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Original Research Article

Effect of oral metronomic chemotherapy on quality of life in advanced or metastatic head and neck cancers

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ABSTRACT

Background: Oral Metronomic chemotherapy (OMCT) is an emerging therapeutic option in advanced/metastatic, head and neck squamous cell carcinoma (HNSCC). It is ideal for frail patients not candidates for platinum-based chemotherapy, and who have minimal response with progressive worsening of quality of life (QOL). To assess the effect of OMCT on changes in quality of life (QOL) in advanced/recurrent HNSCC patients.
Methods: Patients with advanced/metastatic recurrent HNSCC, not amenable to radical therapy were included in the study. QOL was assessed with the European organization for research and treatment of cancer (EORTC) QLQ-C30 and QLQ-H&N 35 questionnaires at enrollment and at regular follow up intervals after starting MC.
Results: Out of 54 patients, 50 % patients had grade 3 or more pain at enrolment, which improved after OMCT with only 5 % having grade 3 or more pain at 6 months. Mean QLQ-C 30 score at the time of presentation was 68.4. With oral MC, there was a steady increase in QOL score QLQ-C30; 75.35 at 2 months, 81.26 at 4 months, and 85.38 at the end of 6 months. Mean QLQ-H and N 35 score at the time of presentation was 62.50, which gradually improved with oral MC; 71.16 at 2 months, 75.43 at 4 months, and 80.69 at the end of 6 months.
Conclusions: The use of oral metronomic therapy with methotrexate, gefitinib and celecoxib significantly improved the QOL and pain control in patients with advanced/recurrent HNSCC.

Keywords: Head neck cancer, Metronomic chemotherapy, Quality of life

INTRODUCTION

Head and Neck squamous cell carcinoma (HNSCC) constitutes a major burden of cancer in Indian population especially males and contributes to significant number of cancer related deaths.[1] Despite advances in management of these tumors the survival of these patients remains dismal, and the course of disease is usually progressive with 50% of these either recurring or progressing.[2] Only a handful of these patients can be salvaged by repeat surgery or re-irradiation.[3] Until recently most of these patients with unresectable local disease or with distant spread were managed primarily by platinum based palliative chemotherapy, which had minimal responses but severe adverse effects, severely compromising the quality of life (QOL).[4] Although the introduction of monoclonal antibodies targeting EGFR and immunotherapies have changed the landscape of disease management, the response rates are still poor. The acceptance of these newer agents is still limited in low- and middle-income countries, including India because of affordability.[5,6] So there remained an unmet need to introduce drugs which are easily deliverable, lesser toxic and cost effective which have good antitumor activity without compromising QOL. Oral metronomic chemotherapy (OMCT) was explored to fulfill these

criteria. It consisted of repeated administration of low dose orally available chemotherapy drugs to maintain low concentration of drugs in blood over a prolonged period to provide maximum therapeutic effect without compromising on QOL. Low level drug concentration in the blood promotes anti-tumor immune responses along with potent antiangiogenetic effects.[7] Various drugs have been studied as OMCT including Cyclophosphamide, Etoposide and Methotrexate in many solid malignancies with varying response rates. Studies suggest overexpression of Cyclooxygenase 2 (COX-2) and Epidermal Growth Factor Receptor (EGFR) in most HNSCC promote cancer cell survival and spread. So, they are being explored as a potential target to derive the desired therapeutic benefit in combination with conventional oral chemotherapeutic agents.[8] One such widely practiced OMCT combination is of Tab. Methotrexate, Tab. Gefitinib, and Tab. Erlotinib. It is affordable and accessible with minimal toxicity. However, whether it can replace intravenous platinum-based chemotherapy in efficacy and its effect on QOL needs to be evaluated. The aim was to evaluate the role of oral metronomic chemotherapy (OMCT) in locally advanced inoperable or metastatic head and neck cancers. To determine its efficacy in terms of pain control and changes in quality of life.

METHODS

This was a single arm, prospective, non-randomized interventional study, conducted in the Department of Medical Oncology, Government Kilpauk Medical College, Chennai, India, over a period of 1 year from May 2023 to May 2024. The study was conducted after getting clearance from institutional ethics committee, Reg. no ECR/1358/Inst/TN/2020, Protocol no. 958/2023. All patients who met inclusion criteria and reported to OPD over the span of 1 year were included in study. Each patient was enrolled after getting a signed informed consent in English/ Tamil. Patients were explained the study and questionnaire in understood language and/or dialect.

Inclusion criteria

The study recruited Eastern Cooperative Group (ECOG) Performance Score 1 or 2 patients. All patients had inoperable locally advanced recurrent or metastatic HNSCC disease and were not candidates for intravenous platinum-based chemotherapy. Only compliant patients motivated for regular follow up were included in study.

Exclusion criteria

The study excluded ECOG Performance score 3 or 4 patients and those who had malignancy of salivary gland, Nasopharynx, thyroid gland or those with multiple malignancies. It also excluded patients desiring Intravenous chemotherapy, raised serum creatinine 2.0 and those who withdrew consent.

A total of Fifty-four patients were recruited over the study period. Their data were collected for sex, age, stage of disease and history of prior treatment, before starting the metronomic chemotherapy (OMCT) protocol. All recruited patients received oral metronomic chemotherapy with Tab. Methotrexate 9 mg/mt2 per oral once a week (D1, D8, D15, D22), Tab Celecoxib 200 mg twice daily, and Tab Gefitinib 250 mg once daily on OPD basis. Each patient completed the two validated questionnaires from European Organization for Research and Treatment of Cancer (EORTC) QLQ-C 30 version 3.0 and (EORTC) QLQ-H and N 35 at baseline and then at regular follow up intervals at 2,4 and 6 months 9, 10. The questionnaire consists of five “Function Scales” (physical, role, emotional, cognitive, and social), a “Global Health Scale”, and nine “Symptom Scales”. A high score for a functional scale represents a high /healthy level of functioning, a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems. An estimated average of items that contribute to the scale constitute a raw score. A linear transformation then standardizes the raw score, so that scores range from 0 to 100; where a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms. The questionnaires have been validated in various studies.[10,11]

Patients were followed up on each visit for general clinical assessment, blood investigations and clinical tumor assessment along with assessment of toxicities according to common terminology criteria for adverse events (CTCAE), version 4.0. The subjective response was assessed by symptoms and clinical examination on each visit aided with radiological assessment as and when needed.

Statistical analysis

Statistical analysis was done with SPSS Software (Version 16). To calculate the score for a scale first the average of the non- missing values was calculated which was later transformed to range score from 0 to 100 provided that the patient has completed at least half the necessary items.

RESULTS

Fifty-four patients were included in the study from May 2022. The median age of the patient with advanced/recurrent HNSCC is 44 years, ranging from 31 to 69 years [Figure 1]. The sex distribution was skewed with 43 males (80%) and only 11 females (20%). Among risk factors, the chewable form of tobacco tops the list with 40%, followed by combined smoking and alcohol smoking, and alcohol [Figure 2]. The performance status was ECOG PS 1 in 32 patients (60%) and it was PS 2 in 22 patients (40%) [Figure 3]. The most common site of HNSCC is an oral cavity (32 patients; 60%), followed by pharynx, larynx, and maxillary sinus [Figure 4]. All

patients received at least one form of previous treatment. 27 patients (50%) received chemoradiation. 17 patients (32%) treated with surgery followed by chemoradiation. 8 patients (15 %) treated with NACT followed by surgery and chemoradiation. 2 patients (3 %) received RT alone as initial treatment [Figure 5]. 32 patients (60 %) had very advanced local disease at presentation which was not amenable to any definitive therapy (stage IVB). 20 patients (36 %) had metastatic disease which progressed post radical therapy (stage IVC). 2 patients (4 %) had a resectable tumor (stage IVA) who were not willing for any form of definitive treatment [Figure 6]. 22 patients (50%) had presented with grade >3 pain; this is reduced to 11 patients (25 %) at the end of 2 months, 8 patients (15 %) at the end of 4 months. Only 3 patients were in grade >3 pain at the end of 6 months [Table 1]. Most common side effect observed in this study was anorexia (24%), followed by nausea, vomiting, mucositis, anemia, fatigue, etc. [Table 2]. Mean QLQ-C 30 score at the time of presentation was 68.4. With oral MC, there was a steady increase in QOL score QLQ-C30; 75.35 at 2 months, 81.26 at 4 months, and 85.38 at the end of 6 months. Mean QLQ-H&N 35 score at the time of presentation was 62.50. QLQ-H&N score steadily increases with oral MC; 71.16 at 2 months, 75.43 at 4 months, and 80.69 at the end of 6 months. In subgroup analysis, both QLQ-C30 and QLQ-H&N 35 significantly correlated with disease progression [Figures 7]. At the time of analysis 28 (52 %) patients had expired and median time of progression was 5 months.

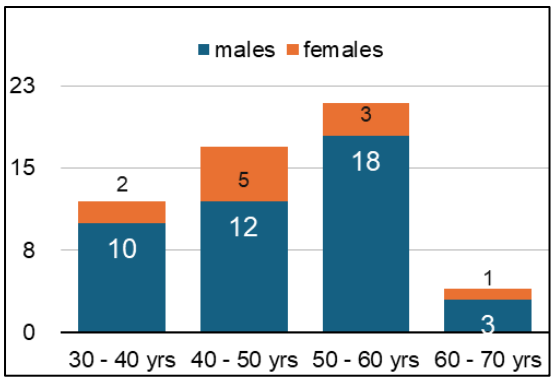

Figure 1: Distribution according to age and sex.

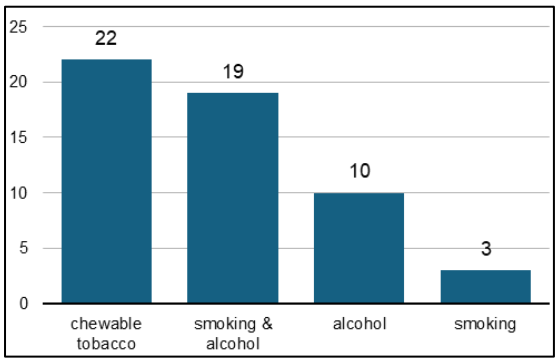

Figure 2: Distribution according to risk factors.

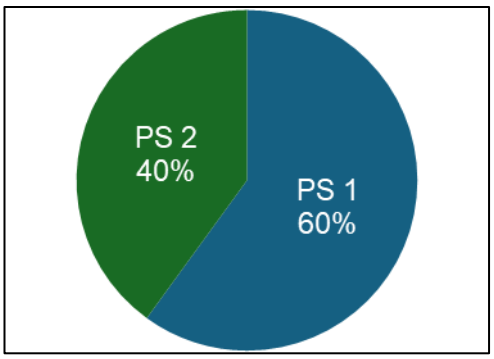

Figure 3: Performance scores.

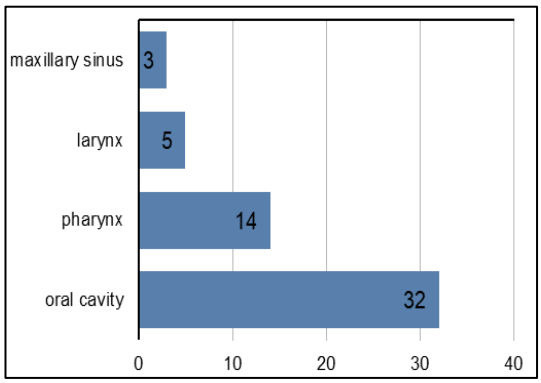

Figure 4: Subsites of head and cancers.

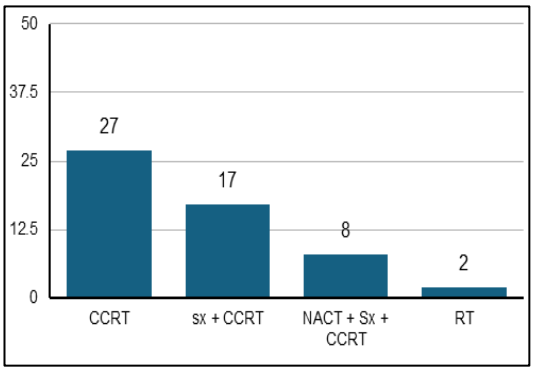

Figure 5: Distribution according to prior treatment.

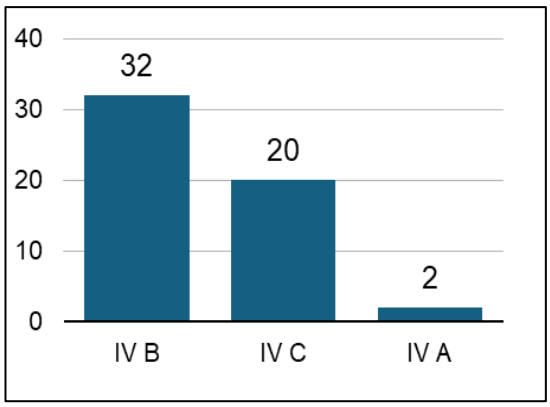

Figure 6: Stage of disease.

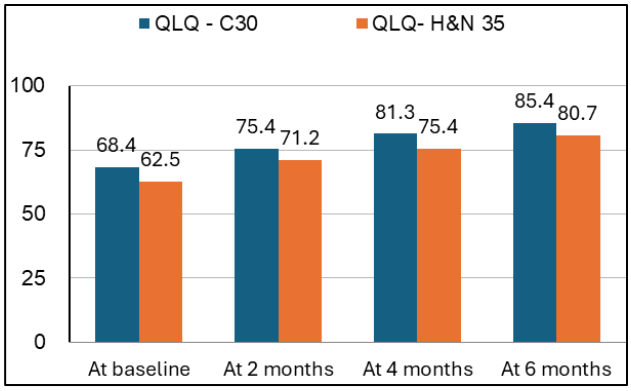

Figure 7: Quality of life scores (QOL).

Table 1: Pain score.

Pain grade	At baseline	2 months	4 months	6 months
<1	0	3 (5%)	8 (15%)	11(20%)
1-2	12 (14%)	24 (45%)	27 (50%)	32 (60%)
2-3	20 (36%)	14 (25%)	11 (20%)	8 (15%)
> 3	22 (50%)	13 (25%)	8 (15%)	3 (5%)

Table 2: Adverse effects.

Anorexia	**13 (24%)**
Nausea and vomiting	12 (22%)
Fatigue	8 (15%)
Anaemia	10 (18%)
Neutropenia	6 (11%)
Thrombocytopenia	4 (7%)
Renal dysfunction	2 (3%)
Mucositis	12 (22%)

DISCUSSION

Head and Neck Squamous Cell Carcinomas (HNSCC) represent a large burden of cancers in India particularly because of patterns of tobacco and alcohol abuse.[2] Most of these patients present in an advanced stage in whom outcomes are poorer even with multimodality therapy. These recurrent and residual HNSCC although can be challenged with salvage surgery and re-irradiation, most patients are not candidates for them either due to previous treatment sequelae or poor general condition.[3] In this setting platinum-based chemotherapy was the corner stone of palliative management in HNSCC until recently. This conventionally employed Cisplatin mostly given at maximum tolerated dose (MTD) of either 100 mg/mt2 or 75 mg/mt2 in combination with other chemotherapy drugs like 5 FU with a goal to completely eradicate tumor cells. However, these regimens were highly toxic with significant side effects like nephrotoxicity, ototoxicity and neurotoxicity. Most patients required frequent dose reduction and interruptions with eventual platinum refractory disease status.[12] So, the current standards of management have moved away from these regimens to lesser toxic and more effective therapies in recent times. Most of these tumors overexpress EGFR, which have been explored as a clinical target with good response rates. The combination of cisplatin, 5 FU along with cetuximab (monoclonal antibody targeting EGFR) in these patients have shown significant benefit in PFS and OS compared to chemotherapy alone, however the response rates in low (36%), and the regimen isn't completely safe.[13] The other option for patients is a combination immunotherapy with pembrolizumab with or without cisplatin and 5 FU.[14] The regimen in well tolerable and effective, however most Indian patients don't afford it. So, in Indian subcontinent which represent the major bulk of the HNSCC there remains a need to address this issue of affordability and accessibility and to replace the toxic palliative regimens with affordable and lesser toxic alternatives.[15,16]

To overcome this Metronomic chemotherapy was initiated at 1/3 to 1/10th of the MTD at frequent intervals and minimal dose interruptions. This concept of metronomic chemotherapy was first suggested by Douglas Hanahan et al in preclinical studies. They showed that lower doses of chemotherapy acts by inducing and maintaining angiogenic dormancy of tumor, where achieving long term symptomatic control of disease.[18] This can be further enhanced by combination of other agents which inhibit tumor growth and formation. This concept was initially suggested by Klement et al and Browder et al, on the anti-angiogenic scheduling of chemotherapeutic agents.[19] Metronomic chemotherapy is better tolerated and have lesser drug resistance. Metronomic chemotherapy act by inhibition of angiogenesis and cancer stem cells. In clinical practice, for patients with lingering toxicity from previous treatment or for those who are not fit for maximum tolerated dose (MTD) chemotherapy, such as the elderly and frail, OMCT becomes a lucrative choice. The most common drug used as oral metronomic chemotherapy in HNSCC was oral methotrexate.[20] Once it was confirmed that the expression of COX 2 enzyme is often unregulated in HNSCC which potentiates angiogenesis.

Celecoxib, a non-steroid anti-inflammatory agent with potent antiangiogenetic effects was evaluated in combination with methotrexate which showed good clinical efficacy without increased toxicity. Once the metronomic chemotherapy became a part of routine clinical practice for HNSCC the intent of disease control was replaced by global wellbeing and Quality of Life (QOL).[21] Noronha V et al, found that there was a statistically significant improvement in pain QLQ-C30 score from baseline to week three and week six in patients receiving metronomic arm with methotrexate compared with the cisplatin arm in patients with R/R HNSCCs.[22] Palan et al evaluated QOL in radically treated head and neck cancers and identified limiting toxicities by QLQ-H and N-35 scale. Most common were sexual problems, trouble with social contact, symptoms of dry mouth, problem-related to senses, difficulty in mouth

opening, and speech problems.[23] Leung et al evaluated QOL in head and neck cancer survivors post RT and observed that tooth problems, dry mouth, and sticky saliva were prominent worst symptoms.[24] Jyothi et al, evaluated QOL in head and neck cancer patients receiving cancer-specific treatments and found a positive correlation between QOL and performance status of the patients. A phase I/II data have suggested that Metronomic chemotherapy have significantly longer median, PFS and OS compared with single agent cisplatin, with fewer adverse effects in metronomic arm.[26] Further studies have demonstrated that the addition of celecoxib to methotrexate is associate with better functional outcomes and lower toxicity showing improvement in QOL over time including pain score and difficulty in deglutition.[27-30]

A phase 2 study showed that the addition of fixed dose Erlotinib (150 mg/day) to Methotrexate and celecoxib was significantly better than second line treatment in platinum refractory HNSCC. It showed that the optimal biological dose (OBD) of methotrexate can be de-escalated from 15 mg/m² to 9 mg per meter square weekly. This triple metronomic therapy is well tolerated.[31] The oral metronomic chemotherapy in HNSCC achieve, comparable control rates compare to standard systemic chemotherapy with platinum. A recent phase 3 trial suggested that the use of metronomic chemotherapy was associated with 22 % decrease in risk of death and 50 % decrease in the risk of disease progression. The median survival of patients was 7.5 months which is less than that achieved with immunotherapy and cetuximab based chemotherapy, however better than platinum-based chemotherapy. MC was well tolerated with only 20 % patients only reporting grade 3 or higher adverse reactions.[32] The burden of HNSCC is most in low- and middle-income countries like India, where the access to advanced molecules is limited. Most of these patients present in advanced stage with higher mean tumor volume, platinum refractory disease status and most of them are located in oral cavity subsite. All of them adversely affect prognosis. Although second line immunotherapy with nivolumab and pembrolizumab have shown improvement in OS, not all patients afford it. So metronomic chemotherapy is a affordable alternative for these patients. These metronomic agents are well tolerated, cost, effective less, toxic, and provides convenience of treatment at home because of enteral administration.

Limitations of this study was that it was a single arm study conducted at a tertiary health care setup in south-India. It is limited by its designs and results may not be applicable to other hospitals. The responses to questionnaires may be limited by the level of understanding and comprehension. Further studies using larger sample size and diverse demographics are required to standardize OMCT for HNSCC patients.

CONCLUSION

The use of oral metronomic therapy with methotrexate, Gefitinib and celecoxib significantly improves the QOL and improves pain control in patients with advanced/ recurrent HNSCC.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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