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Original Article

Oncology Section

Assessment of Quality of Life in Recurrent and Metastatic Head and Neck Cancer after Oral Metronomic Chemotherapy: A Prospective Interventional Study

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ABSTRACT

Introduction: Most of the Recurrent or Metastatic (R/M) Head and Neck Squamous Cell Carcinomas (HNSCC) patients are treated only by palliative treatment. Metronomic Chemotherapy (MC) low doses is an emerging therapeutic option in these patients. It exerts tumour angiogenesis, stimulate anticancer immune response, induces tumour dormancy and offers a significant improvement in Quality of Life (QoL) with minimal toxicity.

Aim: To assess the changes in QoL in patients with Metastatic, Recurrent (M/R) HNSCC receiving MC.

Materials and Methods: This was a prospective interventional hospital-based study from February 2015 to September 2018, conducted at Cancer Research Institute, Himalayan Institute of Medical Sciences, SRHU University, Dehradun, Uttarakhand, India. A total of 175 patients more than 18 years, with Eastern Cooperative Oncology Group (ECOG) performance status score <2, with M/R HNSCC, not amenable to any radical treatment, were equally distributed by lottery method in three arms, in those receiving Capecitabine (Arm A, n: 59), Celecoxib and Methotrexate (Arm B, n: 62); and placebo with best supportive care (Arm C, n: 54). In addition to demographic and baseline clinical characteristics, patients were assessed for physical examination and questioned to score their QoL by European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) at presentation and followed every month for two months.

Results: A total of 175 patients enrolled for the study, the mean age of study population was 56.73±6.84 years with male preponderance 77.71%. A 60% suffered from carcinoma oral cavity (n=105), followed by carcinoma oropharynx (24%) (n=42), carcinoma larynx and carcinoma hypopharynx consisted rest 16% (n=28). Altogether the QoL was quite divergent amongst the three arms. Symptom score for fatigue, dyspnoea, loss of appetite, nausea and vomiting showed rise representing worsening in Arm A and Arm C; whilst these symptoms also showed fall in symptom score in Arm B (fatigue: p-value=0.007; dyspnoea; p-value=0.042; Appetite loss: p-value=0.008 Nausea: p-value=0.02; Vomiting: p-value=0.03). There was a statistically significant improvement in overall EORTC QLQ-C30 score from baseline in the Methotrexate and Celecoxib arm (Arm B) compared with Capecitabine and with placebo.

Conclusion: Metronomic Chemotherapy (MC) with Methotrexate and Celecoxib seems promising and well tolerated in patients with metastatic or advanced HNSCC as compared to Capecitabine or keeping on symptomatic treatment solely.

Keywords: Carcinomas, Low dose chemotherapy, Methotrexate, Palliative

INTRODUCTION

The Head and Neck Squamous Cell Carcinomas (HNSCC) is the sixth most common cancer and eighth most common cause of cancer related deaths worldwide [1]. In developing economies as us, the patients usually present with advance disease at which the optimal treatment remains discord. Despite adequate treatment, incidence of recurrence is nearly 30-40% [2,3]. Since only a few with loco regional recurrence can be rescued by salvage surgery or re-irradiation, thus, most with R/M disease only count for palliative treatment [4]. The individual's comprehensive physical and psychosocial prospects can be best addressed by multi professional attention including the best supportive care [5].

Platinum, taxane and 5-fluorouracil injectable chemotherapies are most commonly used in head and neck cancer as palliation and induction. These injectable chemotherapies are having many side-effects especially in the palliative setting. In palliative treatment, the intention is solely to control the symptoms and improve the QoL. Palliative systemic therapy is used to treat recurrent, relapsed, or newly diagnosed head and neck cancers that are not amenable to any localised therapy upfront [4,6,7].

Palliative systemic therapy in recurrent, residual head and neck cancers are the EXTREME trial 7 regimen (cisplatin, fluorouracil, and cetuximab) and the KEYNOTE-048 trial regimen (pembrolizumab with or without cisplatin and fluorouracil) [8,9]. However, these targeted and immunotherapies are very costly, with only less than 3% of the patients afford these regimes in our country [10,11]. Intravenous chemotherapy is also very commonly used in our country. Outcome of these regimes are very poor and toxicities are quite high [7,9]. In our country, there is a need to develop a cost-effective, easily available and less toxic regime for recurrent residual head and neck cancer patients who require palliative systemic therapy.

The initiation of the "Maximum Tolerated Dose (MTD)" in routine protocols and its toxicity necessitated rest periods between cycles which involves re-growth of tumour cells, as well as growth of resistant clones [12]. To address this, "MC" was coined by Douglas Hanahan [13]. The aim of treatment is to induce and maintain tumour dormancy (angiogenic dormancy), thus leading to long-term asymptomatic control of the disease. The expression of Cyclooxygenase-2 (COX-2) enzyme is increased in head and neck cancers and it is apivotal mediator of angiogenesis [14]. Various protocol of MC for different cancers has been used. The use of low doses of methotrexate has been shown in in-vivo and in-vitro to be antiangiogenic [15]. The combination of celecoxib and methotrexate has been reported in a small study by Glück S et al.,

in chemo-resistant head and neck cancers to have good efficacy without significant toxicity [16].

Capecitabine is an oral fluoropyrimidine prodrug and it has a comparable 5 Fluorouracil (5 FU) plasma level, as that achieved with 5FU intravenous infusion and it has better safety profile [17]. In addition, oral dispensation permits flexibility and promotes patient compliance and limits the hospital stay. The usage has been considered in detail and has been accepted and recognised in breast and colorectal cancer [18] but for head and neck cancer it is still investigational. The present study also assesses the role of Capecitabine as metronomic monotherapy for recurrent and metastatic HNSSC. In this study, authors analysed and compared the changes in QoL of patients with R/M HNSCC receiving the two MC schedules and also with keeping them solely on symptomatic treatment.

The EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer QoL Questionnaire) as reported for cancer patients was a validated tool to assess QoL [20,21]. Objective of this study was to assess the QoL by using (EORTC QLQ-C30) questionnaire in three different arms of placebo (symptomatic treatment), methotrexate and capecitabine in recurrent and metastatic squamous cell carcinoma and compare their change in symptoms score to one another.

MATERIALS AND METHODS

This was a prospective interventional study, conducted from February 2015 to September 2018 in which participants were selected purposely by consecutive sampling technique, from the Outpatient Department (OPD) on a total of 175 patients at Cancer Research Institute, Himalayan Institute of Medical Sciences, SRHU University, Dehradun, Uttarakhand, India. Approval by Institutional Ethics Committee was obtained [Approval no. HIHTU/HIMS/ETHICS/2014/102]. Informed consent was taken in Hindi/English and patients were explained the study and questionnaire in the understood language and/or dialect. All the selected patients were equally distributed by lottery method in three arms, in those receiving Capecitabine (Arm A, n: 59), Celecoxib and Methotrexate (Arm B, n: 62); and placebo with best supportive care (Arm C, n: 54).

Inclusion criteria: Adult patients (above 18 years) who were planned to receive a palliative treatment for relapsed, recurrent and metastatic squamous cell carcinoma of the head and neck region and those patients who had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0-1 [19], measurable disease on examination, and normal end-organ function were included in the study.

Exclusion criteria: Patients with primary tumours in the salivary gland, thyroid, or nasopharynx and patients with uncontrolled co-morbidities, and those who opted injectable chemotherapy, targeted therapy and immunotherapy, and also those patients with serum creatinine >2 mg/dL were excluded from the study.

Sampling technique used was consecutive purposive convenience sampling. All patients underwent investigations with complete haemogram, liver function test and kidney function test prior to MC. Patients in Arm A received Tab Capecitabine 650 mg/m^2 twice daily for three weeks. Those in Arm B received weekly oral Methotrexate 15 mg/m^2 and daily oral Celecoxib 200 mg twice daily for four weeks. Those in Arm C received placebo capsules with best supportive care. Patients were assessed by physical examination and questioned to score their QoL using the EORTC QLQ-C30 at presentation and followed by every month for two months.

QoL was assessed by European Organisation for Research and Treatment of Cancer QoL Questionnaire (EORTC QLQ-C30 Version 3). The questionnaire consists of five "Function Scales" (physical, role, emotional, cognitive, and social), a "Global Health Scale", and nine "Symptom Scales". A linear transformation standardises the raw score, ranging from 0 to 100; a higher score depicts a "better" Global Health Scale and a "worse" Symptoms Scales [20,21]. In the present study, authors employed six symptom scales (namely pain, dyspnoea, nausea, vomiting, fatigue and loss of appetite). Changes observed by the patient for these symptoms were evaluated at every 1 month (corresponding to 1 cycle) interval for 2 cycles. EORTC QLQ-C30 were assessed at baseline, post 1 cycle and post 2 cycle of treatment.

Every patient was assessed for drug related toxicities. The grading for oral mucositis and palmar-plantar erythro-dysesthesia (Hand and foot syndrome) in this study was mainly based on National Cancer Institute Common Toxicity Criteria (NCI-CTC), who gave criteria as Common Terminology Criteria for Adverse Events (CTCAE) version 4 [22].

STATISTICAL ANALYSIS

The statistical analysis was done with Statistical Package for the Social Science (SPSS) version 16. Descriptive analysis was performed. Mean, percentages, and Standard Deviation (SD) were determined. Primarily intra-group comparison was done to check for the change in symptoms from presentation to subsequent visits by Wilk's lambda multivariate analysis of variance (MANOVA) and then the inter-group comparison was done by analysis of variance (ANOVA) and Post-Hoc Test with Tukey's Honestly Significant Difference test (T-HSD) amongst the three arms. All values with p-value ≤0.05 were considered significant.

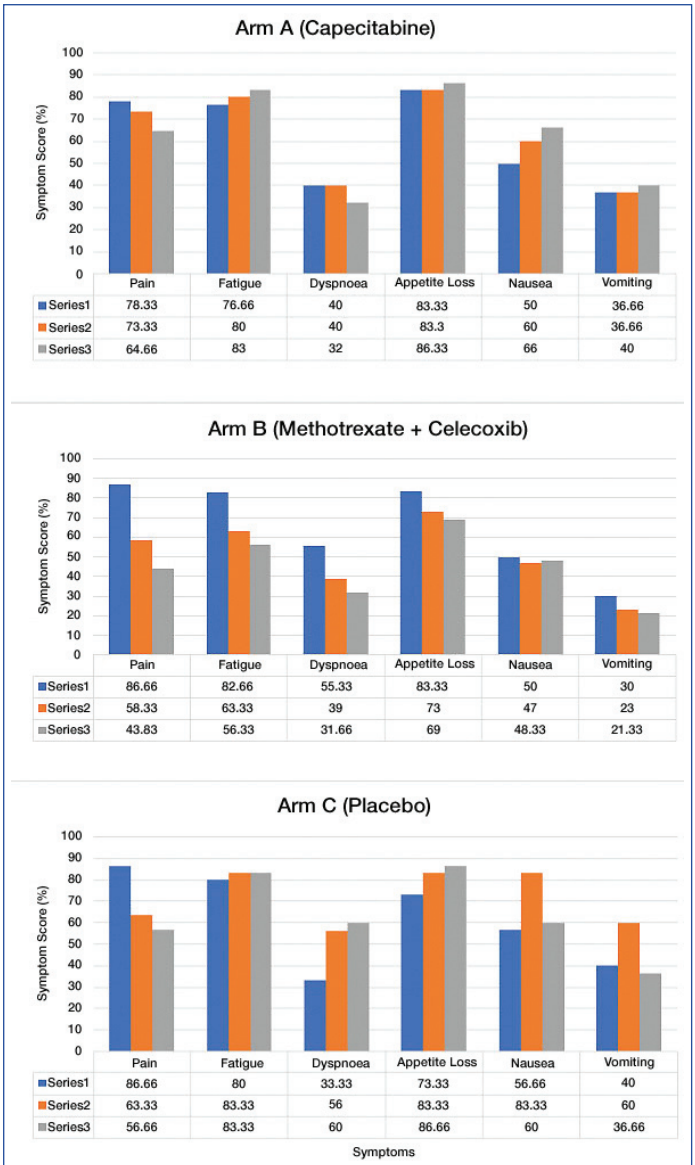
RESULTS

The study recruited 175 eligible patients. The mean age was 56.73±6.84 years. with male preponderance (77.71%, n=136). Out of 175 subjects, 60% suffered from Carcinoma oral cavity (n=105), followed by Carcinoma Oropharynx (24%) (n=42), Carcinoma Larynx and Carcinoma hypopharynx consisted rest 16% (n=28). Most patients had ECOG performance status II (22) (74.29%) (n=130). Smoking and tobacco chewing constituted 91% of the subject pool (n=159). Treatment history along with other details of patient profile are shown in [Table/Fig-1].

R/M HNSCC patients	n	%
Age Mean±(SD) years	56.73±6.84	
Gender		
Male	136	3.48
Female	39	1
WHO performance status		
ECOG PS I:	45	25.71
ECOG PS II	130	74.29
Smoking history		
Smoker	140	80
Non smoker	35	20
Site-wise distribution		
Oral cavity	105	60
Oropharynx	42	24
Larynx and hypopharynx	28	16
Previous treatment received		
Surgery alone	9	
Chemoradiotherapy alone	17	
Chemotherapy alone	3	
Neoadjuvant chemotherapy, followed by surgery	22	
Neoadjuvant chemotherapy, followed by Radiation/chemoradiation	37	
Neoadjuvant chemotherapy, followed by Surgery, followed by Radiation/chemoradiation	16	
Surgery, followed by Radiation/chemoradiation	67	
No prior treatment	4	

[Table/Fig-1]: Demographic details and clinical history of all study subjects (n=175). HNSCC: Head and neck squamous cell carcinomas; R/M: Recurrent/Metastatic; WHO: World health organisation; ECOG: Eastern cooperative oncology group; PS: Performance status

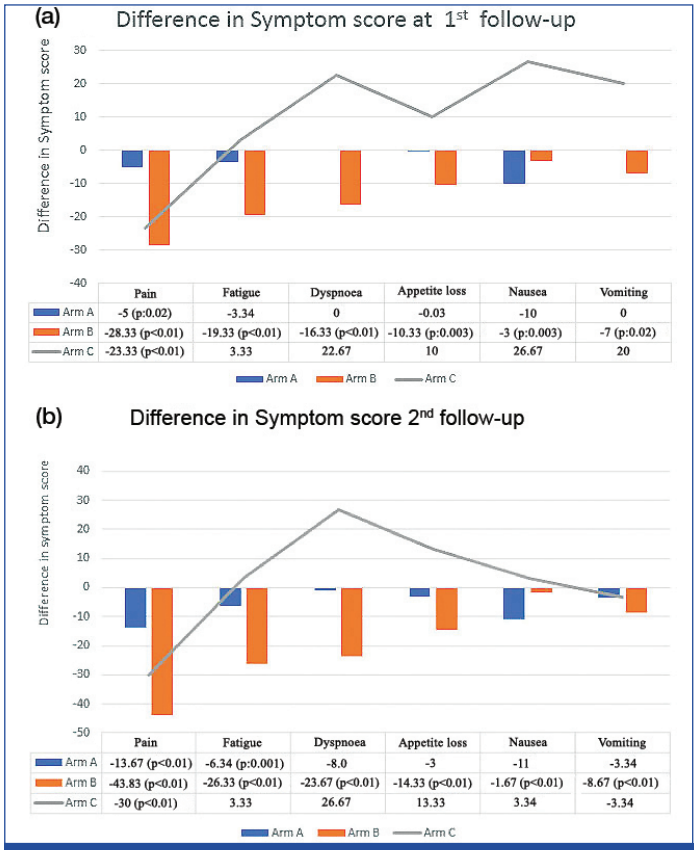
Intragroup/arm assessment is depicted in [Table/Fig-2] (Figure representing changes in symptom scores at first follow-up and second follow-up with respect to those at presentation) for Arm A, B and C individually as obtained by Wilk's lambda Multivariate Analysis of Variance (MANOVA).



[Table/Fig-2]: Intragroup comparison: Series 1: Symptoms at presentation; Series 2: Symptoms at 1st follow-up (After 1st cycle); Series 3: Symptoms at 2nd follow-up (after 2nd cycle).

There was observed decrease in symptom score for pain in all the three arms (Arm A: p-value=0.015; Arm B: p-value <0.001; Arm C: p-value <0.001). Symptom score for fatigue, dyspnoea, loss of appetite, nausea and vomiting showed rise representing worsening in Arm A and Arm C; whilst these symptoms also showed fall in symptom score in Arm B (Fatigue: p-value=0.007; Dyspnoea: p-value 0.042; Appetite loss: p-value=0.008 Nausea: p-value=0.02; Vomiting: p-value=0.03).

Inter-group assessment is depicted in [Table/Fig-3] (Figure representing significant changes in symptom score in the three arms) as made by Analysis of Variance (ANOVA) and Post-Hoc Test with Tukey's honestly significant difference test (T-HSD). There was a significant improvement in all symptoms in Arm B with significant differences in symptom score after first as well as second cycle (i.e., at first and second follow-up). All patients were compliant to the treatment protocol and reported in the Outpatient Department (OPD) in time with no loss to follow-up.



[Table/Fig-3]: Inter-group comparison: a) Difference in Symptom Score at first follow-up amongst the three arms; b) Difference in symptom score at second follow-up amongst the three arms.

Minimal toxicities were noted. Only one patient developed Grade 3 oral mucositis requiring discontinuation of MC in Arm B. The other episodes of mucositis seen were either grade 1 or grade 2 in 42 patients (24%) (Arm A: 24, Arm B: 14, Arm C: 04). Grade 3 Palmar-plantar erythrodysesthesia was seen only in one patient requiring discontinuation in Arm A. The 24 patients (13.71%) reported with grade 1 and 9 patients (5.14%) with grade 2 Hand and foot syndrome in Arm A, which were managed without halting the treatment. There was no evidence of any febrile neutropenia. The details of toxicities are shown in [Table/Fig-4].

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mucositis oral	Asymptomatic/mild; not requiring intervention	Moderate pain, not interfering with oral intake; modified diet	Severe pain, interfering oral intake	Life-threatening consequences; urgent intervention	Death
Arm A	10	14	-	-	-
Arm B	05	09	01	-	-
Arm C	-	04	-	-	-
Palmar-plantar erythrodysesthesia	Minimum skin changes or dermatitis (e.g., Erythema, oedema, hyperkeratosis) without pain	Skin changes or dermatitis (e.g., Peeling, blisters, bleeding, oedema or hyperkeratosis) without pain	Severe skin changes or dermatitis (e.g., Peeling, blisters, bleeding, oedema or hyperkeratosis) without pain, limiting self-care		
Arm A	24	09	01		
Arm B	-	-	-		
Arm C	-	-	-		

[Table/Fig-4]: Toxicities as assessed by Common Terminology Criteria for Adverse Events (CTCAE) Version 4.
(Also, mentioned are the Grades of toxicities observed in our patients during follow-up).

DISCUSSION

In modern therapeutics, health assessment of patients with malignancy is established not only on clinical or laboratory indicators but on the sequelae of therapy as well, which might indicate the change of QoL [23]. So, in oncology, global well-being forms surrogate intent apart from cure [24]. Currently, QoL has been introduced as one of the endpoints for therapy in chronic disease states and as an early indicator of progression of disease [25]. EORTC QLQ-C30 is one of the most acknowledged instruments to assess the QoL in cancer patients. Using this, the current study evaluated the changes in QoL in patients receiving MC. The present study shows that MC can be a conceded process for improvement of QoL in cancer patient.

Congruency was also drawn from various published work done with assessment of QoL in patients with MC in R/M HNSCC. Noronha V et al., found that there was a statistically significant improvement in pain QLQ-C30 score from baseline to week three (p-value=0.036) and week six (p-value=0.034) in the metronomic arm with methotrexate compared with the cisplatin arm [26].

Patil V et al., compared the Functional Assessment of Cancer Therapy (FACT H and N) and Trial Outcome Index (TOI) mean score at baseline with the mean score at two months (effect size- 0.5055, large), four months (effect size- 0.3323, medium), and six months (effect size- 0.3080, medium) which revealed improvement in these scores with MC with methotrexate and celecoxib, thus associating it with improvement in QoL and less time spent in TOX (toxicity) state [27] which is similar to the results of the present study.

The study by Kandipalli S et al., revealed that the Functional Score (FS) evaluation at the end of six months compared to baseline was statistically significant (p-value=0.004), especially for pain and difficulty in swallowing with MC [28]. Authors managed swallowing difficulty of this study patients by nasogastric tube placement.

In a work done by Patil V et al., to provide evidence-based guidance for selecting the most appropriate therapy in the current COVID-19 pandemic situation, weekly methotrexate-celecoxib seems viable to have low potential for immunosuppression and is affordable. The schedule has the added advantage of being oral further limiting hospital visits. This regimen was also associated with an improvement in Progression-Free Survival (PFS) and Overall Survival (OS) over intravenous single-agent cisplatin [29]. Although, authors have not used targeted therapy like Geftinib and Erlotinib but Parikh PM et al., showed that addition of Erlotinib to a MC schedule of methotrexate and celecoxib resulted in a promising PFS (median estimated PFS was 148 days (95% confidence interval 95.47-200.52 days) [30].

Kumar KSS, also assessed QoL by EORTC: QLQ-C30 and QLQ-H&N 35 questionnaires at 2, 4, and 6 months after starting oral metronomic. Out of 50 patients, 37 patients (74%) become pain-free at the end of six months. A decreased pain grade was observed in another 13 patients (26%). Metronomic (methotrexate and celecoxib) significantly improves the QoL and improves pain control in patients with advanced/recurrent HNSCC [31]. The QoL achieved with oral MC in the present study were positive, and showed that this treatment was effective and better tolerated. In the present study, less than 5% of patients given oral MC developed grade 3 or higher adverse events, whereas 80% of patients treated with the EXTREME trial regimen or the KEYNOTE-048 regimen 8 of pembrolizumab with cisplatin and fluorouracil developed grade 3 or higher adverse events [8,9].

In the present study, pain parameter was observed with statistical significant improvement amongst the groups with Group B (Low dose Oral Methotrexate) producing better symptomatic improvement compared to Group A with oral Capecitabine, which may be ascribed to the adverse events of the drug, despite small dosage (like neuropathies or subjective variations). Pain, dyspnoea, nausea, vomiting, fatigue and loss of appetite significantly improved in majority of patients who received MC with oral Methotrexate.

Despite the confines, this study attempts to explain the interaction between MC and its response to QoL symptom scales. The present study assessed the MC response in terms of change in QoL for the patients of surgically and medically not amenable head and neck malignancies.

Limitation(s)

Although the patients were explained the study and the subjective assessments were done in the form of questionnaire in their understood language/dialect, probability was high regarding understandability and irrelevant answers in the present study population. Other limitations were no objective assessments and heterogeneity in groups which includes disease-site, stage and grade, discordance may be present. Further inclusive analysis is required to settle the standard of MC and supportive care with QoL for the patients of R/M HNSCC which are else not amenable.

CONCLUSION(S)

A wide foray by the malignancy certainly unsettles the general well-being. The efficacy criteria frequently considered are usually deficient; if amalgamated with individual's HRQOL; it might signify an integrated approach towards the disease process. The present study exhibit that MC with Methotrexate and Celecoxib seems promising and well tolerated in patients with metastatic or advanced HNSCC as compared to Capecitabine or keeping on symptomatic treatment solely.

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