all cancers [1]. In India, approximately 0.7 million new cases of HNCs are being diagnosed annually; while about 33% of the 0.3 million cancer related deaths are attributed to tobacco related cancers [2]. Cigarette-smoking and alcohol consumption are the main factors for SCCHN in the Western population, whereas the use of tobacco chewing, Areca nut and Epstein-Barr virus is a common cause of SCCHN in Southeast Asian population. Majority of the patients with SCCHN in India present at an advanced stage and pose a challenge for treatment.

Although surgery and radiotherapy (RT) remains the mainstay in the management of initial stages of HNCs, chemotherapy involving the use of drugs such as cisplatin, is recommended along with radiotherapy, in non-resectable and locally advanced cases of squamous cell carcinoma of the head and neck (LASCCHN). However, such an approach may not be beneficial in advanced cases, where the prognosis with such therapies remains dismal [3]. Additionally, risk of toxicity is higher with combination therapies; average survival of patients with LASCCHN on combination therapy was reported to be as low as 12 months [4] [5] [6] [7] [8].

Hence, novel treatment strategies are preferred which act by binding to specific target of cancer cell and improve the survival of such cancers. Among these, targeting the epidermal growth factor receptor (EGFR) has been a widely explored strategy in anticancer therapy, owing to its association with malignant transformation of squamous cells and its presence in epithelial tumors, especially in squamous cell carcinomas of head and neck (SCCHN) [9].

Overexpression of EGFR has been widely noted in SCCHN and is known to worsen the prognosis. This has been attributed to promotion of angiogenesis and proliferation following EGFR activation, which in turn facilitates tumor growth and metastasis [10]. The EGFR expression has also been linked to metastases and radiation resistance in these tumors [9]. Therefore, blockade of EGFR activity has been evaluated for its effect on sensitizing the tumors to ionizing radiation, as it would suppress the tumor growth by interrupting EGFR-mediated signal transduction pathways [9] [11]. This strategy is considered to be quite useful in SCCHN, where RT has been the traditional approach [9]. Similarly, EGFR overexpression is also known to cause resistance to chemotherapeutic agents [12]. Thus, the use of EGFR inhibitors may enhance tumor

cell killing by limiting the free radical-induced AKT-mediated cell survival [13].

Several EGFR antagonists, including monoclonal antibodies, antisense oligonucleotides, small tyrosine kinase inhibitors, ligand-conjugates as well as cancer vaccines, have been evaluated for their role in SCCHN [14]. Antibodies (IMC-C225, also called cetuximab), small tyrosine kinase inhibitors (gefitinib, erlotinib), and pharmacological inhibitors of downstream mediators of the EGFR signaling pathway (tyrphostins) are the most frequently employed EGFR antagonists. Encouraging results have been noted with these EGFR antagonists, when used with conventional therapy [15] [16] [17].

Researchers were specifically interested in developing EGFR-specific monoclonal antibodies that could inhibit the EGFR-mediated growth-signaling pathway, especially in EGFR-dense cancer cells, resulting in tumor cell death. Interestingly, better locoregional tumor control and survival was noted with cetuximab plus RT or chemotherapy combination as compared to standard radiation therapy in locally advanced SCCHN [6]. However, Pfister et al. noted that while cetuximab plus RT or cetuximab with chemoradiotherapy (CRT) was effective in such cases, the trial had to be discontinued early, owing to the significant drug-related toxicities [6]. RTOG 0522, a randomized phase III trial of radiation plus cisplatin with or without cetuximab for Stage III to IV head and neck carcinoma showed that adding cetuximab to radiation-cisplatin did not improve outcome and hence should not be prescribed routinely [18].

Hence, safer EGFR agents with lesser toxicity were sought, as anti-EGFR antibodies were associated with significant clinical efficacy despite high toxicity. Among these, nimotuzumab (or h-R3), a humanized monoclonal antibody (mAb), which recognizes the EGFR external domain with intermediate affinity ($K_d = 10^{-8}$) has been researched widely [19].

Nimotuzumab has high affinity and specificity to EGFR and also reduces immunogenicity. Its remarkable antiproliferative, pro-apoptotic, and antiangiogenic properties have been noted in numerous clinical trials [20] [21]. Additionally, the pharmacokinetic properties of nimotuzumab is different compared to other anti-EGFR antibodies; nimotuzumab has a prolonged half-life and a higher area under the curve compared to other anti-EGFR antibodies [20].

The efficacy of this drug in patients with advanced epithelial-derived tumors has been noted in clinical trials involving >4000 patients worldwide. It has been noted to have low toxicity (with no skin rash) when it was used alone or in combination with radiotherapy [21] [22].

The objective of this study was to assess the efficacy and safety of nimotuzumab with concurrent chemoradiation in inoperable LASCCHN patients.

2. Material and Methods

2.1. Study Design

This was a single-centre, single arm, retrospective analysis which evaluated the efficacy of nimotuzumab along with chemoradiation in 35 patients with histo-

logically confirmed inoperable LASCCHN (stages III-IV). All patients were treated at Max Super Speciality Hospital from May 2013 to July 2015. Initial safety and efficacy evaluation was conducted at 3 months post-treatment. Patients were followed up till date or death.

The study was approved by the respective institutional review board and conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and Declaration of Helsinki (1996). Informed consent was obtained from all patients before study initiation.

2.2. Patient Eligibility

Patients aged 18 - 70 years with histologically proven stage III or IVA (T1-T4a, N0-N2) SCCHN who were suitable for concurrent CRT/RT, and met the following criteria were included:

- ECOG performance status of 0, 1 and 2 with a life expectancy of >6 months.
- Adequate hematological function, renal and liver function.

Exclusion criteria included evidence of distant metastases or concurrent secondary malignancy, chemotherapy within 3 months before enrollment, prior RT to the head and neck, prior immunotherapy, increased risk of lethal infections and pharmacokinetic interactions with nimotuzumab, or history of allergy with similar biological compounds. Pregnant/lactating females and patients on other investigational drugs/devices were also excluded.

2.3. Intervention

The patients had been administered 6 - 7 cycles of intravenous (IV) cisplatin 35 mg/m² and IV nimotuzumab 200 mg for 6 - 7 weeks, along with radiotherapy of 66 - 70 Gy/35 fractions. The initial evaluation was done at 3 months, post treatment. Patients were followed up till date or death.

Nimotuzumab 200 mg suspension was formed by diluting 4 vials (50 mg each) in 250 mL of 0.9% saline. This was infused intravenously as a single dose over a period of 1 hour through an indwelling cannula placed either in the forearm or the antecubital vein. The total number of doses administered was six to seven (1 per week).

Cisplatin was administered once a week for six to seven weeks as a continuous intravenous infusion over 2 hours after diluting 50 mg in 1 L saline. Chemotherapy was preceded by hydration with 1 - 2 L of fluid infused over 8 - 12 hours. The dosages administered were similar to that reported in pivotal trials [23].

All patients received intensity modulated radiotherapy (IMRT) with image-guided radiation therapy (IGRT), 66 - 70 Gy/35 fractions once a day for 5 days per week.

2.4. Assessments

Baseline measurements included recording of medical history, physical and local examinations, head and neck PET/CT scan. Tumor response was evaluated us-

ing response evaluation criteria in solid tumors (RECIST 1.1) criteria at 12 weeks after the last cycle of chemotherapy using PET/CT scan. All patients were assessed for toxicity and adverse events were reported as per common terminology criteria for adverse events v 4.0.

2.5. Primary Endpoint

The primary endpoint included response rates for outcomes including complete response (CR) and partial response (PR). CR was defined as disappearance of all target lesions; PR, as $\geq 30\%$ reduction in the sum LD of target lesions compared to the baseline sum LD; *objective* response rate (ORR), as the sum of CR and PR. Safety was assessed based on the incidence, severity, and relationship to study drug of the AEs and serious adverse events (SAEs).

2.6. Secondary Endpoint

Secondary endpoints included assessment of overall survival at 1 and 1.5 years, and relapse free survival at 1 and 1.5 years and safety.

2.7. Statistical Analysis

Data were evaluated using a Chi-square test and Fisher's exact probability test, as appropriate. Median overall survival and relapse free survival along with 95% CI, mean, was estimated by the Kaplan-Meier method.

3. Results

3.1. Patient Characteristics

A total of 35 patients having LASCCHN were included in this study between May 2013 and July 2015. Majority of these patients were males ($n = 31$). Median age of patients was 54 years (38 - 67). Oropharynx was the most commonly involved region ($n = 19$), while most of the cancers were diagnosed to be in stage IVA ($n = 23$; **Table 1**).

All the patients were medically or surgically unresectable and hence chemoradiation + nimotuzumab therapy was administered. All the patients were administered with the below regimen.

- ❖ Cisplatin: 35 mg/m² (6 - 7 cycles)
- ❖ Radiation: 66 - 70 Gy/35 fractions
- ❖ Nimotuzumab: 200 mg (6 - 7 weeks)

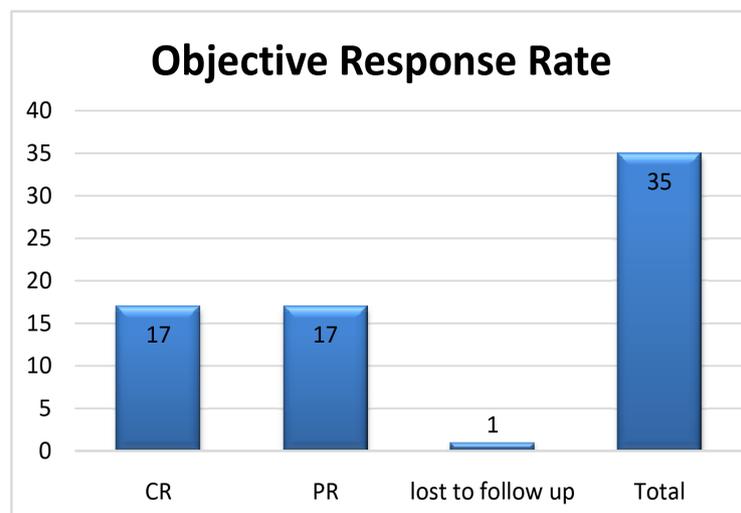
Among the total population, 34 patients were followed up till date or death; 1 patient was lost to follow up. The median duration of follow up was 20 months. The final analysis was based on the outcomes noted in 34 patients.

3.2. Primary Endpoint

Objective response rate was observed in 97% of the patients with 17 patients (48.6%) achieving complete response and 17 patients (48.6%) achieving partial response (**Figure 1**).

Table 1. Details about the regions involved and stage of cancer.

Region involved	N (%)
Maxilla	1 (3)
RetroMolar Trigone (RMT)	2 (6)
Hypopharynx	3 (9)
Larynx	5 (14)
Tongue	5 (14)
Oropharynx	19 (54)
Stage	N
IIIA	6 (17)
IIIB	6 (17)
IVA	23 (66)

**Figure 1.** Response rate with nimotuzumab with chemoradiation.

3.3. Secondary Endpoint

3.3.1. Survival Analysis

Twenty nine and 24 patients were evaluable for one year and 1.5 years survival analyses, respectively. The one year survival rate was noted to be 90% (**Figure 2**), while 1.5 year survival rate was 71% (**Figure 3**).

3.3.2. Relapse

Relapse was noted in only 6 (35%) among those with CR (n = 17), while it was reported in 15 cases (88%) among those with PR (n = 17).

3.3.3. Relapse Free Survival

Thirty one and 29 patients were evaluable for relapse free survival at one year and 1.5 years, respectively. Relapse free survival rate at 1.5 years was 45% (**Figure 4**), while the median relapse free survival was 15.4 months.

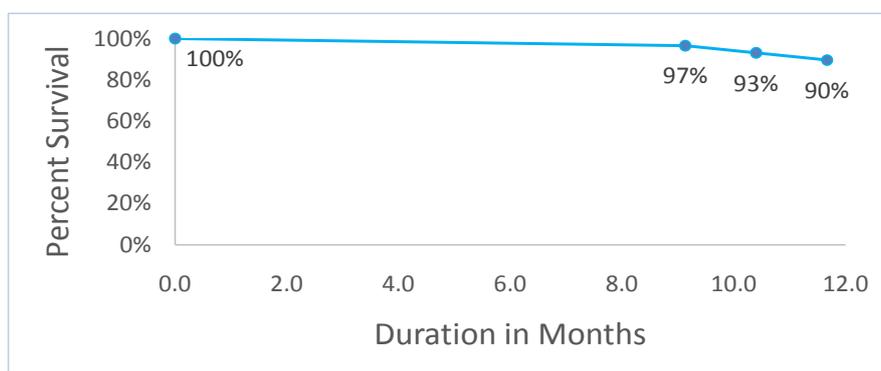


Figure 2. Kaplan Meier survival plot for survival analysis at 1 year (n = 29).

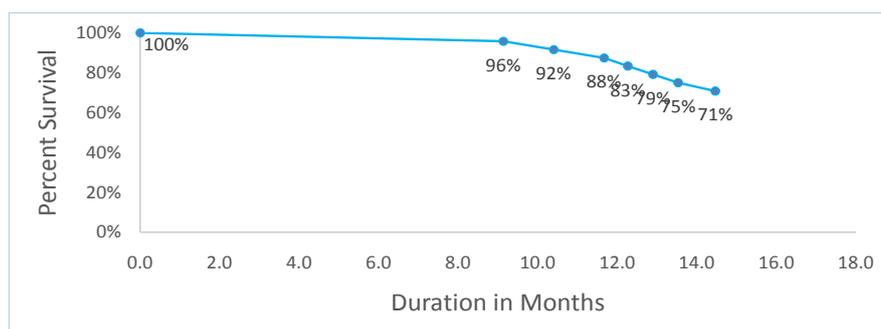


Figure 3. Kaplan Meier survival plot for survival analysis at 1.5 years (n = 24).

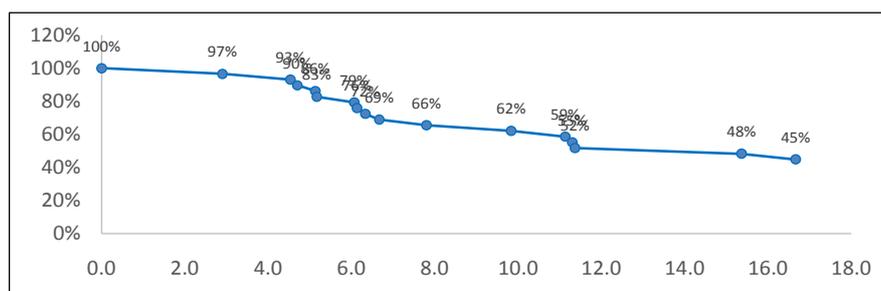


Figure 4. Kaplan Meier plot for RFS at 1.5 years (n = 29).

3.4. Safety

Nimotuzumab was observed to be safe with no additional adverse events (Hypersensitivity, allergic reaction and skin changes) were reported during the study period (Table 2). Adverse events were reported as per common terminology criteria for adverse events v 3.0 (CTCAE).

Table 2. Adverse events encountered.

	Absent	Grade 1	Grade 2	Grade 3	Grade 4	Total
Oral mucositis	0	20	12	3	0	35
Local Skin reactions	0	18	17	0	0	35
Nausea	0	17	18	0	0	35
Vomiting	10	22	3	0	0	35

4. Discussion

A clear measure related to the efficacy of nimotuzumab in association with chemoradiation was noted in this study, where an objective response rate was observed in 97% of the patients. The findings are especially important owing to the fact that such a response was noted even in advanced stages of tumors (23/35 stage IVA, 12/35 Stage III). Additionally, relapse free survival rate at 1.5 years was 45%, while the median relapse free survival was 15.4 months.

Overall response post-treatment was 100% with CRT + nimotuzumab in the BEST trial [23], while it was 97% in the current study. Similar outcomes were also noted in terms of survival rates. While the survival rate at 12 months in the BEST trial was 80% [23], in the current study, it was 90% and 71% at the end of 12 months and 18 months, respectively.

In a similar study by Karandikar *et al.*, the disease control rate at 24 weeks posttreatment with nimotuzumab was 81% and the overall survival for all patients ranged from 10 months to 33 months [24].

The anti-EGFR agents are suggested to have a dual mode of action; inhibition of the EGFR-signaling pathway which causes reduction in the rate of cellular proliferation, and negating the EGFR-mediated radioresistance, and sensitization of malignant cells to concomitant RT [25]. Immunohistochemistry studies of tumor specimens conducted before and after treatment with the combination of h-R3 (Nimotuzumab-humanized anti EGFR mAb) and RT revealed that anti-tumor response correlated with antiproliferative and antiangiogenic effect of h-R3. This lead to the conclusion that h-R3 may enhance the radiocurability of unresectable head and neck neoplasms [9].

According to Crombet *et al.*, h-R3 has several differences when compared to IMC-C225 (also called as Cetuximab), the most widely evaluated anti-EGFR antibody. h-R3 is a humanized antibody with a larger proportion of human sequence; it has a lower magnitude affinity to EGFR than IMCC225; it is obtained by humanizing a murineantibody elicited against the EGFR of human placenta (and not of cultured cells); and, it has different pharmacokinetic properties [9].

The anti-EGFR activity of nimotuzumab was further confirmed in the study by Rodríguez *et al.*, where a significant survival improvement was noted in EGFR positive patients, (MOS = 16.5 mo) as compared to control patients (MOS = 7.2 mo), while no such advantage was noted in EGFR negative patients [26].

The efficacy of nimotuzumab with chemoradiation was reported to be significantly higher when compared to chemoradiation alone, in an Indian study involving patients with advanced (SCCHN). An overall response rate of 96% was noted in the combination group, while it was about 72% in the chemoradiation alone group [27].

Accordingly, addition of nimotuzumab to conventional therapy was associated with prolonged survival in the current study. This can be attributed to the augmented tumour response to chemotherapy following anti-EGFR therapy; as EGFR overexpression can cause resistance to chemotherapeutic agents along

with radio-resistance. Additionally, free radicals formed following exposure to ionizing radiation can create a state of intracellular oxidative stress. Free radicals such as H₂O₂ are known to trigger Akt signalling through an EGFR-dependent pathway and elevated Akt activity can protect against oxidative stress-induced apoptosis [28].

The use of EGFR inhibitors may limit the free radical-induced Akt-mediated cell survival following irradiation and hence enhance tumor cell killing [23].

Complete and partial response was noted in equal number of patients in the current study. In a phase-II study by Wu *et al.*, the complete remission (CR) rates of the combination group (radiotherapy combined with h-R3) at three time points were significantly higher ($p < 0.05$) than those of the radiotherapy alone group [29].

Long term survival benefits were also reported in the BEST trial, wherein a survival rate of 57% was noted at month 60, with CRT + nimotuzumab [23]. Considerable percentage of patients in the current study did not have a relapse until 1.5 years. Additionally, looking at higher relapse rate in PR patients, using nimotuzumab in the maintenance setting in PR may be useful to reduce the relapse rates even further.

Severe acne-like skin rash is a common toxicity seen with the use of anti-EGFR agents and often leads to discontinuation of therapy [9]. Compared to cetuximab, nimotuzumab was associated with lesser incidence of acute mucositis reaction, weight loss and rash, in patients with nasopharyngeal carcinoma [30]. However, nimotuzumab was observed to be safe in the current study with no adverse effects reported during the course of the study. Other similar studies have also reported to an exceptional safety profile of nimotuzumab [22] [26], as noted in our study. However, a high incidence of skin toxicities (60% - 80%) was reported with other EGFR antibodies [31].

The enhanced safety of nimotuzumab has been attributed to fact that it requires bivalent binding for stable attachment; which leads to selective binding to cells expressing moderate to high EGFR levels and hence, lesser risk of adverse effects [3]. Additionally, healthy tissues are spared as the nimotuzumab monovalent interaction is transient when EGFR density is low [32].

Overall improvement in the quality of life improvement along with a reduction of the general and specific symptoms of the disease, has also been reported with the combination therapy of nimotuzumab plus RT [26].

The study had a few limitations. This was a retrospective study and it was not matured yet to determine the median overall survival benefit. The number of patients involved in this study is also slightly less to draw definite conclusions. Nevertheless, this study reiterates the benefits noted across other studies and highlights aspects such as relapse free period, which have not been evaluated in detail in several trials.

5. Conclusion

Nimotuzumab with chemoradiation can be considered to be a safe and effica-

cious option in patients with LASCCHN. Findings of this study hence validate the need for anti-EGFR agent in the treatment paradigm. Nevertheless, further follow-up will help in evaluating median overall survival. Larger studies are needed to verify the findings noted in this retrospective study.

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