Impact of Oral Metronomic Therapy on Quality of Life in Advanced/Recurrent Head and Neck Squamous Cell Carcinoma Patients

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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 head and neck squamous cell carcinoma (HNSCC) patients. To develop rational therapeutic strategies, it is important to identify molecular targets that are linked to the pathogenesis of HNSCC.

Aim: The aim of the study was to assess the effect of oral MC on changes in quality of life (QOL) in advanced/recurrent HNSCC patients.

Materials and Methods: Patients with advanced, metastatic, and recurrent HNSCC patients who are not amenable to local treatment with surgery, radiotherapy, and chemotherapy were included in the study. QOL assessed with the European organization for research and treatment of cancer (EORTC) QLQ-C30 and QLQ-H&N 35 questionnaires.

Results: In this study, 50 patients were included, 37 patients (74%) become pain-free at the end of 6 months. A decreased pain grade was observed in another 13 patients (26%). Mean QLQ-C 30 score at the time of presentation was 68.67, 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 61.53, 72.16 at 2 months, 76.43 at 4 months, and 81.69 at the end of 6 months. In subgroup analysis, both QLQ-C30 and QLQ-H&N 35 significantly correlated with disease progression.

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

Key words: Head neck cancer, Metronomic chemotherapy, Quality of Life

INTRODUCTION

According to the International Agency for Research on Cancer, head and neck squamous cell carcinoma (HNSCC) is the 10th most common cancer worldwide. Three percent of all newly diagnosed cancers in humans are HNSCC. The incidence of HNSCC is increasing with age. HNSCC is common in Asian countries. HNSCC accounts for 9–10% of the incidence of cancer in India. HNSCC is the third commonest cancer in India. Among Indian males, HNSCC forms second leading cancer. Most of the patients with HNSCC present in an advanced stage and they frequently recur after initial therapy. Long waiting lists for treatment and poor access to tertiary cancer centers increases the burden of advanced stage HNSCC. Metronomic chemotherapy (MC) is defined as chronic, equally spaced, and low doses of chemotherapeutic drugs without extended rest periods. Metronomic chemotherapies are now called metronomic scheduling of antitumor therapy (MSAT). In this study, we evaluated the impact of oral metronomic therapy on quality of life (QOL), in patients with advanced/recurrent HNSCC, as a palliative treatment.

Aim

The aim of the study was to assess the effect of oral MC on changes in QOL in advanced/recurrent HNSCC patients.
MATERIALS AND METHODS

This study was designed to assess the QOL in advanced/recurrent HNSCC patients, who progress or recurred after earlier treatment or who have a residual tumor, who are treated with oral metronomic therapy with methotrexate and celecoxib, like the palliative treatment. In this study, we included advanced, metastatic, and recurrent HNSCC patients who are not amenable to local treatment with surgery, radiotherapy (RT), and chemotherapy. Fifty participants, while on oral metronomic therapy, completed two validated questionnaires at baseline and during regular clinical follow-up visits at 2, 4, and 6 months. Informed consent was obtained after explaining the study details, from all patients, before enrollment. The oral metronomic scheduling of anticancer therapy (MSAT) consists of oral methotrexate 15 mg/m² once a week and oral...
Statistical analysis was done with SPSS Software (Version 16). One-way analysis of variance was used to establish the significance of disease response on QOL scores, QLQ-C30 and QLQ-H&N 35.

**RESULTS**

Fifty patients were enrolled in this study, from January 2019 to June 2019. The median age of the patient with advanced/recurrent HNSCC is 45 years, ranging from 20 to 65 years [Figure 1]. The sex distribution was skewed with 43 males (86%) and only seven females (14%) with HNSCC enrolled in this study [Figure 2]. Among risk factors, the chewable form of tobacco tops the list with 44%, followed by combined smoking and alcohol [Figure 3], smoking, and alcohol. The performance status was ECOG PS 1 in 32 patients (64%) and it was PS 2 in 18 patients (36%) [Figure 4]. The most common site of HNSCC is an oral cavity (30 patients; 60%), followed by pharynx, larynx, and maxillary sinus [Figure 5]. Forty-four patients (88%) had locally advanced HNSCC, which is not amenable to any definitive therapy (stage IVB). Four patients (8%) had metastatic disease (stage IVC). Two patients (4%) had a resec
table tumor (stage IVA) who was not willing for any form of definitive treatment [Figure 6]. All patients received at least one form of previous treatment. Twenty-six (52%) patients received chemoradiation. Ten patients (20%) treated with surgery followed by chemoradiation. Another eight (16%)
patients treated with NACT followed by surgery and chemoradiation. Four patients (8%) received RT alone as initial treatment. NACT followed by surgery and RT was the initial treatment received in two patients (4%) [Figure 7]. Twenty patients (40%) of patients presented with grade >3 pain; this is reduced to five patients (10%) at the end of 2 months, two patients (4%) at the end of 4 months. None of the patients were in grade >3 pain at the end of 6 months. Thirty-seven patients (74%) become pain-free at the end of 6 months. A decreased pain grade was observed in another 13 patients (26%) [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 68.67. 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 61.53. QLQ-H&N score steadily increases with oral MC; 72.16 at 2 months, 76.43 at 4 months, and 81.69 at the end of 6 months. In subgroup analysis, both QLQ-C30 and QLQ-H&N 35 significantly correlated with disease progression [Figures 8 and 9].

**DISCUSSION**

HNSCC includes a heterogeneous group of malignant tumors, constitute about 3% of all newly diagnosed cancers in humans.[7,9] Around 90% of head and neck neoplasms are HNSCC.[1] Tobacco and alcohol, the common carcinogens associated with HNSCC.[1]

Surgery and RT are the only curative treatments for head and neck carcinomas.[1] Chemotherapy used alone in HNSCC is not curative, although it enhances the effects of RT and thus is routinely used as part of combined modality treatment in patients with stage III or IV disease.[3,10] In India, the majority of patients (two-thirds) with HNSCC presents in an advanced stage in whom the outcome is poorer even with multimodality therapy which includes surgery, radiation, and chemotherapy. [11] Hanahan et al. coined the term MC, in the year 2000.[12] The definition of MC is the administration of chemotherapy drugs at minimal doses with minimal drug-free periods, emerging as a novel form of chemotherapy utilization. In clinical practice, when considering patients with residual toxicity from previous treatment or those who may not be considered fit for maximum tolerated dose (MTD) chemotherapy, such as the elderly and frail, MC become more attractive, as toxicity associated with MSAT is minimal.[13] Lower treatment-related adverse effects observed with the use of MC. The cost of a metronomic regimen may be lower than MTD chemotherapy, as a result of fewer side-effect associated expenditures and the usage of inexpensive oral drugs such as cyclophosphamide and methotrexate.[13] Palan et al. evaluated QOL in radically treated head and neck cancers and the problematic domains identified by QLQ-H&N-35 scale were sexual problems, trouble with social contact, symptoms of dry mouth, problem-related to senses, difficulty in mouth opening, and speech problems. About 70.8% of the respondents used painkillers for their pain management.[4] Leung et al. evaluated QOL in head and neck cancer survivors after RT and observed that tooth problems, dry mouth, and sticky saliva were prominent worst symptoms.[14] 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.[15]

**CONCLUSION**

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

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How to cite this article: Kumar KSS. Impact of Oral Metronomic Therapy on Quality of Life in Advanced/Recurrent Head and Neck Squamous Cell Carcinoma Patients. Int J Sci Stud 2020;8(2):130-134.

Source of Support: Nil, Conflicts of Interest: None declared.