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Original Research Article

Nimotuzumab Supplementation to Conventional TPF Regimen for Locally Advanced Head and Neck Cancer: An Individual Institutional Investigation

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Abstract:

Background: The current standard therapy approach for locally advanced HNSCC involves using initiation chemotherapy with 5-fluorouracil, cisplatin, and docetaxel, followed by definitive concomitant chemoradiation. However, the survival rates with this regimen are still quite low. Therefore, the study was conducted to evaluate the effectiveness and side effect profile of adding nimotuzumab to the traditional TPF induction chemotherapy.

Methods: Forty individuals were enrolled for the study with advanced locally metastatic HNSCC. Patients who had previously undergone induction therapy with TPF plus N (nimotuzumab in addition to docetaxel, cisplatin, and 5-fluorouracil) then received definitive concomitant chemoradiation with carboplatin. After completing the induction chemotherapy and concomitant chemoradiation, we utilized PET-CT scans to assess the treatment responses.

Results: We discovered that, with a minimum two-year follow-up period, the progression-free survival (PFS) was 15 mo. and the median survival time (OS) was 37 mo., both of which were significantly improved. Individuals who attained a complete radiological response (CR) did not meet the OS and PFS medians. The median PFS and OS for individuals with a partial response were 16.6 and 33.5 mo., respectively. Notably, the subsites of the oropharynx, oral cavity, and hypopharynx showed comparable response and survival rates. The majority of adverse effects were grade 1/2 or lower, and the majority of patients showed good tolerance to the medication.

Conclusions: Nimotuzumab coupled to the usual TPF regimen may improve response and survival rates among individuals with advanced locally diagnosed head and neck cancer. Any response at all could be a reliable indicator of survival, regardless of the head and neck cancer's primary site.

Introduction

Oral carcinoma, a type of head and neck malignancy, is the second most common and fatal cancer in India [1]. While alcohol consumption and smoking are well-known risk variables for head and neck cancer in Western populations, in India, the primary factors contributing to this type of cancer are the use of smokeless tobacco, Epstein-Barr virus infection, and chewing betel nut [2]. Factors like limited literacy, low education, and socio-economic status also play a role in the higher incidence of advanced head and neck squamous cell cancer (HNSCC) in India [3]. A significant 60% of HNSCC patients in India are diagnosed with advanced disease, with 39% classified as stage III and 23% as stage IV, leading to higher mortality rates [4].

The standard therapy for HNSCC involves concurrent chemoradiation. In recent years, the use of docetaxel, cisplatin, and 5-fluorouracil (TPF) as an induction regimen has increased due to the survival benefits seen in trials like TAX-323 and TAX 324. However, the efficacy of this approach in inoperable cases remains a topic of debate, especially in oral malignancies [5].

The epidermal growth factor receptor (EGFR), a poor prognostic marker, exhibits an aberrant rise in nearly 90% of patients of HNSCC [6]. Monoclonal antibody cetuximab, which targets EGFR, is authorized for use in the first treatment of locally progressed hairless HNSCC in conjunction with radiation therapy. It is also licensed for use in recurrent metastatic cases with 5-FU and cisplatin. Nevertheless, there are serious side effects linked to cetuximab treatment, including dermatitis, hypomagnesemia, rash, and sepsis [7]. When combined with chemotherapy and radiation therapy for locally advanced HNSCC, another anti-EGFR treatment called nibotuzumab has demonstrated effectiveness with low toxicity [8]. Using nimotuzumab as part of the induction therapy, along with platinum and 5-FU, has improved response

rates for locally advanced nasopharyngeal cancer without added adverse effects [9].

Despite various therapeutic strategies, the median survival for HNSCC remains low at around 19 mo. [10]. Given the promising safety and efficacy data from previous studies, this current study aims to evaluate the pros and cons of incorporating nimotuzumab into the standard TPF induction regimen for patients with locally advanced HNSCC.

Materials and Methods

Darbhanga Medical College served as the study's site. Forty patients (over the age of eighteen) with locally advanced HNSCC who were enrolled between 2005 to 2015 and followed up until 2015 to 2020. Participants in the study were people who had never received treatment before and had a performance status (PS) of 1 or lower. They also had unresectable locally advanced cancer, classified as stage III or IV by the tumor-node-metastasis (TNM) classification, and no metastases. The study excluded patients with tumors located in the nose, paranasal cavity, or nasopharynx.

Treatment Protocol

The patients were treated according to the following protocol.

On day 1, 200 mg of nimotuzumab were injected intravenously. Intravenous administration of docetaxel (75 mg/m2), cisplatin (75 mg/m2), and 5-FU (750 mg/m2) was done every 21 days for three cycles. Following three induction cycles of TPF with Nimotuzumab (TPF + N), all patients had CRT with carboplatin, and PET-CT was used to evaluate the response. Eight weeks following CRT, a second PET-CT scan was performed to assess the response. Patients who still had disease had the choice of undergoing salvage surgery.

Evaluation of Treatment

Based on the PET-CT SCAN imaging technique, RECIST (version 1.1) was used to assess radiological response. NCI-CTCAE version 4.0 was used to grade adverse effects [6].

Statistical Analysis

SPSS 23 was the tool used for data analysis. The following are provided for continuous variables: mean and standard deviation for data that is normally distributed, range and median for data that is skewed, and percentages and frequencies for categorical variables. A statistically significant probability value was one that was less than 0.05.

Results

Patient Characteristics

A cohort of 40 individuals was enrolled, consisting of 22 males and 18 females. The median age observed in the study population was 55 years. The majority of patients exhibited a favorable Eastern Cooperative Oncology Group (ECOG) performance status of 1, with a prevalence of 94%. The majority of participants in our study exhibited an absence of comorbidities (64%), whereas the remaining individuals presented with type 2 diabetes and hypertension (34%). Of the patient population, 50% exhibited no deleterious habits, whereas the remaining 49% engaged in the consumption of tobacco and alcohol. The majority of patients diagnosed with oral cancer accounted for 54% of the total, with the remaining cases distributed between hypopharynx (34%) and oropharynx (9%). The cohort classified as Stage III encompassed 45% of the patient population, while the remaining 55% were categorized as Stage IV. The comprehensive baseline characteristics are delineated in Table 1.

Analysis of Patients' Responses

All forty patients successfully tolerated and completed three cycles of induction TPF in combination with neoadjuvant therapy, followed by concurrent chemoradiotherapy with carboplatin. A total of six patients who exhibited residual disease demonstrated willingness and subsequently underwent salvage surgery following the completion of their therapeutic regimen. A comprehensive response rate of 11% was attained subsequent to the administration of induction TPF + N, which subsequently escalated to 25% following the implementation of chemoradiotherapy. A partial response of 34% was achieved upon completion of the therapeutic intervention. The overall response rate subsequent to induction therapy with TPF + N and concurrent chemoradiotherapy was determined to be 64%. Nevertheless, a notable proportion of patients, specifically 24%, exhibited disease progression despite undergoing induction therapy with TPF (docetaxel, cisplatin, and fluorouracil) in addition to neoadjuvant chemoradiotherapy.

Examining Patient Survival Data

The average OS in this trial was 37 mo., and the PFS persisted for 15 mo.. A statistically significant correlation was found between the study's response rates and the survival results. The OS and PFS rates of patients who had a full response fell below the predefined threshold for non-response (NR). The PFS as well as OS times for the patients in the partial response group were 16.6 and 33.5 mo., respectively.

Table 1: Baseline features (number or percentage, range, and median are used to express the data).

Variables	N=40
Median age	**55**
Gender (%)	
Male	**54%**
Females	**44%**
Performance status (%)	
PS-1	**94%**
PS-2	**4%**
Comorbidities (%)	
No comorbidities	**64%**
Hypertension	**9%**
Diabetes mellitus	**9%**
Hypertension + diabetes mellitus	**14%**
Site of cancer (%)	
Oral cavity	**59%**
Hypopharynx	**29%**
Oropharynx	**9%**
Tumour (T) and nodal (N) stage (%)	
T2	**54%**
T3	**14%**
T4	**29%**
N(%)	
N0	**4%**
N1	**44%**
N2	**49%**
Stage (%)	
Stage III	**45%**
Stage IV	**55%**

Adverse Impact Overview

All study participants demonstrated successful tolerance and completion of the initial treatment and concurrent chemoradiotherapy (CRT) in accordance with the predetermined protocol. A cohort comprising nine individuals required dosage modification due to the manifestation of grade 3 or 4 toxicity. The predominant toxicities observed in the study population were primarily categorized as grade 1 or 2, thereby obviating the need for any modifications to the prescribed dosage regimen. The predominant grade 3/4 toxicities were observed in the form of nausea or vomiting (24%) and neutropenia (39%), both of which were effectively addressed using conservative therapeutic interventions. Grade 3/4 mucositis was detected in a subset of patients, specifically 34% of the study population. This occurrence may have been influenced by the simultaneous administration of chemoradiotherapy (CRT). The primary presentation of neuropathy was predominantly categorized as grade 1/2, impacting approximately 29% of the patient cohort, whereas grade 3 neuropathy was identified in 11% of the total patient population. Significantly, a cutaneous eruption was exclusively observed in 9% of the subjects included in the study, all of whom displayed grade 1 severity. No instances of hypomagnesemia were detected in any of the patients.

Discussion

In the Indian population, head and neck malignancies, particularly oral carcinoma, rank as the second most prevalent and deadly cancers, with 60% of individuals being diagnosed at an advanced local stage. The influential TAX 323 study demonstrated the benefits of an induction TPF (docetaxel, cisplatin, and fluorouracil) regimen for HNSCC. Though, the overall survival rates in that cohort remained suboptimal [10]. The present study aimed to estimate the effectiveness, safety, and acceptability of a treatment regimen combining TPF with nimotuzumab as an induction therapy for locally advanced HNSCC, based on previous evidence of nimotuzumab's favorable effectiveness in combination with chemoradiation without increased adverse effects [8].

In the current study, it was observed that a CR rate of 11% after administering induction TPF plus N, which elevated to 25% after completing chemoradiation therapy. These CR rates showed a modest improvement compared to findings reported by Vermorken *et al*. [10], who reported a CR rate of 6.6% after induction therapy with TPF and 19.9% after concomitant chemoradiation.

The study results showed an overall survival rate of 37 mo. and a median progression-free survival of 15

mo.. Compared to Vermorken *et al*.'s study, where PFS as well as OS were 11.0 mo. and 18.8 mo., the results were notably better [10]. This improvement may be attributed to including a higher proportion of patients with T2 disease (54%) and the addition of nimotuzumab to the induction TPF therapy.

The study found no significant differences in survival rates among different subsites of the primary tumor. Median OS for oral cavity, hypopharynx, and oropharynx malignancies was 33.5 mo., 37 mo., and 34 mo., respectively.

This study is among the first to explore the efficacy of EGFR antibodies in treating oral cavity malignancies. While Bonner *et al*. showed that cetuximab was effective in locally advanced HNSCC when combined with radiation therapy, their group did not include patients with oral cavity primaries [12].

Every patient finished their initial TPF plus N and CRT with carboplatin without any problems. While the majority of side effects were grade 1/2 and did not require dose change, nine patients needed modifications due to grade 3/4 toxicity. Neutropenia (39%) and nausea or vomiting (24%), which were grade 3/4 toxicities, were treated cautiously. Mucositis of grade 3/4 was seen in 34% of individuals; participants undergoing concurrent carboplatin and chemoradiation were more likely to experience this condition. While 6.7% of patients had considerable nausea or vomiting, 6% received severe diarrhea, 7.5% had grade 3/4 neutropenia, and 11.2% had grade 3/4 stomatitis, the adverse event profile was little different from that of TAX 323 [10]. Our smaller sample size and variations in the ethnic makeup of the research group could be the cause of this variance.

Only 9% of individuals experienced the skin rash and hypomagnesemia commonly associated with cetuximab, and these cases were all grade 1. Nimotuzumab's affinity is ten times lower than cetuximab's, and it necessitates bivalent binding for a durable interaction with EGFR on cell membranes. Nimotuzumab selectively binds to EGFR on cell surfaces with moderate to high EGFR density, allowing for bivalent interactions. This property may explain its lower toxicity profile compared to cetuximab [13].

It is probably because of their combined action that nimotuzumab and chemotherapy work well together. Chemotherapy causes damage to DNA, which starts the repair process and stops the cell cycle at the G1 phase. EGFR blockage now obstructs signal transduction pathways that are essential for cell division and repair, which leads to the eventual death of the cell [14]. A humanized IgG1 monoclonal antibody called nimotuzumab showed comparable antiproliferative effects on squamous cell carcinoma cells *in vitro* [15].

Conclusion

Nimotuzumab may be a highly useful supplement to induction TPF, improving response rates and survival without causing additional harm. As our study showed, nimotuzumab added to routine induction could help even the subset of patients with initial tumors of the oral cavity. Total remission after chemotherapy and radiation therapy might be a good indicator of overall survival. To verify the same, larger randomized multicentric investigations will be required.

References

1. Globocan 2018: India factsheet-India Against Cancer n.d. http://cancerindia.org.in/globocan-2018-india-factsheet/.
2. P. Joshi, S. Dutta, P. Chaturvedi, and S. Nair, Head and neck cancers in developing countries, Rambam Maimonides Medical Journal, 2014; 5(2): Article ID e0009.
3. Environmental Effects on Head and Neck Cancer in India, https://ascopubs.org/doi/abs/10.1200/jco.2009.27.15_suppl.e17059.
4. M. R. Kulkarni, Head and neck cancer burden in India, International Journal of Head and Neck Surgery, 2013; 4(1): 29–35.
5. Karabajakian, M. Gau, T. Reverdy, E. M. Neidhardt, and J. Fayette, Induction chemotherapy in head and neck squamous cell carcinoma: a question of belief, Cancers (Basel), 2019; 11.
6. Levels of TGF-Alpha and EGFR Protein in Head and Neck Squamous Cell Carcinoma and Patient Survival. NCBI n.d. https://www.ncbi.nlm.nih.gov/pubmed/9625170.
7. J. B. Vermorken, R. Mesia, F. Rivera et al., Platinum-based chemotherapy plus cetuximab in head and neck cancer, New England Journal of Medicine, 2008; 359(11): 1116–11 27.
8. V. M. Patil, V. Noronha, A. Joshi et al., "Results of a randomized phase III study of nimotuzumab in combination with concurrent radiotherapy and cisplatin versus radiotherapy and cisplatin alone, in locally advanced squamous cell carcinoma of the head and neck, Journal of Clinical Oncology, 2018; 36:15_suppl: 6000.
9. Y. Lu, D. Chen, J. Liang et al., Administration of nimotuzumab combined with cisplatin plus 5-fluorouracil as induction therapy improves treatment response and tolerance in patients with locally advanced nasopharyngeal carcinoma receiving concurrent radiochemotherapy: a multicenter randomized controlled study, BMC Cancer, 2019; 19.
10. J. B. Vermorken, E. Remenar, C. Van Herpen et al., Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer, New England Journal of Medicine, 2007; 357(17): 1695–1704.

11. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009.
12. J. A. Bonner, P. M. Harari, J. Giralt et al., Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival, The Lancet Oncology, 2010; 11(1): 21–28.
13. S. Li, K. R. Schmitz, P. D. Jeffrey, J. J. W. Wiltzius, P. Kussie, and K. M. Ferguson, Structural basis for inhibition of the epidermal growth factor receptor by cetuximab" Cancer Cell, 2005;7(4): 301–311.
14. G. Garrido, I. A. Tikhomirov, A. Rabasa et al., Bivalent binding by intermediate affinity of nimotuzumab: a contribution to explain antibody clinical profile, Cancer Biology & Therapy, 2011; 11(4): 373–382.
15. R. S. Herbst and D. M. Shin, "Monoclonal antibodies to target epidermal growth factor receptor-positive tumors, Cancer, 2002; 94: 5:1593–1611.