Efficacy and safety of concurrent chemoradiotherapy with or without Nimotuzumab in unresectable locally advanced squamous cell carcinoma of head and neck: Prospective comparative study - ESCORT-N study

Ashok Kumar, Nilotpal Chakravarty1, Sharad Bhatnagar, G. S. Chowdhary2

Abstract

Background: Nimotuzumab is an anti-epidermal growth factor receptor monoclonal antibody which can be added to chemoradiotherapy (CRT) to improve efficacy for management of locally advanced squamous cell carcinoma of the head and neck (LASCCHN). We prospectively evaluated the efficacy and safety of nimotuzumab with CRT for LASCCHN and compared with CRT alone. Materials and Methods: In this prospective study, 29 LASCCHN (Stage III–IVb) patients received Nimotuzumab plus CRT or CRT alone. Treatment included six cycles of cisplatin (40–50 mg/week) and radiotherapy (60–70 Gy). Tumor response was evaluated as per response evaluation criteria in solid tumors criteria. MoS was estimated using the Kaplan–Meier method. Toxicity and adverse events (AEs) were assessed as per CTCAE v 4.0. Results: At 24 weeks after completion of treatment, the tumor response rate (complete response, partial response, stable disease) was 53.3% and 35.7% favoring nimotuzumab arm while progression of disease was 40% and 35.7% in Nimotuzumab plus CRT and CRT groups, respectively. However, the objective response rate was 57% and 30% in favor of nimotuzumab arm. At median follow-up of 45.5 months, MoS was 33 months in Nimotuzumab plus CRT and 27 months in CRT group. The 5-year survival rate was 33.3% in Nimotuzumab plus CRT versus 7.1% in CRT group. Nimotuzumab was observed to be safe with no additional AEs such as hypersensitivity, hypomagnesemia, and allergic reaction was reported. Conclusion: Addition of Nimotuzumab to standard CRT showed improved survival rate in unresectable, LASCCHN patients without producing additional toxicity.

Key words: Locally advanced head-and-neck carcinoma, monoclonal antibody, nimotuzumab

Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth leading cancer by incidence worldwide. In India, there is rising burden and majority present in locally advanced stages. Radiotherapy (RT) is the standard of care for the initial stages, while concurrent chemoradiotherapy (CRT), particularly cisplatin, is used for unresectable and locally advanced cases of SCCHN. However, despite superior therapeutic outcomes, they are associated with low survival benefit and increased risk of toxicities. This warrants the need to explore novel treatment strategies to improve the overall survival (OS) outcome of SCCHN.

Overexpression of the epidermal growth factor receptor (EGFR) is detected in more than 80% cases of SCCHN and correlates with poor prognosis, locoregional failure, and distant metastases. Thus, EGFR-based targeted therapies have attracted attention in the treatment of head-and-neck cancers.

Nimotuzumab (BIOMAb EGFR) is a new humanized anti-EGFR monoclonal antibody (MAB) that binds to the extracellular domain of the EGFR with intermediate affinity and high specificity which results in the blockade of receptor-dependent signal transduction pathways and provides antitumor effects. The advantage of nimotuzumab over other anti-EGFR MAb is its benign adverse effect profile. The BEST trial demonstrated that addition of nimotuzumab to CRT or RT provided long-term survival benefit in inoperable, locally advanced SCCHN (LASCCHN). Recently, there is growing evidence in the literature documenting the efficacy and safety of Nimotuzumab in LASCCHN. Authors in their individual research have documented that the addition of the Nimotuzumab to concurrent CRT have improved therapeutic outcomes and survival with minimal toxicities. However, majority studies are restricted with short-term assessment.

This study was carried out to evaluate the efficacy and safety of nimotuzumab with CRT in patients with LASCCHN and compared with CRT alone.

Materials and Methods

This was an open-labeled, prospective, comparative clinical study carried out in patients with LASCCHN attending radiation oncology unit at a tertiary care hospital in Delhi (India). Approval from the ethical committee was obtained. The study included patients aged 18–70 years with histologically proven stage III or IV squamous cell carcinoma and were suitable for concurrent CRT, unfit for surgery, Karnofsky performance score (KPS) ≥60% and adequate hematologic, hepatic, and renal functions. We excluded patients aged ≤18 years, KPS ≤60%, distant metastases or concurrent secondary malignancy and nasopharyngeal malignancy, prior chemotherapy, RT or immunotherapy, history of allergy with similar biological to nimotuzumab compound, inadequate hematologic, renal and hepatic function, uncontrolled infection and any other systemic diseases. Pregnant/lactating females were also excluded from the study.

Two treatment arms (A and B) were defined. Patients were randomized to receive the treatment by simple randomization method.

Arm A-CRT plus nimotuzumab: Chemotherapy (cisplatin - 40–50 mg/m² dose, once a week for 6 weeks) + RT (60 Gy to 70 Gy @ 2 Gy/# for 5 days/week over 6–7 weeks) + Nimotuzumab (200 mg/dose, once a week for 6 weeks).

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Kumar A, Chakravarty N, Bhatnagar S, Chowdhary GS. Efficacy and safety of concurrent chemoradiotherapy with or without Nimotuzumab in unresectable locally advanced squamous cell carcinoma of head and neck: Prospective comparative study - ESCORT-N study. South Asian J Cancer 2019;8:108-11.
Arm B: CRT: Chemotherapy (cisplatin - 40–50 mg/m² dose, once a week for 6 weeks) + RT (60 Gy to 70 Gy @ 2 Gy/day for 5 days/week over 6–7 weeks).

Follow-up for survival was performed every 3 months up to 60 months.

**Parameters evaluated**

The tumor response was evaluated using the response evaluation criteria in solid tumors (RECIST version 1.1). The responses assessed included complete response (CR), partial response (PR), the progression of disease (PD), and stable disease (SD) based on Positron emission tomography – computed tomography (PET-CT/CT) findings. All patients were evaluated using PET–CT scans and metabolic response evaluated. PETCT scan was done 3 monthly for 1 year and then yearly for the next 5 years or earlier in case of clinical suspicion of progression. The objective response rate (ORR) and clinical benefit rate were calculated. OS was calculated from the date of randomization till the date of death or last date of follow-up. Association of OS with various factors, i.e., age, gender, histopathological grade, and chemotherapy was also analyzed. Adverse events (AE’s) were assessed and graded by the National Cancer Institute’s Common Toxicity Criteria version 4.

**Statistical analysis**

Statistical analysis was performed using SPSS software (version 19.0, IBM Corporation, New York). Descriptive statistics was used to express the data. Median OS along with 95% confidence interval (CI) was estimated by the Kaplan–Meier method.

**Results**

A total of 29 patients of LASCCHN participated in this study. The median age was 55 years (36–70 years), with majority being males (96.6%). Majority had Stage IV disease and the most common site was oropharynx (75.9%). The baseline characteristics are summarized in Table 1.

Tumor response – At 24 weeks postcompletion of treatment, higher clinical benefit rate (CR + PR + SD) was observed in the Nimotuzumab plus CRT treatment group: Tumour response at 24 weeks in two arms

Survival outcome – 5-year survival rate was 33.3% in Arm A versus 7.1% in Arm B. The MoS was 27 months for Arm A and 33 months fin Arm A. Although this is not statistically significant in both arms (40% vs. 35.7%) [Table 2].

Survival outcome – 5-year survival rate was 33.3% in Arm A versus 7.1% in Arm B. The MoS was 27 months for Arm B and 33 months fin Arm A. Although this is not statistically significant in both arms (40% vs. 35.7%) [Table 2].

**Discussion**

The findings suggest that the addition of nimotuzumab to concurrent chemoradiotherapy (CCRT) improves the survival curve than CCRT alone in LASCCHN. LASCCHN pose a clinical challenge to manage despite advances, options and strategies currently available. CCRT remains standard of care.
Nimotuzumab is a humanized anti-EGFR MAb which exerts a dual action. First, it binds to the extracellular domain of the EGFR with intermediate affinity and high specificity which results in the blockade of receptor-dependent signal transduction pathways and exerts antitumor effects.[15] Second, it enhances the tumor radiosensitivity by inhibiting the radiation-induced activation of DNA-PKcs (blocking the PI3K/AKT pathway).[16] BEST trial showed that the addition of nimotuzumab to CCRT resulted in improved survival rates than CRT alone in LASCCHN. The survival rate achieved in nimotuzumab plus CRT group at 5-year was 33.3%, while it was 7.1% in CRT group.[14] However, majority studies are restricted by short-term assessment. In our study, addition of nimotuzumab to the standard CCRT resulted in improved survival rates than CRT alone.[11‑14] Nimotuzumab was found to be safe and well tolerated in all patients. Nimotuzumab plus CRT caused a 64% reduction in risk of death. Benefit of addition of nimotuzumab to CRT was 57% versus 26% in CRT alone arm. Addition of nimotuzumab was found to be safe without serious adverse effects.[11] Somani et al. documented that at 6 months posttreatment with nimotuzumab and CRT, the ORR was 80.7%, with 34 patients (59.6%) achieving CR, and 12 (21%) achieving PR, SD in 8 (14%) patients and progressive disease in 3 (5.2%) patients. Nimotuzumab was found to be safe and without

### Table 3: Subgroup analysis of overall survival between the two groups with various factors

| Parameter                      | CRT plus Nimotuzumab (Arm A=15) | CRT (Arm B=14) |
|-------------------------------|----------------------------------|----------------|
| Age                           |                                  |                |
| ≤65                           | 13 (86.7) 37.6 (27.3-48.0)       | 13 (92.9) 28.9 (19.3-38.4) |
| >65                           | 2 (13.3) 12.0 (12.0-12.0)        | 1 (7.1) 33 (33-33) |
| Gender                        |                                  |                |
| Male                          | 15 (100) 35.8 (25.6-46.1)        | 13 (92.9) 30.1 (20.7-39.5) |
| Female                        | 0 (0) - (-)                      | 1 (7.1) 18 (18-18) |
| Histo-pathological type       |                                  |                |
| MDSCC                         | 8 (53.3) 30.0 (19.3-40.7)        | 8 (57.1) 33.4 (19.3-47.5) |
| PDSCC                         | 4 (26.7) 46.0 (22.2-69.7)        | 1 (7.1) 24 (24-24) |
| SCC                           | 1 (6.7) 21.0 (21.0-21.0)         | 2 (14.3) 19 (0.0-46.4) |
| WDSCC                         | 2 (13.3) 43.5 (20.6-66.3)        | 3 (21.4) 28 (18-37.8) |
| Chemotherapy type             |                                  |                |
| Cisplatin 40 mg               | 11 (73.3) 35.2 (21.9-48.4)       | 10 (71.4) 30.8 (19.5-42.2) |
| Cisplatin 50 mg               | 2 (13.3) 31.50 (22.6-40.3)       | 3 (21.4) 26 (6-45.8) |
| Carboplatin                   | 2 (13.3) 43.5 (20.6-66.3)        | 0 - (-)         |
| Capcitabine                   | 0 (0) - (-)                      | 0 (0) - (-)     |

**SCC=Squamous cell carcinoma, PDSCC=Poorly differentiated SCC, WDSCC=Well differentiated SCC, MDSCC=Moderately differentiated SCC, CI=Confidence interval, CRT=Chemo-radiotherapy, OS=Overall survival**

### Table 4: Adverse events in chemo-radiotherapy plus nimotuzumab (Arm A) and chemo-radiotherapy (Arm B) treatment group

| Incidence of adverse events | Nimotuzumab (n=15), n (%) | CRT (n=14), n (%) |
|-----------------------------|---------------------------|------------------|
| Anemia                      | 15 (100.0) 77.8 (77.8)    | 14 (77.8) 77.8    |
| Leukopenia                   | 15 (100.0) 72.2 (72.2)    | 14 (77.8) 77.8    |
| Skin reaction                | 15 (100.0) 77.8 (77.8)    | 14 (77.8) 77.8    |
| Anorexia                     | 15 (100.0) 77.8 (77.8)    | 14 (77.8) 77.8    |
| Hypomagnesemia (<1.8 mg/dl)  | 0 (0.0) 5.6 (5.6)          | 1 (5.6) 5.6       |
| Skin rash                    | 0 (0.0) 0.0 (0.0)          | 0 (0.0) 0.0       |
| Dysphagia                    | 15 (100.0) 77.8 (77.8)    | 14 (77.8) 77.8    |
| Mucositis                    | 15 (100.0) 77.8 (77.8)    | 14 (77.8) 77.8    |
| Salivary gland changes       | 14 (93.3) 50.0 (50.0)     | 9 (64.3) 50.0     |
| Weight loss                  | 14 (93.3) 77.8 (77.8)     | 14 (77.8) 77.8    |
| Alopecia                     | 15 (100.0) 77.8 (77.8)    | 14 (77.8) 77.8    |

**CRT=Chemoradiotherapy**

in patients with LASCCHN.[4‑6] The MACH-NC data laid the foundation for CCRT over other strategies. It detected reduction in deaths in favor of CCRT (hazard ratio: 0.81; 95% CI: 0.78–0.86; P < 0.0001), and determining absolute survival benefit of 6.5% at 5 years.[6] However, they are associated with some increased risk of toxicities.[6] This warrants the discovery of novel treatment strategies to improve treatment outcomes without compromising the safety. EGFR represents a promising novel biological target in head-and-neck cancers. The overexpression of the EGFR levels is closely related to cancer cell growth, proliferation, invasion, metastasis, apoptosis, and poor prognosis. Inhibiting EGFR pathway can inhibit tumor cell proliferation, differentiation, tumor angiogenesis, and promote treatment response of chemotherapy and radiation.[13]

Nimotuzumab was found to be safe and without serious adverse effects.[11] BEST trial documented that at 6 months posttreatment with nimotuzumab and CRT, the ORR was 80.7%, with 34 patients (59.6%) achieving CR, and 12 (21%) achieving PR, SD in 8 (14%) patients and progressive disease in 3 (5.2%) patients. Nimotuzumab was found to be safe and without
serious adverse effects.\textsuperscript{[13]} Subramanium et al. in a retrospective study also documented that addition of nimotuzumab to induction chemotherapy with taxanes, platins, and fluorouracil regimen followed by concurrent Chemoradiotherapy (CRT) in inoperable, LA-SCCN patients resulted in improved tumor response rates and was well tolerated without any added toxicity.\textsuperscript{[14]}

In our study, the AE profile observed in Nimotuzumab plus CRT group were similar to that of CRT group. The common AE’s observed were Grade I/II which included mucositis, anemia and leukopenia which are similar to previous studies.\textsuperscript{[15,11‑14]} No Grade IV and V toxicity were observed in Nimotuzumab plus CRT group. No typical anti-EGFR-related toxicity like severe rash or hypomagnesemia or infusion reaction was observed. Nimotuzumab was observed to be safe with no added toxicity in this study. The benign adverse effect profile of Nimotuzumab over other Anti-EGFR drugs can be attributed to the fact that it requires bivalent binding for stable attachment, leading to selective binding to tumor cells expressing moderate-to-high EGFR levels.\textsuperscript{[17]} It spares the healthy tissues which have low EGFR levels and thus avoids severe toxicities.\textsuperscript{[15,17]}

An important aspect of tumor response is functional and metabolic response and thus PET-CT scan was done for all patients in pretreatment setting and on follow-up’s. Seng Chuan Ong et al. reviewed the clinical utility of PET-CT in assessing the neck after CCRT for LASCCHN and concluded that 18F-Fluorodeoxyglucose (18F-FDG) PET/CT after CRT has a high negative predictive value (NPV) and specificity for excluding residual locoregional disease. Isles M G et al. reviewed the role of PET-CT in follow-up of LASCCHN and concluded that the sensitivity and specificity for detecting residual or recurrent disease was 94% and 82%, respectively. Yao M et al. studied the clinical significance of post-RT 18F FDG PET in the management of head-and-neck cancer and reported that the sensitivity, specificity, positive predictive value, and NPV in the neck was 86%, 97%, 71%, and 99%, respectively. Kyzas PA and Evangelou E et al. assessed the diagnostic accuracy of 18F-FDG PET in detecting lymph node metastases in patients with head-and-neck squamous cell carcinoma. In 32 studies which included 1236 patients, FDG PET sensitivity was 79% and specificity was 86%.

In summary, the addition of Nimotuzumab to CCRT showed improved survival rate in LASCCHN patients without producing additional toxicity. Although robust multicenter, randomized control trials with larger sample size are needed to validate these results. The study had limitations, the sample size was small, and the study was conducted at a single hospital setting.

Conclusion

Addition of Nimotuzumab to CCRT showed improved tumor response rate and survival in LASCCHN patients without producing additional toxicity. The important highlights of this study were the safety, efficacy, and benign adverse effect profiles such as skin rash and serum magnesium levels. No incidence of skin rashes and hypomagnesemia was reported during treatment and follow-up period. PET-CT scan was done for all patients to assess the functional and metabolic response, i.e., pretreatment and posttreatment follow-up (3 monthly for 1 year and then yearly).

Acknowledgment

The authors would like to thank all the patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Dayal PK, Mani NJ, Bhargava K. Prevalence of oral cancer and precancerous lesions in ‘pan’/‘supari’ chewers. Indian J Public Health 1978;22:234-45.
3. Tuljapurkar V, Dhar H, Mishra A, Chakraborti S, Chaturvedi P, Pai PS. The Indian scenario of head and neck oncology-challenging the dogmas. South Asian J Cancer 2016;5:105-10.
4. Vermorken JB, Specenier P. Optimal treatment for recurrent/metastatic head and neck cancer. Ann Oncol 2010;21 Suppl 7:vii252-61.
5. Reddy BK, Lokesh V, Vidyasagar MS, Shenoy K, Babu KG, Shenoy A, et al. Nimotuzumab provides survival benefit to patients with inoperable advanced squamous cell carcinoma of the head and neck: A randomized, open-label, phase IIIb, 5-year study in Indian patients. Oral Oncol 2014;50:498-505.
6. Pignon JP, Le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14.
7. Aguilin M. New approaches to EGFR inhibition for locally advanced or metastatic squamous cell carcinoma of the head and neck (SCCHN). Curr Opin Otolaryngol Head Neck Surg 2009;17:268-72.
8. Perez R, Moreno E, Garrido G, Crobett T. EGFR-targeting as a biological therapy: Understanding nimotuzumab’s clinical effects. Cancers (Basel) 2011;3:2014-31.
9. Ramakrishnan MS, Eswaraiah A, Crobett T, Piedra P, Saurez G, Iyer H, et al. Nimotuzumab, a promising therapeutic monoclonal for treatment of tumors of epithelial origin. MAbS 2009;1:41-8.
10. Xu S, Ramos-Suazarte M, Bai X, Xu B. Treatment outcome of nimotuzumab plus chemotherapy in advanced cancer patients: A single institute experience. Oncotarget 2016;7:33391-407.
11. Bhatnagar AR, Singh DP. A comparative study of a monoclonal antibody against EGFR (nimotuzumab) used in combination with chemoradiation versus chemoradiation alone in the treatment of locally advanced inoperable squamous cell carcinoma of the head and neck. J Clin Oncol 2012;30 Suppl 30:51.
12. Kumar A, Misra KC. To assess the possibility of combining MAb (Nimotuzumab) with concurrent chemoradiation in patients with locally advanced squamous cell carcinoma of head and neck. Scientific abstracts. Indian J Med Paediatr Oncol 2012;33:1.
13. Somani N. Nimotuzumab with concurrent chemo-radiotherapy in patients with locally advanced squamous cell carcinoma of head and neck (LASCCHN). J Cancer Ther 2015;6:356-61.
14. Subramaniam S, Balasundaram V, Nithya S, Kiran P. Nimotuzumab with induction chemotherapy and chemo-radiation in patients with advanced head and neck cancer. J Cancer Ther 2015;6:146-52.
15. Wykosky J, Fenton T, Furnari F, Cavanaugh WK. Therapeutic targeting of epidermal growth factor receptor in human cancer: Successes and limitations. Chin J Cancer 2011;30:5-12.
16. Qu YH, Hu SL, Xu XY, Wang RZ, Yu HY, Xu JY, et al. Nimotuzumab enhances the radiosensitivity of cancer cells in vitro by inhibiting radiation-induced DNA damage repair. PLoS One 2013;8:e70727.
17. Garrido G, Tikhomirov IA, Rabasa A, Yang E, Gracia E, Iznaga N, et al. Bivalent binding by intermediate affinity of nimotuzumab: A contribution to explain antibody clinical profile. Cancer Biol Ther 2011;11:373-82.