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Original Article

Oncology Section

Synergistic Potential of Methotrexate and Gefitinib: A Promising Palliative Approach for Advanced and Recurrent Head and Neck Cancers

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ABSTRACT

Introduction: Head and Neck Cancers (HNCs) in India account for 30% of all cancers, out of which 60-80% of patients present with advanced disease, leaving the patients with limited survival and poor Quality of Life (QoL). Poor nutritional conditions, advanced disease presentation, limited tolerance, and socio-economic constraints necessitate the development of appropriate and effective palliative treatment options that are also easily available. One such palliative approach has been explored, and its relevance and applicability are discussed here.

Aim: To study the role of weekly intramuscular injection Methotrexate (MTX) along with oral Tablet Gefitinib in advanced unresectable, recurrent, or residual HNCs.

Materials and Methods: A retrospective analysis of 50 patients was carried out in the Department of Radiation Oncology, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India. All patients included had advanced HNC and were ineligible for curative treatment. All received weekly intramuscular injection MTX 40 mg/m^2 and Tablet Gefitinib administered orally in a dose of 250 mg once daily. These patients were assessed for tumour response, acute toxicities, symptomatic relief, and median survival. All the data were recorded in Microsoft Excel and analysed using Statistical Package for Social Sciences (SPSS) software version 28.0.

Results: This study included 50 patients (45 males, 5 females) with a mean±SD age of 49±8.8 years, all diagnosed with histologically confirmed squamous cell carcinoma, predominantly at stage 3 (six patients) and stage 4 (44 patients). Median survival was 5.9 months. According to RECIST (Response Evaluation Criteria in Solid Tumours) criteria, no complete responses were observed; 18 (36%) had a partial response, 21 (42%) had stable disease, and 11 (22%) had progressive disease. The treatment was well-tolerated, providing notable relief in pain and dysphagia symptoms. In terms of toxicity, grade-3 mucositis was observed in 10 patients, and none had grade-4. Grade-3-4 neutropenia and anaemia were seen in six and eight patients, respectively.

Conclusion: The use of MTX and gefitinib combination in advanced HNCs has the potential to substantially alleviate pain, provide symptomatic relief concerning dysphagia and speech, and hence improve the overall QoL.

Keywords: Chemotherapy, Metronomic, Neoplasms, Squamous cell carcinoma, Upper aerodigestive tract neoplasms

INTRODUCTION

Globally, 57.5% of HNCs occur in Asia, particularly in India, where they account for approximately 30% of all cancers [1]. According to GLOBOCAN 2020 data, cancer of the lip and oral cavity is the most common cancer in males in India, while in females, it ranks as the fourth most common [2]. The majority of HNCs present in locally advanced stages (stages III and IV). Lack of knowledge among the population, socio-economic restraints, and limited availability of medical care to the susceptible population contribute to the higher incidence of locally advanced HNCs [3]. This trend is also attributed to widespread habits such as tobacco consumption, alcoholism, and prevalent bidi and cigarette smoking across all segments of society in India. Squamous cell carcinomas constitute approximately 95% of these HNCs [4].

Advanced HNC patients quite often experience residual disease, recurrence, or metastasis, compromising survival and QoL. Extensive prior treatments reduce tolerance to standard chemotherapy. Around 60-80% of HNC patients present in an advanced stage [5], and this problem is further complicated by the non availability of tertiary cancer centres in every region of India and financial burdens, which increase the time between the diagnosis and definitive treatment [6]. Effective, affordable, and well-tolerated palliative treatments are essential to improve overall survival and QoL. There are no evidence-based guidelines for the standard practice of palliative care in advanced HNCs. Surgery is typically not an option for patients with advanced lesions and poor performance status because a sizeable amount of disease would still be present [3]. Chemotherapy aims to relieve symptoms, prevent complications, and improve overall and progression-free survival, as well as QoL. The chosen treatment regimen should prioritise being well-tolerated, cost-effective, and associated with minimal toxicity to ensure optimal patient outcomes.

Numerous phase II-III studies [7-9] comparing combination chemotherapy to single-agent therapy have consistently shown a statistically significant improvement in tumour response with the former but at the expense of increased rates of toxicity. In cases where prior combination chemotherapy has been ineffective and concerns about toxicity arise, single-agent chemotherapy is currently recommended [10]. Notably, earlier studies have indicated that MTX along with tablet Gefitinib for recurrent HNCs can offer a good QoL on an outpatient basis [9,11].

MTX has diverse applications in treating cancers like breast cancer, HNCs, osteogenic sarcoma, and more. While it demonstrates widespread distribution and favourable response rates, it has potential toxicities. Myelosuppression is the dose-limiting toxicity. Mucositis, often emerging 3-7 days post-MTX therapy, can also be dose-limiting. Nausea, vomiting, and dermatological manifestations may occur [4].

Approximately 80-90% of Head and Neck Squamous Cell Carcinomas (HNSCCs) exhibit increased expression or contain genetic variations in Epidermal Growth Factor Receptor (EGFR), and

these changes directly influence overall survival and progression-free survival [12-14]. Hence, gefitinib, an EGFR tyrosine kinase inhibitor, plays a significant role as targeted therapy in HNCs. In previous studies [9,15], the combination of MTX with Gefitinib, an EGFR targeting agent, has shown notable positive effects and response rates in advanced HNCs. Gefitinib toxicity may manifest in the form of elevation in blood pressure, pruritus, dry skin with mainly a pustular, acneiform skin rash, mild nausea, vomiting, and mucositis [11,16].

In lower-middle-income countries like India, especially in rural, illiterate, and below poverty-line populations, the accessibility and affordability of MTX and gefitinib chemotherapy make it a viable option. Recognising its notable positive effects, authors undertook a retrospective analysis within the department at Sarojini Naidu Medical College, Agra, Uttar Pradesh, India where most patients belong to the lower socio-economic strata. This analysis focused on patients with advanced recurrent or metastatic HNCs who underwent intramuscular administration of MTX weekly along with tablet Gefitinib orally once daily. The evaluation encompassed an assessment of subjective and objective responses and the toxicity profile associated with this treatment approach. Hence, the aim of the study was to carry out a retrospective analysis and study the role of weekly intramuscular injection MTX at a dose of 40 mg/m^2 along with Tablet Gefitinib administered orally in a dose of 250 mg once daily in advanced unresectable, residual, recurrent HNCs.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Radiation Oncology, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India. All procedures performed were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study included patients diagnosed with advanced (stage 3-4), residual, or recurrent HNCs between the years 2018 and 2021, and the data were analysed retrospectively from their case records in 2023. These patients were either deemed ineligible for curative treatment or had previously undergone curative treatment (in the form of surgery, chemotherapy, or radiotherapy) but experienced recurrence or residual disease, necessitating palliative care. The chosen palliative treatment for these patients involved the administration of intramuscular MTX (inj. MTX) at a weekly dosage of 40 mg/m^2 [17,18] with tablet Gefitinib administered orally in a dose of 250 mg once daily [16].

Inclusion criteria:

- Histologically proven Squamous Cell Carcinoma (SCC) of the head and neck
- Stage 3-4 disease/residual disease/recurrent disease
- Absence of contraindications for the prescribed therapy
- Availability of all clinical, pathological details, and supporting evidence.

Exclusion criteria:

- Patients eligible for curative treatment.
- Cancers of the nasopharynx, thyroid, and secondaries of the neck with unknown primary
- Pregnant or lactating females.

Study Procedure

A total of 50 patients met the criteria and were deemed suitable for inclusion in this study. The analysis was conducted retrospectively by examining the case records of these patients to assess the outcomes and implications of the palliative treatment.

Analysis: Baseline characteristics of the patients were systematically documented from their clinical case records. The American Joint Committee on Cancer (AJCC 8th edition)-TNM system [19] was employed for staging the disease. Weekly assessments were conducted to evaluate tolerance, treatment response, and treatment-related toxicity. Subjective response, specifically concerning pain, was gauged using the Mankoski Pain Scale [20] as follows:

0- Pain-free

1- Very minor annoyance - occasional minor twinges. No medication needed.

2- Minor annoyance - occasional strong twinges. No medication needed.

3- Annoying enough to be distracting. Mild painkillers are effective (aspirin, ibuprofen).

4- Can be ignored if you are really involved in your work, but still distracting. Mild painkillers relieve pain for 3-4 hours.

5- Can't be ignored for more than 30 minutes. Mild painkillers reduce pain for 3-4 hours.

6- Can't be ignored for any length of time, but you can still go to work and participate in social activities. Stronger painkillers (codeine, acetaminophen-hydrocodone) reduce pain for 3-4 hours.

7- Makes it difficult to concentrate and interferes with sleep. You can still function with effort. Stronger painkillers are only partially effective. Strongest painkillers relieve pain (extended-release form of oxycodone, morphine).

8- Physical activity severely limited. You can read and converse with effort. Nausea and dizziness set in as factors of pain. Strongest painkillers reduce pain for 3-4 hours.

9- Unable to speak. Crying out or moaning uncontrollably- near delirium. Strongest painkillers are only partially effective.

10- Unconscious. Pain makes you pass out. The strongest painkillers are only partially effective.

The score was further categorised as mild, moderate, and severe according to the Mankoski scale [20]:

- Mild pain is defined as a score of 0-3
- Moderate pain is defined as a score of 4-6
- Severe pain is defined as a score of 7-10

Dysphagia was graded according to modified Takitas Grading [21] from 1-6 as mentioned below:

- Grade-1- able to swallow solids normally;
- Grade-2- mild difficulty in swallowing solids, needs water to swallow;
- Grade-3- not able to swallow solids, only swallows semisolids;
- Grade-4- not able to swallow solids and semisolids, only swallowing liquids;
- Grade-5- not able to swallow liquids but able to swallow saliva;
- Grade-6- not able to swallow saliva also, complete dysphagia.

Objective tumour response was analysed in alignment with RECIST Criteria 1.1 [22]. The evaluation of chemotherapy-related toxicity focused on parameters such as neutropenia and anaemia, adhering to the Common Terminology Criteria for Adverse Events (CTCAE) classification [23]. Regular monitoring and documentation of these criteria allowed for a comprehensive analysis of the treatment outcomes and associated effects in the studied patient cohort.

STATISTICAL ANALYSIS

All the data were recorded in Microsoft Excel and analysed using SPSS software version 28.0.

RESULTS

In this study, a total of 50 patients met the inclusion criteria, and their demographic details are summarised in [Table/Fig-1]. Among the participants, 45 were males and five were females, with a mean±SD age of 49±8.8 years. The distribution of primary tumour sites included the oral cavity in 35 (70%) patients, oropharynx in

8 (16%). Among the previously treated patients (42 in total), seven received radiotherapy only, nine received chemotherapy only, and 26 underwent concurrent chemoradiation. Additionally, eight patients were selected for upfront MTX therapy [Table/Fig-2].

Particulars		n (%)
Age (years) M±SD	Mean	49±8.8
Sex	Males	45 (90)
	Females	5 (10)
Primary tumour site	Oral cavity	35 (70)
	Oropharynx	8 (16)
	Larynx	2 (4)
	Hypopharynx	4 (8)
	Maxillary sinus	1 (2)
Habits	Tobacco	42 (84)
	Alcohol	33 (66)
	Smoking	48 (96)
Histopathology	SCC	50 (100)
Stage	3	6 (12)
	4	44 (88)

[Table/Fig-1]: Patient demographics.
SCC: Squamous cell carcinoma

Type of treatment	n (%)
RT only	7 (14)
CT only	9 (18)
CTRT	26 (52)
Upfront MTX	8 (16)

[Table/Fig-2]: Type of treatment.
RT: Radiotherapy; CT: Chemotherapy; CTRT: Concurrent chemotherapy and radiotherapy; MTX: Methotrexate

Treatment time varied from a minimum of five weeks to a maximum of 35 weeks. Since the majority received injections on an outpatient weekly basis, the hospital stay ranged from 0 to 3 days. The average cost per cycle per patient was calculated to be INR 50/- as most of the time, the above-mentioned drugs were available through government supply. The median survival duration was determined to be 5.9 months [Table/Fig-3]. In terms of treatment-related toxicity, 6 (12%) out of 50 patients developed grade-3 or 4 neutropenia, 8 (16%) patients experienced anaemia, and 10 (20%) patients complained of MTX-induced oral mucositis; however, all were well-managed conservatively. One (2%) patient developed a local injection site abscess. Gefitinib-induced acneiform rash and pruritus were witnessed in 1 (2%) patient, which was well managed by antihistaminic medications and topical moisturisers. Overall, the treatment was well-tolerated by most patients, with significant symptomatic relief observed in terms of pain and dysphagia as well as speech.

Particulars		
Patients receiving at least five weeks of treatment		50 (100)
Average treatment cost per cycle per patient		Rs. 50/-
Days of hospitalisation	Minimum	0
	Maximum	3
No. of chemotherapy cycles received	Minimum	5
	Maximum	35
Toxicity, n(%)	Neutropenia	6 (12)
	Anaemia	8 (16)
	Mucositis	10 (20)
	Local site abscess	1 (2)
	Pruritus and rash	1 (2)
Survival (months)	Minimum	3
	Maximum	9
	Median survival	5.9

[Table/Fig-3]: Average treatment cost, days of hospitalisation, toxicity and survival.

As per the RECIST 1.1, none of the patients exhibited a complete response, other criteria is shown in [Table/Fig-4].

Response criteria	n (%)
Complete response	0
Partial response	18 (36)
Stable disease	21 (42)
Progressive disease	11 (22)

[Table/Fig-4]: Response assessment- RECIST 1.1 criteria.

Subjective symptomatic response, measured in terms of pain and dysphagia, was also evaluated, and pain was measured using the Mankoski Pain Scale [Table/Fig-5]. Before treatment, all 50 patients were assessed: none had mild pain. After five weeks of treatment, 5 (10%) patients experienced mild pain, 35 (70%) had moderate pain, and 10 (20%) had severe pain. The distribution shifted from predominantly severe pain before treatment to mostly moderate pain after, with some patients reporting being pain-free. This indicates an overall improvement in symptomatic pain.

Grading mankoski	Before treatment	After five cycles chemotherapy, n (%)
0-3	0	5 (10)
4-6	12 (24)	35 (70)
7-10	38 (76)	10 (20)
Total patients	50	50

[Table/Fig-5]: Pain assessment- Mankoski pain criteria.

Out of the 50 patients, 28 (56%) had dysphagia. Before treatment, out of the 28, none had grade-1 dysphagia. After five weeks of treatment, 2 (4%) patients had grade-1 dysphagia [Table/Fig-6]. Before treatment, most patients were in the grade-3-5 category, but after treatment, most were in the grade-2-4 category, indicating subjective improvement in dysphagia for all patients [Table/Fig-7].

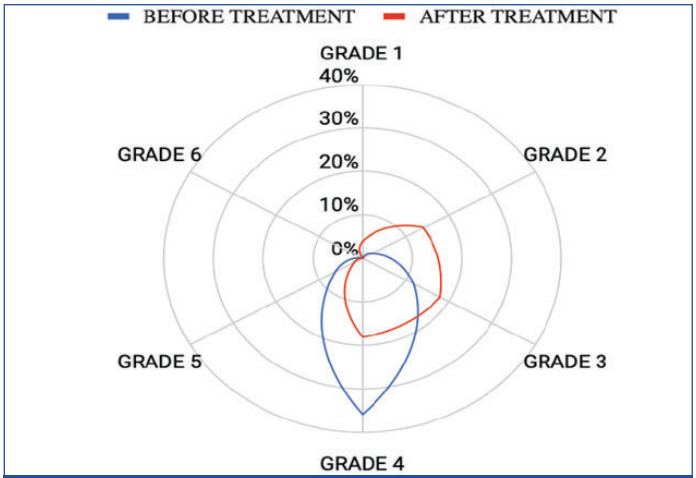
Dysphagia modified takitas grading	Before treatment n (%)	After five cycles chemotherapy n (%)
1	0	2 (4)
2	1 (2)	7 (14)
3	6 (12)	9 (18)
4	18 (36)	9 (18)
5	3 (6)	1 (2)
6	0	0
Total patients	28	28

[Table/Fig-6]: Dysphagia assessment- modified Takitas dysphagia grading.

Gross reduction in lesion size was also seen with lesions almost disappearing in some patients [Table/Fig-8a], resolution in orocutaneous fistulas in some [Table/Fig-8b], and reduction of ulcerated and excoriated lesions in some patients [Table/Fig-8c].

DISCUSSION

The present study's analysis demonstrated that patients with advanced HNCs undergoing weekly MTX and gefitinib chemotherapy exhibited positive responses and good tolerance to the treatment. The adverse effect profile was acceptable and manageable. The ease of administration is also linked with good adherence to the treatment, along with disciplined follow-up. Nominal side-effects were observed, which were well-managed, and there was significant symptomatic improvement. The primary objective of this study was to alleviate distressing symptoms such as pain and



[Table/Fig-7]: Distribution of dysphagia grading before and after treatment. Before treatment it can be clearly seen that the distribution favoured grades 3, 4 and 5; whereas after treatment, distribution is towards grades 2, 3 and 4, representing an overall improvement.

[Table/Fig-8]: Response seen in some of the patients after five cycles of chemotherapy. a) The patient had two huge exophytic proliferative growths, both having associated orocutaneous fistulas. After only five weeks of treatment, there was a drastic reduction in lesion size and almost disappearance of the fistulas. b) The patient had a large orocutaneous fistula at presentation. After five weeks of treatment, the fistula had completely resolved with fibrosis left behind. c) The patient had an excoriated ulcerative lesion with soft tissue exposure and bleeding points. After five weeks of treatment, there was reduction in lesion size, fibrosis was induced and no bleeding points were seen.

difficulty in swallowing. Additionally, treatment-related toxicities and the QoL were evaluated. Given the lower socio-economic status of the patients, who sought assistance beyond the incurable stage, improving QoL and addressing cost concerns were crucial. Aggressive multimodality approaches were often unsuccessful due to poor performance status and unresectability in these advanced cases. Palliative treatment and/or best supportive care were deemed necessary.

In the period between 2000-2020, many studies [4,24-26] were conducted investigating the role of MTX as a palliative treatment option in advanced HNCs. One such study was conducted by Banipal RPS and Mahajan MK which revealed that 38.8% of patients exhibited a favourable response, characterised by a reduction in tumour size by over 50%, while 39% of patients maintained stable disease with injection MTX [4]. A 22.2% portion of patients experienced disease progression with single-agent chemotherapy. Following six weekly treatments with the injection of MTX, 63% of patients reported being free of pain, and 16% noted a reduction in pain. The median survival, coupled with good QoL, was determined to be 5.4 months. The present study's findings aligned with these results, showing a median survival of 5.9 months.

A more recent study by Guigay J et al., compared two different agents for palliative treatment of advanced HNCs in the elderly. One arm received 2-weekly intravenous cetuximab, and the other arm received weekly intravenous MTX. The primary objective was not reached as no benefit of cetuximab compared with MTX was observed in terms of failure-free survival in this frail older population. However, the study confirmed that both cetuximab and MTX are viable options for recurrent and metastatic HNC patients, especially in the frail and old population [10].

While the present study explored the efficacy of the combination of MTX and gefitinib, Irshad R et al., compared the two treatment options in a randomised prospective comparative study. They observed that gefitinib has marginally better results than MTX in recurrent HNCs, with gefitinib having a slight advantage of being taken orally rather than intravenously, so there is no need for hospitalisation or i.v. cannulation. But on the whole, both MTX and gefitinib turn out to be good options in a resource-poor setting with acceptable toxicity and great efficacy profiles [15]. Tang X et al., in their meta-analysis of seven randomised control trials on the efficacy and safety of gefitinib in advanced HNSCCs concluded that for recurrent patients, gefitinib is a promising agent, which is equivalent to MTX and MTX + fluorouracil, and tends to improve QoL [11].

The synergistic potential of MTX and gefitinib has been demonstrated previously [9,26]. In a retrospective analysis conducted by Anuradha V et al., from 2007 to 2008, patients were administered gefitinib (250 mg/day), MTX at 50 mg intramuscularly weekly, or a combination of both [9]. Another regimen included 5-FU at 750 mg/m^2/day for four days along with cisplatin at 75 mg/m^2/day on day 1 in a 21-day cycle. MTX combined with gefitinib showed the highest median survival and superior overall QoL when compared to other treatment regimens. Weekly MTX demonstrated relative cost-effectiveness, followed by the combination of MTX with gefitinib. The combination of 5-FU with cisplatin appeared less favourable due to elevated complication rates and prolonged hospital stays. The present study revealed comparable findings, indicating cost-effectiveness, favourable tolerance, good patient adherence to the therapy, and an improvement in the QoL.

The trend is now shifting towards a more easy-to-administer palliative therapy with the advent of oral metronomic chemotherapy. An increasing number of studies have been conducted in recent years [26-28] to investigate the efficacy of MTX in oral formulation along with gefitinib and celecoxib. As demonstrated by Dusi VS et al., the gefitinib and MTX combination was well tolerated by patients with advanced HNCs with poor performance status [26]. The majority of the patients who were otherwise not eligible beyond palliative care now had better QoL and longer Progression Free Survival (PFS). In their research, Naidu PD et al., found that oral metronomic chemotherapy results in patients achieving prolonged survival [27]. Patil V et al., in their trial comparing MTX and celecoxib-based metronomic chemotherapy with intravenous cisplatin also concluded that oral metronomic chemotherapy is non inferior to intravenous cisplatin concerning overall survival in HNCs in the palliative setting and is associated with fewer adverse events [28].

Though combination chemotherapy utilising drugs such as Cisplatinum, 5-fluorouracil, or taxanes yields higher response rates and potentially improved progression-free survival in comparison to single-agent MTX [9,28], there is no indication of an overall survival advantage. In this context, weekly MTX and daily gefitinib stand out as a practical and accepted treatment choice. Hence, MTX with gefitinib combination therapy could be a promising approach for patients with advanced HNCs, especially in lower-middle-income countries like India, providing positive outcomes while being manageable and cost-effective.

Limitation(s)

A single institute, smaller sample size, and retrospective study are the prominent limitations of this study.

CONCLUSION(S)

MTX and gefitinib, when used in advanced HNC cases, act synergistically and contribute to substantial pain reduction and an

overall improved QoL, hence proving to be a promising palliative approach. Locoregional disease control and improved socio-economic compliance can be accomplished, and this approach is deemed advantageous due to its lower toxicity, cost-effectiveness, and convenient administration leading to better treatment adherence and better response rates.

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