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Research Article

Nimotuzumab with Intensity Modulated Radiation Therapy (IMRT) in the Concurrent Setting of Locally Advanced Head and Neck Cancers unfit for Chemoradiation

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Abstract
Purpose/Objective(s): Nimotuzumab, a humanized anti-EGFR antibody has been demonstrated to be safe and effective with radiation therapy. It has been approved in over 22 countries including India for indications like locally advanced head and neck squamous cell carcinoma (LAHNSCC). We prospectively evaluated the role of concurrent Nimotuzumab with radiation therapy in patients unfit for cisplatin due to age, renal profile or cardiac parameters. Our hypothesis was Nimotuzumab and Intensity modulated radiation therapy results in good locoregional control with equivalent efficacy & toxicity compared to concurrent cisplatin based chemoradiation in LAHNSCC. Aim: This study aims to evaluate locoregional response of nimotuzumab and intensity modulated radiation therapy (IMRT) as the primary endpoint and treatment related toxicity as the secondary endpoint. Methods: Between August 2021 to March 2023, 25 patients of oropharynx, hypopharynx & larynx cancer were treated with concurrent nimotuzumab and radiation therapy. Patients were treated with simultaneous integrated boost protocols with concurrent Inj Nimotuzumab 200mg IV weekly for 6 weeks. Results: median age of patients was 64 years & most common site was oropharynx (14 /25). With a median follow up of 18 months, 18(72%) patients were locoregional controlled; 3 (12%) patient had residual disease at primary site; 2 (8%) patient had residual disease at node and 2(8%) patient progressed to systemic disease. One patient developed grade III skin toxicities (4%) and Grade 3 mucositis was seen in 5 (20%) patients. No major treatment breaks were noticed and none of the patients had any cardiac event or renal toxicity. Conclusion: Addition of nimotuzumab to radiation therapy is safe and efficacious based on the good locoregional control and further studies are required to comment upon its long-term survival benefits in LAHNSCC.

Keywords: Locally advanced Head and neck cancers (LAHNCs), Nimotuzumab, IMRT-SIB

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INTRODUCTION

Head and neck cancers (HNCs) are a major public health problem. They constitute approximately 5% of all cancers diagnosed globally with about 0.7 million new cases being diagnosed annually in India.[1] Owing to the increased prevalence of smoking & alcohol consumption in India, the majority of patients present with advanced disease & poor performance status[2.] Radical Radiotherapy alone is used as a treatment modality in early. cases, whereas concurrent chemoradiotherapy is the recommended treatment for unresectable and locally advanced stages of the disease.[3]

The MACHNC meta-analysis showed that concurrent chemoradiotherapy (CCRT) provides a better 5-year overall survival benefit, and cisplatin-based CCRT is the recommended treatment for patients with unresectable LAHNSCC [4]. However, platinum-based CCRT has toxic effects, which can impact patients' compliance to chemoradiation and cause acute and late side effects. Moreover, a significant number of patients are ineligible for platinum-based chemotherapy due to factors such as impaired performance status, reduced nutritional status, geriatric age, and significant comorbidities like renal dysfunction, otologic disorders, and hypersensitivity to platinum-based therapy[5]. For these patients, radiotherapy alone is the only treatment option available. The management of unresectable and platinum-ineligible locally advanced SCCHN is a clinical challenge; therefore, new strategies for the successful management of such cases are necessary. Some of the efforts to intensify treatment & improve outcomes included the use of neoadjuvant chemotherapy, altered fractionation radiation schedules, adding a second chemo sensitizer, or adding epidermal growth factor receptor (EGFR)-targeted antibodies. At the forefront of these researches are therapies involving molecular targets such as epidermal growth factor receptor (EGFR). Squamous cell cancers of the head and neck usually express epidermal growth factor receptor (EGFR), the overexpression of which correlates with radiation resistance, poor treatment response, increased rate of metastasis, and hence poor survival[6]. Thus, EGFR-based targeted therapies have gained attention to improve treatment outcomes. The availability of MoAb targeting EGFR is a major breakthrough in several decades that has led to further improvement in the OS of patients with advanced SCCHN after concurrent chemoradiation. Among EGFR-targeting antibodies, Nimotuzumab is a humanized IgG1 monoclonal antibody targeting the extracellular domain of EGFR. It has demonstrated blocking ability against EGF and TGF alpha binding to EGFR and has observed inhibitory activity on tumor cell growth, angiogenesis, and apoptosis[7]. Further, experimental observations demonstrated that in contrast to other approved anti-EGFR antibodies, the intrinsic properties of nimotuzumab require bivalent binding for stable attachment to the cellular surface, leading to nimotuzumab having the maximum clinical benefit with minimum side effects[8,9].

Various studies have demonstrated that the addition of nimotuzumab to radiotherapy in locally advanced

recurrent & metastatic setting has some clinical benefits in terms of improved response rates & survival compared to radiotherapy alone[10-12]. Some studies have also retrospectively reviewed the benefit of adding Nimotuzumab to cisplatin-unfit patients of LAHNSCC.[13]. The prospective evidence on the beneficial outcomes achieved by combining nimotuzumab with radiation in unresectable and platinum-ineligible patients is limited in India and needs to be explored. Therefore, the purpose of the present study was to prospectively analyze the safety and therapeutic benefits of concurrent nimotuzumab with radiotherapy in locoregionally advanced HNSCC who were ineligible for conventional cisplatin based chemoradiation.

Materials & Methods

This study aims to evaluate the locoregional response of nimotuzumab and intensity-modulated radiation therapy as the primary endpoint and treatment-related toxicity as the secondary endpoint. Histologically confirmed squamous cell carcinoma of oropharynx, hypopharynx, and larynx with age ≥18 years, stage III-IVb, ECOG 0-2 were included in the study. Any Patients with serious hypersensitivity disorder or previously treated by chemotherapy/radiation therapy/immunotherapy were excluded from the study. All patients had to be deemed unsuitable for concurrent cisplatin due to age, renal profile, or cardiac parameters & had to sign a written informed consent before participation in the study. Baseline workup included a direct laryngoscopy, and contrast-enhanced computed tomography (CECT) /PETCT as appropriate and as per clinician preference. Other investigations included chest X-rays, USG Abdomen, pure tone audiometry, complete hemogram, kidney and liver function tests before starting treatment. Patients underwent IMRT planning by simultaneous integrated boost. The protocols for IMRT used were 66 Gy to high-risk region, 60 Gy to intermediate-risk region and 54 Gy to low-risk region in 30 fractions. All critical structures were contoured and appropriate constraints were given. The patients were administered injections of nimotuzumab (200mg IV) weekly for six weeks along with radiation therapy.

During treatment weekly, clinical assessment was done for each patient and toxicities were noted. The first post-treatment visit was done 2-3 weeks after completion of radiotherapy. Subsequent visits were scheduled as monthly for the first 3 months, then 2 monthly for the next 6 months & 3 monthly thereafter. At each follow-up visit, a complete physical examination was combined with an assessment of the toxicity using CTCAE version 4. Laryngoscopy/ CT scan/ PET CT was done at three

months post radiation to evaluate locoregional disease status. SPSS version 4 Was used for appropriate statistical tests.

RESULTS

Twenty-five patients of Head and neck cancers were treated with IMRT-SIB schedules with concurrent Inj. Biomab (Nimotuzumab) (200mg iv) weekly for six weeks between August 2021 to March 2023. Median age was 64 years (range 49-75 years) with 21 males (84%) and 4 females (16%) Most of the patients had ECOG scores of 1. The most frequent site was the oropharynx in 14/25 patients followed by the hypopharynx & then the larynx. Most of the patients belong to stage III. The baseline characteristics of patients are summarized in Table 1.

Table1: Baseline characteristics of platinum ineligible loco regionally advanced HNSCC patients

Characteristics	Value (%)
Total patients (n)	25 (100)
Mean age (years) Range	64 49-75
Gender Male Female	 21 4
Performance status ECOG 0 ECOG - 1 ECOG - 2	 5 14 6
Anatomical subsites Oropharynx Hypopharynx Larynx	 14 5 4
T stage T1 T2 T3 T4	 0 8 7 10
N stage N0 N1 N2 N3	 4 10 7 4
Overall TNM stage (AJCC 7th) Stage III Stage IV	 10 15

Tumor response analysis

With a median follow-up of 18 months, 18(72%) patients were locoregional controlled; 3 (12%) patients had the residual disease at the primary site; 2 (8%) patients had the residual disease at the node and 2(8%) patient's progressed to metastatic disease.

Table 2: Overall tumor response in patients treated with nimotuzumab and SIB-IMRT (n=25)

Overall tumor response	N (%)
locoregional controlled	18 (72)
Residual at primary	3(12)
Residual at node	2(8)
Progressive disease	2(8)

Safety and toxicity analysis

The side effects encountered during the treatment are summarized in Table 3. The common side effects encountered during treatment was mucositis (%), followed by vomiting (%) & skin reactions. Most of the toxicities were either grade 1(%) or grade 2(%). Grade 3 mucositis was seen in 5 patients & one patient developed grade 3 skin toxicities. No grade 4, and 5 toxicities were observed. No major treatment breaks were noticed. None of the patients had any cardiac event or renal toxicity. Nimotuzumab was observed to be safe, and no added toxicity was reported

Table 3: Side effects encountered during the treatment

Side effects	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Total (%)
Mucositis	3	15	5	23 (36.50)
Skin Reaction	9	10	1	20 (31.7)
Vomiting	3	2	0	5(7.93)
Diarrhea	1	0	0	1(1.58)
Rash	1	1	0	2(3.17)
Fever	**2**	**0**	**0**	**2 (3.17)**
Anemia	2	0	0	2 (3.17)
Neutropenia	3	0	0	3 (4.76)
Fatigue	**2**	**3**	**0**	**5 (7.9)**
Total	26	31	6	63 (100)

DISCUSSION

Most studies on anti-EGFR monoclonal antibodies in combination with radiotherapy in SCCHN have been reported from western countries and few of them have included nimotuzumab. As Indian patients are culturally and ethnically different from their western counterparts, the course of disease and response to various chemotherapeutic regimens is different in an Indian scenario. Nimotuzumab offers an interesting option after studies proved its efficacy when given concurrently in recurrent & metastatic SCCHN. Most importantly it proved to be efficacious without displaying the advanced side effects of other anti-EGFR monoclonal antibodies. In the present prospective study, we found that addition of nimotuzumab to radiation has resulted in improved locoregional response in platin ineligible locally advanced head and neck squamous cell Cancer. Our Findings of improved locoregional response are consistent with similar results observed by various authors in locally advanced, metastatic & recurrent. setting.

In 2010, Rodriguez et al[14] conducted a randomized, placebo-controlled, trial on 106 patients with advanced locoregional (unresectable) platinum ineligible SCCHN. Both arms received RT and patients were randomized to receive additional nimotuzumab (n = 54) or placebo (n = 52). About 59.5% of patients receiving nimotuzumab plus irradiation achieved complete response while it was only 34.2% of the individuals treated with irradiation plus a placebo. Thus, nimotuzumab as an add-on to standard radiation treatment can be a promising option in locally advanced SCCHN unfit for chemoradiation.

Few Indian studies have also reported the advantageous role of nimotuzumab in locally advanced, recurrent & metastatic HNSCC [15-19]

Subramanian et al [15] retrospectively reviewed the role of Nimotuzumab in 14 unresectable, recurrent, and/or metastatic HNSCCs. Tumor response rate, overall survival (OS) & toxicity were analyzed. At 24 weeks after the completion of treatment, the overall response rate was 75%. Survival rates at 1, 2, and 3 years were 77.80%, 64.81%, and 64.81%, respectively. All AEs were either Grade I (66.7%) or Grade II (33.3%). No Grade III or Grade IV AEs were observed. No added toxicity was observed due to nimotuzumab.

ESCORT-N study by Ashok et al[16] prospectively evaluated the Efficacy and safety of concurrent chemoradiotherapy with or without Nimotuzumab in LAHNSCC. At 24 weeks after the completion of treatment, the tumor response rate was 53.3% and 35.7% in Nimotuzumab plus CRT and CRT groups favoring the nimotuzumab arm. At a median follow-up of 45.5 months, Overall survival was 33 months in Nimotuzumab plus CRT and 27 months in the CRT group. The 5-year survival rate was 33.3% in Nimotuzumab plus CRT versus 7.1% in the CRT group. Nimotuzumab was observed to be safe with no additional AE's such as hypersensitivity, hypomagnesemia, and allergic reaction was reported.

Another randomized multicentric trial by Reddy et al [20] studied the role of nimotuzumab to two regimens, namely, radiotherapy and chemoradiotherapy in 92 LAHNSCC patient's Overall response at month 6 post treatment was 100% and 70% with CRT + nimotuzumab and CRT while its 76% and 37% with RT + nimotuzumab and RT, respectively. At 5ear, OS was 57% with CRT + nimotuzumab, 26% with CRT (P = 0.03), 39% with RT + nimotuzumab, and 26% with RT (P > 0.05). Risk of death was 64% lower with CRT + nimotuzumab than with CRT and 24% lower with RT + nimotuzumab than with RT.

In the present study, the common side effects observed during treatment were mucositis, followed by skin toxicity, which are similar to documented studies with nimotuzumab. the combination treatment was well tolerated with very few grade III toxicity & no grade IV or V toxicity.

The incidence of common anti-EGFR-related toxicity such as severe skin rash, and infusion reactions are none with Nimotuzumab and this can be explained by the bivalent binding of Nimotuzumab in contrast to Cetuximab. Garrido et al [21] have clearly demonstrated the implications of this difference in binding to EGFR with nimotuzumab.

Thus, all toxicities are significantly lower with nimotuzumab than with cetuximab. This not only includes rash/dermatitis but also more severe ones such as cardiotoxicity, and acute death necessitating premature termination of the study)

Hence, adding nimotuzumab to radiation is an effective & well-tolerated means to improve response rates & local control for locally advanced SCCHN unfit for cisplatin-based chemoradiotherapy. One possible limitation of the study is the lack of complete follow-up to give an assessment of survival which would allow a comprehensive comparison with other studies and a better assessment of the efficacy of the regimen. The findings of our study may have significant implications for clinical practice. The clinical outcome of patients receiving nimotuzumab with radiotherapy for LA SCCHN has been observed to be similar to that reported from a combination of chemotherapy with radiotherapy. The major finding in our study was that nimotuzumab displayed efficacy without producing clinically significant toxicity which is typical of other monoclonal antibodies.

Conclusion: The addition of nimotuzumab to radiation therapy in the form of IMRT is safe and efficacious based on the locoregional response. The long-term survival benefits based on this encouraging response rate need to be further evaluated especially in patients with inoperable locally advanced squamous cell carcinoma of the head and neck in randomized settings.

References

1. Joshi P, Dutta S, Chaturvedi P, Nair S. Head and neck cancers in developing countries. Rambam Maimonides Med J 2014;5
2. Hashibe M, Brennan P, Chuang SC, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomark Prev. 2007; 18:541–50.
3. Anderson G, Ebadi M, Vo K, Novak J, Govindarajan A, Amini A. An Updated Review on Head and Neck Cancer Treatment with Radiation Therapy. Cancers (Basel). 2021 Sep 30;13(19):4912. doi: 10.3390/cancers13194912. PMID: 34638398; PMCID: PMC8508236.
4. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): A comprehensive analysis by tumor site. Radiother Oncol. 2011; 100:33–40
5. A survey of on platinum ineligible in head and neck cancer patients in India Pawar, D. et al. Annals of Oncology, Volume 28, x161
6. Zimmermann M, Zouhair A, Azria D, Ozsahin M. The epidermal growth factor receptor (EGFR) in head and neck cancer: its role and treatment implications. Radiat Oncol. 2006 May 2; 1:11. doi: 10.1186/1748-717X-1-11. PMID: 16722544; PMCID: PMC1524965.
7. Crombet Ramos T, Mestre Fernández B, Mazorra Herrera Z, Iznaga Escobar NE. Nimotuzumab for Patients with Inoperable Cancer of the Head and Neck. Front Oncol. 2020 May 27; 10:817. doi: 10.3389/fonc.2020.00817. PMID: 32537431; PMCID: PMC7266975.
8. Ramakrishnan MS, Eswaraiah A, Crombet T, Piedra P, Saurez G, Iyer H, Arvind AS. Nimotuzumab, a promising therapeutic monoclonal for treatment of tumors of epithelial origin. MAbs. 2009 Jan-Feb;1(1):41-8. doi: 10.4161/mabs.1.1.7509. PMID: 20046573; PMCID: PMC2715181.
9. Garrido, G., Tikhomirov, I. A., Rabasa, A., Yang, E., Gracia, E., Iznaga, N., Fernández, L. E., Crombet, T., Kerbel, R. S., & Pérez, R. (2011). Bivalent binding by intermediate affinity of nimotuzumab: a contribution to explain antibody clinical profile. *Cancer biology & therapy*, *11*(4), 373–382. https://doi.org/10.4161/cbt.11.4.14097
10. Yadav A, Goyal P, Agrawal CR, Bothra SJ, Jain P, Choudhury KD, Gupta SK, Sharma M, Bajaj R, Upadhyay A, Dash P, Doval DC. Efficacy and tolerability of nimotuzumab in combination with chemotherapy in recurrent and metastatic squamous cell carcinoma of head and neck at a cancer center in Northern India. Indian J Cancer 2020; 57:76-83
11. 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 IIb, 5-year study in Indian patients. Oral Oncol 2014; 50:498-505.
12. Subramanium 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.
13. Srinivas KS, Sundaram R, Divyambika CV, Chaudhari S. Nimotuzumab with intensity-modulated radiation therapy in unresectable and platinum-ineligible locally advanced head-and-neck cancer. South Asian J Cancer. 2020 Jan-Mar;9(1):43-46. doi: 10.4103/sajc.sajc_29_19. PMID: 31956621; PMCID: PMC6956585.
14. Rodríguez, M. O., Rivero, T. C., del Castillo Bahi, R., Muchuli, C. R., Bilbao, M. A., Vinageras, E. N., Alert, J., Galainena, J. J., Rodríguez, E., Gracias, E., Mulén, B., Wilkinson, B., de Armas, E. L., Pérez, K., Pineda, I., Frómeta, M., Leonard, I., Mullens, V., Viada, C., Luaces, P., … Crombet, T. (2010). Nimotuzumab plus radiotherapy for unresectable squamous-cell carcinoma of the head and neck. *Cancer biology & therapy*, *9*(5), 343–349. https://doi.org/10.4161/cbt.9.5.10981
15. Subramanian S, Sridharan N, Balasundaram V, Chaudhari S. Efficacy and safety of nimotuzumab in unresectable, recurrent, and/or metastatic squamous cell carcinoma of the head and neck: A hospital-based retrospective evidence. South Asian J Cancer. 2018 Jul-Sep;7(3):188-192. doi: 10.4103/sajc.sajc_87_18. PMID: 30112336; PMCID: PMC6069342.

16. Kumar A, Chakravarty N, Bhatnagar S, 15. 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 Apr-Jun;8(2):108-111. doi: 10.4103/sajc.sajc_38_18. PMID: 31069191; PMCID: PMC6498712.
17. Somani N. Nimotuzumab in concurrent chemoradiotherapy in patients with locally advanced head and neck cancer (LASCCHN). J Cancer Ther 2015; 6:356-61.
18. Bahl A. Nimotuzumab with concurrent chemoradiation in inoperable locally advanced squamous cell carcinoma of head and neck: An Indian experience. Available from: http://www.uaecancercongress.ae/pdf/UAECC2016_H&N_SP_20160919.pdf. [Last accessed on 2017 Mar 12].
19. Subramanian S. Nimotuzumab in induction chemotherapy in patients with advanced head and neck cancer – Retrospective study. J Cancer Ther 2015; 6:146-52.
20. Reddy, B. K., Lokesh, V., Vidyasagar, M. S., Shenoy, K., Babu, K. G., Shenoy, A., Naveen, T., Joseph, B., Bonanthaya, R., Nanjundappa, Bapsy, P. P., Loknatha, Shetty, J., Prasad, K., & Tanvir Pasha, C. R. (2014). Nimotuzumab provides survival benefit to patients with inoperable advanced squamous cell carcinoma of the head and neck: a randomized, open-label, phase IIb, 5-year study in Indian patients. *Oral oncology*, *50*(5), 498–505. https://doi.org/10.1016/j.oraloncology.2013.11.008
21. Garrido, G., Tikhomirov, I. A., Rabasa, A., Yang, E., Gracia, E., Iznaga, N., Fernández, L. E., Crombet, T., Kerbel, R. S., & Pérez, R. (2011). Bivalent binding by intermediate affinity of nimotuzumab: a contribution to explain antibody clinical profile. Cancer biology & therapy, 11(4), 373–382. https://doi.org/10.4161/cbt.11.4.14097