

# Outcome of Oral Metronomic Therapy with Methotrexate and Celecoxib in Advanced/Recurrent Head and Neck Squamous Cell Carcinoma

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## Abstract

**Introduction:** Metronomic chemotherapy (MC) is an emerging therapeutic option in clinical oncology and it may prove useful at least in metastatic HNSCC patients. To develop rational therapeutic strategies, it is important to identify molecular targets that are linked to the pathogenesis of HNSCC.

**Aim:** This study aims to assess the efficacy and toxicity of oral MC with methotrexate and celecoxib in the treatment of advanced/recurrent HNSCC.

**Methods:** Patients who received MC for advanced/recurrent HNSCC were analyzed. The combination of weekly oral methotrexate 5 mg twice daily for 2 days/week and oral celecoxib 200 mg twice daily was offered as MC. The efficacy was noted in terms of clinical benefit rate (CBR), pain control, changes in quality of life (QOL), and median time to progression (TTP).

**Results:** A total of 50 patients were included in this study. At the end of 6 months, 4 patients (8%) had partial response (PR), 28 patients (56%) had stable disease (SD), and 18 patients (36%) had progressive disease. The CBR (complete response+PR+SD) was 64% at 6 months. The median TTP was 8 weeks. At the end of 6 months, 60% of patients were pain free. The most common (>20% of patients) treatment-related adverse events were nausea (22%), vomiting (22%), and mucositis (20%). 6 patients (12%) developed anorexia and 3 patients (6%) developed fatigue. Mean QOL scores were improved with this MC.

**Conclusion:** Oral MC with methotrexate and celecoxib for patients with advanced/recurrent HNSCC was effective, well tolerated, provides good pain control, and improves QOL with least toxicity profile.

**Key words:** Head neck cancer, Low-dose chemotherapy, Metronomic chemotherapy

## INTRODUCTION

Head and neck cancer is the 10<sup>th</sup> most common cancer worldwide. Cancers arising in the head and neck constitute about 3% of all newly diagnosed cancers in humans.<sup>[1]</sup> The incidence of head and neck squamous cell carcinoma is >500,000 cases per year worldwide and 40,000–60,000

cases per year in the United States, where it comprises approximately 3%–5% of all new cancers and 2% of all cancer deaths.<sup>[2]</sup> Approximately 27% of these patients are women.<sup>[3]</sup> Most patients are older than 50 years, and incidence increases with age; the male-to-female ratio is 2:1–5:1.<sup>[2]</sup> The usual time of diagnosis is after the age of 40, except for salivary gland and nasopharyngeal cancers, which may occur in younger age groups.<sup>[1]</sup> A large majority of these present in an advanced stage, a problem compounded further by poor access to tertiary cancer centers and increasingly long waiting lists for treatment at these centers.<sup>[4]</sup> An increasing incidence of oral tongue squamous cell carcinoma in non-smoking Caucasian women has been reported that does not appear to be driven by prior human papillomavirus (HPV) infection, whereas

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the incidence of other oral cavity cancers is declining.<sup>[1,5]</sup> For many primary sites, tobacco use is associated with an increased risk. Alcohol has also been implicated as a causative factor; the effects of alcohol and tobacco may be synergistic.<sup>[1,6]</sup> Most mucosal squamous cancers of the head and neck, particularly those of the oral cavity, larynx, and hypopharynx, are still associated with these etiologic factors as well as other cultural habits such as oral tobacco use, and in other countries, betel and areca nut chewing.<sup>[1]</sup> HPV infection (HPV; most commonly HPV-16) plays a role in the development of certain head and neck cancers, particularly those in the oropharynx.<sup>[1,7]</sup> Prior tobacco exposure adversely affects the prognosis of HPV-related oropharynx cancers.<sup>[1,8]</sup> Early localized disease is curable by surgery and irradiation. However, two-thirds of the patients in India present with advanced stages of the disease (Stages III and IV) in whom the outcome is poorer even with multimodality therapy which includes surgery, radiation, and chemotherapy.<sup>[9]</sup> Metronomic chemotherapy (MC) is defined as chronic, equally spaced, and low doses of chemotherapeutic drugs without extended rest periods.<sup>[4]</sup> MCs are now called “metronomic scheduling of anticancer therapy (MSAT).”<sup>[4]</sup> In this Phase II trial, we evaluated the effectiveness and toxicity of MC with oral methotrexate and celecoxib for palliative intent chemotherapy in advanced/recurrent head and neck cancers.

### Aim

This study aims to assess the response, efficacy, and toxicity profile of oral MC with methotrexate and celecoxib in the treatment of advanced/recurrent head and neck squamous cell carcinoma patients, who had failed earlier treatment strategies and has residual or recurrent tumors.

## MATERIALS AND METHODS

This open-label, multi-center Phase II study was designed to assess the response rate, quality of life (QOL), pain control, and toxicity profile in patients with advanced/recurrent head and neck squamous cell carcinoma who had failed earlier treatment strategies and has residual or recurrent tumors, who are treated with oral metronomic therapy with methotrexate and celecoxib, as the palliative treatment. This is a study of patients with metastatic, recurrent, and locally advanced HNSCC which were not amenable to local treatment with surgery, radiotherapy ± chemotherapy. The primary objective was to evaluate the overall response rate (disease control rate [DCR] and CBR) and toxicity of oral metronomic chemotherapy with methotrexate and celecoxib in patients with advanced/recurrent head and neck squamous cell carcinoma. The DCR defined as the total of complete response (CR), partial response (PR), and stable disease (SD). The CBR defined as

the total of CR, PR, and SD lasting for at least 6 months. A secondary objective was to assess the effect of oral metronomic therapy on QOL and symptom control, mainly pain control. The study was conducted after approval from the institutional ethical committee and in accordance with their regulations. Written informed consent was obtained from all patients before screening assessments or enrollment. The oral MSAT consists of oral methotrexate 15 mg/m<sup>2</sup> once a week and oral celecoxib 200 mg twice daily. All patients treated on an outpatient basis. The chemotherapy was continued till disease progression, intolerable side effects, or patients' desire to stop. Schifeling *et al.* showed that a dose of 15 mg/m<sup>2</sup> of methotrexate saturates HNSCC tumor dihydrofolate reductase, and thus, dose escalation may have limited value.<sup>[10]</sup> This is the reason for using methotrexate at doses of 15 mg/m<sup>2</sup> in this study. The complete history including detailed history of the primary tumor and biology, management, and status at last follow-up; history of recurrent/metastatic disease including duration of disease, previous sites of involvement, prior treatments and their effect, current symptoms, performance status, socioeconomic background, and comorbidities (e.g., cardiac diseases, hypertension, diabetes mellitus, thromboembolic diseases, and renal or liver disease). Detailed physical examination was done at each clinical visit, including general clinical assessment, specific assessment of tumor response, and for toxicities developed, if any. QOL assessed with the European organization for research and treatment of cancer QLQ-C30 and QLQ-H and N35 questionnaires at 2, 4, and 6 months. Blood counts, renal function tests, and liver function tests at baseline before starting oral MC. Response to treatment assessed clinically at 2, 4, and 6 months and with imaging whenever necessary. Tumor responses were evaluated based on response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Toxicity of oral metronomic therapy is graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 4.03. Nutritional status of all patients assessed with the body mass index (BMI). Normal BMI ranges from 18.5 to 24.9. BMI of <18.5 constitutes underweight. In overweight, BMI ranges from 25 to 29.9. BMI of >30 constitutes obesity. Socioeconomic status of the patient assessed with Modified Kuppaswamy's Socioeconomic Scale, 2012.

## RESULTS

A total of 50 patients were enrolled in this study. The median age was 47 years (range 20–65). The sex distribution was skewed with 38 males (76%) and only 12 females (24%). Among risk factors, chewable form of tobacco tops the list with 34%, followed by combined smoking and alcohol,

smoking, and alcohol. No risk factor was identified in 7 patients (14%). According to Modified Kuppaswamy's Socioeconomic Scale, 26 patients (52%) come under Class V (lower), followed by Class IV (lower/upper lower) in 13 patients (26%), Class III (middle/lower middle) in 8 patients (16%), and Class II (upper middle) in 2 patients (4%). Only one patient falls under Class I (upper). The performance status was ECOG PS 1 in 37 patients (74%) and it was PS 2 in 13 patients (26%) [Table 1]. Nutritional status of patients assessed with BMI. Normal BMI (18.5–24.9) was identified in 36 patients (72%). 11 patients (22%) had BMI of <18.5 (underweight). Three patients (6%) had a BMI of 25–29.9 (overweight). All patients had squamous cell carcinoma with the oral cavity being the primary in 25 patients (50%), followed by pharynx (17 patients, 34%), larynx (5 patients, 10%), and maxillary sinus (3 patients, 6%) [Table 2]. All patients received at least one form of previous treatment. 30 (60%) patients received neoadjuvant chemotherapy and chemoradiation. 9 (18%) patients treated with NACT followed by surgery and chemoradiation. Another 9 patients (18%) treated with surgery followed by chemoradiation. NACT followed by surgery and RT was the initial treatment received in 1 patient (2%). 1 patient (2%) received RT alone as an initial treatment. Staging of the primary tumor was done according to AJCC cancer staging manual, seventh edition. 47 patients (94%) had locally advanced disease not amenable to locoregional

therapy (Stage IV A). 2 patients (4%) had metastatic disease (Stage IV C). 1 patient (2%) had a resectable tumor (Stage IV A) who was unwilling for either surgery or radiotherapy despite repeated counseling [Table 3]. None of the patients achieved a CR. At the end of 2 months, a PR was obtained in 2 patients (4%), 36 patients (72%) had SD, and 12 patients (24%) had progressive disease (PD). Thus, 38 patients (2 patients with PR and 36 patients with SD) able to show disease control with a DCR of 76% [Table 4]. At the end of 6 months, 4 patients (8%) had a PR, 28 patients (56%) had SD, and 18 patients (36%) had PD. Eight patients, who initially achieved SD at the end of 2 months, lost their disease stabilization and progressed over the next 4 months. Two patients with metastatic disease (Stage IV C) progressed while on oral metronomic therapy. One patient with Stage IV A disease,

**Table 1: Patient characteristics**

Characteristics	n=50 (%)
Age (years)	
20–29	3 (6)
30–39	14 (28)
40–49	14 (28)
50–65	19 (38)
Gender	
Male	38 (76)
Female	12 (24)
Risk factors	
Smoking	7 (14)
Alcohol	4 (8)
Chewable tobacco	17 (34)
Smoking+alcohol	15 (30)
No risk factor	7 (14)
Socioeconomic status (Modified Kuppaswamy's Socioeconomic Scale)	
Class I	1 (2)
Class II	2 (4)
Class III	8 (16)
Class IV	13 (26)
Class V	26 (52)
Performance status at baseline (ECOG)	
1	37 (74)
2	13 (26)
Nutritional status (BMI)	
Normal	36 (72)
Underweight	11 (22)
Overweight	3 (6)

**Table 2: Site of HNSCC**

Site	Frequency (%)
Oral cavity	25 (50)
Buccal mucosa	13 (26)
Tongue	8 (16)
Alveolus	2 (4)
Palate	1 (2)
Floor of mouth	1 (2)
Pharynx	17 (34)
Nasopharynx	4 (8)
Oropharynx	9 (18)
Hypopharynx	4 (8)
Larynx	5 (10)
Supraglottis	4 (8)
Subglottis	1 (2)
Maxillary sinus	3 (6)

**Table 3: Prior treatment received**

Characteristics	n=50 (%)
Chemoradiation	30 (60)
NACT+surgery+chemoradiation	9 (18)
Surgery+chemoradiation	9 (18)
NACT+surgery+RT	1 (2)
RT alone	1 (2)
AJCC stage	
IVA	1 (2)
IV B	47 (94)
IV C	2 (4)

**Table 4: Response to oral metronomic chemotherapy**

Response	Response at the end of 2 months n (%)	
CR	0 (0)	0 (0)
PR	2 (4)	4 (8)
SD	36 (72)	28 (56)
PD	12 (24)	18 (36)

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

who was unwilling for either surgery or radiotherapy despite repeated counseling, showed SD, both at the end of 2 months and 6 months [Table 5]. The median time to progression (TTP) was 8 weeks (95% confidence interval: 7.95–8.04) [Figure 1]. All treatment-related adverse events were Grade 1 or 2 in severity. The most common (>20% of patients) treatment-related adverse events were nausea (22%), vomiting (22%), and mucositis (20%). 6 patients (12%) developed anorexia and 3 patients (6%) developed fatigue. 6 patients (12%) developed anemia of Grade 1 or 2. 1 patient (2%) developed Grade 1 thrombocytopenia and another patient developed Grade 1 neutropenia. One patient had Grade 1 renal dysfunction. None of the patients had Grade 3 or 4 adverse events and there were no patients with febrile neutropenia or treatment-related deaths. None of the patients developed cardiac or pulmonary adverse events during treatment with oral metronomic therapy [Table 6]. 19 patients (38%) presented with Grade >3 pain; this is reduced to 4 patients (8%) at the end of 2 months, 1 patient (2%) at the end of 4 months. None of the patients were in Grade >3 pain at the end of 6 months. At the end of 6 months, 60% of patients were pain free with another 38% of patients reported a decrease in pain [Table 7]. Mean QLQ-C 30 score at the time of presentation was 76.38. With oral MC, there was a steady increase in QOL score QLQ-C 30; 78.34 at 2 months, 80.36 at 4 months, and 83.78 at the end of 6 months. Mean QLQ-H and N35 score at

the time of presentation was 64.58. QLQ-H and N score steadily increases with oral MC; 70.1 at 2 months, 73.7 at 4 months, and 79.46 at the end of 6 months. In subgroup analysis, both QLQ-C30 and QLQ-H and N35 accurately correlated with disease progression.

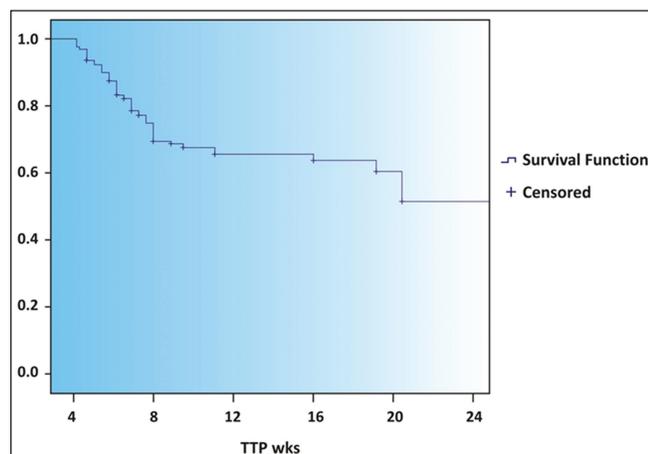
## DISCUSSION

HNSCC is the third most common cancer in India and the second most common cancer in Indian males.<sup>[5]</sup> In India, HNSCC accounts for 9–10% of the incidence of cancer.<sup>[11]</sup> A large majority of these present in an advanced stage.<sup>[4]</sup> Many of these patients are treated upfront with palliative therapy. Even if treatment is given with curative intent, a significant proportion of patients has recurrent disease.<sup>[12]</sup> The treatment options in patients with advanced and recurrent head and neck cancers that are not amenable for local treatment are limited.<sup>[13]</sup> Many different combination chemotherapy regimens with platinum as one of the agents have been used in such situations. However, none of them was clearly superior to each other, and overall survival was not statistically improved with respect to the increase in the number of agents used.<sup>[14]</sup> The use of cetuximab in combination with cisplatin and 5-fluorouracil led to an improvement in overall survival with respect to the cisplatin and 5-fluorouracil combination.<sup>[15]</sup> However, in resource-poor settings, the use of this combination is limited. The goal of therapy in this situation is to reduce tumor burden and related symptoms and ultimately prolong survival while maintaining the QOL by maximizing therapeutic potential and minimizing treatment-related toxicity. Low-

**Table 5: Response rates at the end of 6 months, according to stage**

Stage	All n (%)	Response at 6 months		
		PR	SD	PD
		n (%)	n (%)	n (%)
IV A	1 (2)	0 (0)	1 (2)	0 (0)
IV B	47 (94)	4 (8)	27 (54)	16 (32)
IV C	2 (4)	0 (0)	0 (0)	2 (4)

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease



**Figure 1: Survival function**

**Table 6: Incidence of adverse events**

Events	All	Grade 1	Grade 2
	n (%)	n (%)	n (%)
Mucositis	10 (20)	6 (12)	4 (8)
Anorexia	6 (12)	6 (12)	0 (0)
Nausea	11 (22)	8 (16)	3
Vomiting	11 (22)	11 (22)	0 (0)
Fatigue	3 (6)	3 (6)	0 (0)
Anemia	6 (12)	4 (8)	2
Neutropenia	1 (2)	1 (2)	0 (0)
Thrombocytopenia	1 (2)	1 (2)	0 (0)
Renal dysfunction	1 (2)	1 (2)	0 (0)

**Table 7: Effect of oral metronomic therapy on symptom control (pain control)**

Pain grade	At baseline	At 2 months	At 4 months	At 6 months
	n (%)	n (%)	n (%)	n (%)
<1	0 (0)	0 (0)	10 (20)	30 (60)
1–2	5 (10)	22 (44)	26 (52)	19 (38)
2–3	26 (52)	24 (48)	13 (26)	1 (2)
>3	19 (38)	4 (8)	1 (2)	0 (0)

dose methotrexate and cyclooxygenase-2 inhibitors have an anti-angiogenic effect in head and neck cancer cell lines.<sup>[16]</sup> Celecoxib, a COX-2 inhibitor, proved effective for treating HNSCC through multiple mechanisms. Celecoxib enhances the cytotoxicity of methotrexate in HNSCC.<sup>[17]</sup> The use of methotrexate in the neoadjuvant and adjuvant setting in advanced HNSCC has been well documented. However, most of these studies had used MTD modality.<sup>[4]</sup> Rentschler *et al.* randomized patients to either receive or not receive methotrexate in escalating doses. All patients received standard surgery and post-operative radiation therapy. In this study, there was no significant difference in actuarial disease-free survival (DFS) or overall survival between the groups.<sup>[18]</sup> However, Rao *et al.* effectively targeted the perioperative period. Methotrexate in a dose of 50 mg/m<sup>2</sup>/IV was given on the 3<sup>rd</sup>, 10<sup>th</sup>, and 17<sup>th</sup> post-operative days. At 24 months, the DFS for Stages III and IV HNSCC patients in the treated group was 61% as opposed to 37% in the control arm.<sup>[19]</sup> Schifeling *et al.* showed that a dose of 15 mg/m<sup>2</sup> of methotrexate saturates HNSCC tumor dihydrofolate reductase, and thus, dose escalation may have limited value.<sup>[10]</sup> A literature search yielded only one registered on-going trial assessing MSAT in HNSCC (NCT00855881); this is a prospective trial evaluating the role of maintenance MSAT in treated HNSCC where CR has been achieved.<sup>[20]</sup> Banipal RP *et al.* reported the efficacy of single-agent weekly methotrexate in symptom control and QOL improvement in patients with recurrent head and neck cancers.<sup>[21]</sup> PR was achieved in 38.8% of patients; another 39% of patients able to achieve SD. 22.2% of patients progressed while on single-agent chemotherapy. Overall 83.3% of patients have shown improvement in QOL in terms of symptomatic control. After 6 weekly treatments with injection methotrexate, 63% of patients were pain free with 16% of patients reported a decrease in pain. 87.5% of patients have shown improvement in speech and diet. Median survival with good QOL is 5.4 months. Patil *et al.*, from Tata Memorial Hospital, Mumbai, reported the effectiveness and toxicity of MC with these agents for palliative intent chemotherapy in head and neck cancers.<sup>[13]</sup> There was a CR in 2 patients (3.5%), a PR in 7 (12.3%), SD in 41 (71.9%), and progression in 6 patients (10.5%). The median progression-free survival was 153 days and overall survival was 186 days. The investigators concluded that MC is well-tolerated and has a potential role in the palliative treatment of head and neck cancer. In another study, Patil *et al.* reported the efficacy and toxicity profile of MC using oral methotrexate and celecoxib for palliation in oral cavity cancers.<sup>[13]</sup> CBR was 66.67%. The estimated median PFS was 5.2 months. The investigators concluded that the use of MC schedule might be useful in the palliative treatment of patients with advanced head and neck cancer. The toxicity noted with this schedule was minimal. In

this Phase II study, we evaluated the effectiveness and toxicity of MC with oral methotrexate and celecoxib for palliative intent chemotherapy in advanced/recurrent head and neck cancers. We observed a DCR of 76% at the end of 2 months and a CBR of 64% at the end of 6 months. We also observed a median TTP of 8 weeks. The adverse events observed in this study were minimal, mostly Grade 1 or 2 in severity. No Grade 3 or 4 adverse events observed during this study. In this study, pain control was achieved in 32 patients (64%). The control of pain in this study with metronomic is effective. The response to oral metronomic therapy significantly correlates with pain control at the end of 6 months (Statistical inference:  $X^2=17.827$ ,  $Df=4$ ,  $P=0.001<0.05$  significant). We further observed that this MC regimen significantly improved the QOL in patients with advanced/recurrent head and neck squamous cell carcinoma (Statistical inference: One-way ANOVA: QLQ-C30:  $F=309.328$ ,  $P=0.000<0.05$  significant; QLQ-H and N35:  $F=29.342$ ,  $P=0.000<0.05$  significant). In subgroup analysis, patients with PD showed significantly decreased QLQ-C30 and QLQ-H and N35 score from baseline score. The analysis of our data showed results which were consistent with previously reported Phase II trials.<sup>[13]</sup> In resource-limited countries like India, MC is an attractive option in advanced cancer patients. This oral MC with methotrexate and celecoxib in advanced/recurrent head and neck cancer is of low cost, well tolerated, easy to access strategy, and sound therapeutic efficacy in developing countries.

## CONCLUSION

The oral MC with methotrexate and celecoxib as shown to be a very feasible and convenient regimen with mild side effects and substantial efficacy in patients with advanced/recurrent head and neck squamous cell carcinoma. This oral MC regimen is effective in pain control and significantly improved the QOL in patients with advanced/recurrent head and neck squamous cell carcinoma. The regimen needs further validation in randomized controlled Phase III design in advanced/recurrent head and neck squamous cell carcinoma.

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