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Metronomic Therapy in Palliation of Oral Cancer Patients – A Home Based Approach at the End of Life

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Abstract

Introduction: Despite the development of targeted therapies for the management of oral cancer patients, the cost of treatment is a concern in middle– and low–income countries. The present study assessed the feasibility of low–cost metronomic therapy as an alternative treatment modality in patients with unresectable or inoperable oral cancers.

Methodology: The study was a prospective, single–arm study. Unresectable, inoperable, and metastatic lip and oral cavity cancers were started on metronomic therapy, a combination of oral methotrexate 15 mg/m^2 once a week and oral celecoxib 200 mg twice daily, as palliative therapy. The primary endpoint was overall survival. The secondary endpoints were a response to metronomic therapy, compliance, and toxicity.

Results: From June 2018 to May 2020, 25 patients were started on metronomic therapy. The median age was 60 years. The median overall survival was 8.8 months. At eight weeks of therapy, 11 patients (44%) had a partial response, ten patients had stable disease (40%), and four patients had progressive disease (16%). The compliance with the therapy was 100%, and one patient (4%) developed grade III toxicity.

Conclusions: Considering the resource constraints and cost limitations in low and middle–income countries, oral metronomic therapy in the form of methotrexate and celecoxib should be regarded as a suitable regimen in the palliative treatment of patients with unresectable, metastatic, or advanced, recurrent cancers.

Keywords: Metronomic therapy, Oral cancer, palliative care, methotrexate, celecoxib

Introduction

The past few decades have seen an exponential rise in targeted cancer therapies in developed countries, which has increased the patient's as well as physicians' expectations of treatment with high cure rates and minimal toxicity. However, the developing countries face the challenge of growing cancer burden and low survival due to lower socioeconomic status, inadequate health sector infrastructure, late–stage diagnosis, and lack of health insurance. The challenge oncologists face in developing countries is not just finding a cure, but also affordable cancer care for the patients. [(1)] Unconventional thinking is needed to answer the resource constraints faced. Metronomic therapy is one such approach that has been exploited in recent years to treat advanced oral cancers.

Lip and oral cavity cancers rank sixteenth in cancer detection incidence worldwide, with South–central Asia accounting for 45% of these cases. [(2)] Due to continued usage of tobacco, lack of awareness regarding the severity of the disease, and poor access to dedicated tertiary cancer centers, most of the patients present in a stage not amenable to local therapy. Palliative systemic therapy, either intravenous chemotherapy or targeted therapy, is recommended in such a scenario. However, the cost of treatment and its associated toxicity has led to a decrease in compliance in low–income and middle–income countries. A recent phase III trial has shown promising results with metronomic therapy in patients treated with palliative intent. It has paved the way for

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adopting it as a routine practice in developing countries.[3] The present study aimed to gather comprehensive data on the feasibility of using metronomic therapy in a palliative setting for oral cancer patients.

Patients and Methods

The present study is a prospective, single–arm, observational study. The study population included patients presenting to a tertiary care center in Eastern India with lip and oral cavity cancers, age more than 18 years, and histologically proven squamous cell carcinoma. Patients presenting with unresectable or inoperable cancer and metastatic cancer, either primary or recurrent, were included in the study. Clinically unresectable or inoperable cancer was defined as gross infratemporal fossa involvement, direct skull base involvement, multiple satellite nodules over the skin, prevertebral fascia involvement, carotid artery encasement, poor performance status of the patient or not suitable for surgery because of severe comorbidities. Patients receiving conventional chemotherapy or chemoradiotherapy in the previous two months were excluded from the study. Ethical approval was obtained from the Institutional Ethics Committee (T/IM–NF/Surg.Onco./18/75). Written informed consent was taken from all patients before participation. The study was conducted as per the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guideline.

Study Interventions

The metronomic therapy schedule was planned to comprise oral methotrexate 15 mg/m^2 once a week and oral celecoxib 200 mg twice daily, both before food. Response evaluation was done at eight weeks by the investigator using the clinical criteria of the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Clinical photographs of the patients were taken at every visit and reviewed to assess the response. Hematological counts were monitored every four weeks during the therapy. The toxicity of chemotherapy was graded according to the National Cancer Institute (NCI) Common Toxicity Criteria Version 5. Compliance was assessed by a review of strips of medicine consumed by the patient.

Study End Points

The primary endpoint was overall survival. The overall survival was calculated from the start of metronomic therapy to death from any cause or last date of follow–up. The secondary endpoints were a response to metronomic therapy, compliance, and toxicity. The secondary endpoints were assessed at eight weeks by clinical examination and imaging.

Results

From June 2018 to May 2020, 25 patients fulfilling the inclusion criteria were started on metronomic therapy with a palliative intent on an out–patient basis. The median age was 60 years (Range: 35 to 88 years) with a male to female ratio of 5.2:1. The baseline characteristics of the study population are depicted in Table 1. Alveobuccal was the most common site of involvement (48%), with Stage IV, the most common presentation (64%).

The median dose of methotrexate prescribed was 25 mg (Range 20– 25mg). After eight weeks of therapy, 11 patients (44%) had a partial response, ten patients had stable disease (40%), and four patients had progressive disease (16%) (Figure 1: A–F). Seventeen patients (68%) reported subjective improvements in symptoms.

Patient Characteristics – (n=25)	
Age (Mean)	61.6 years (SD: +/– 15)
Gender	
Male	21 (84%)
Female	4 (16%)
Addiction	
Tobacco chewing	25 (100%)
Smoking	7 (28%)
Comorbidities	
Hypertension	5 (20%)
Diabetes	3 (12%)
Presentation	
Primary	14 (56%)
Recurrent	11 (44%)
Sub–site Involvement	
Alveobuccal	12 (48%)
Tongue	7 (28%)
Buccal mucosa	3 (12%)
Hard palate	2 (8%)
Floor of mouth	1 (4%)
Type of Lesion	
Ulceroinvasive (UIG)	11 (44%)
Ulceroproliferative (UPG)	12 (48%)
Verrucous	2 (8%)
Skin Involvement	9 (36%)
Bone Involvement	12 (48%)
Node Positivity	15 (60%)
Stage (AJCC 8th Edition)	
I	1 (4%)
II	2 (8%)
III	6 (24%)
IV	16 (64%)

Table 1: Baseline characteristics of the study population

Figure 1: A–B: Carcinoma lower lip with partial response at 8 weeks of therapy; C–D: Carcinoma left lower gingivobuccal sulcus with clinical fixed N3 nodes – partial response at 8 weeks of therapy; E–F: Carcinoma right buccal mucosa with partial response after 8 weeks of therapy.

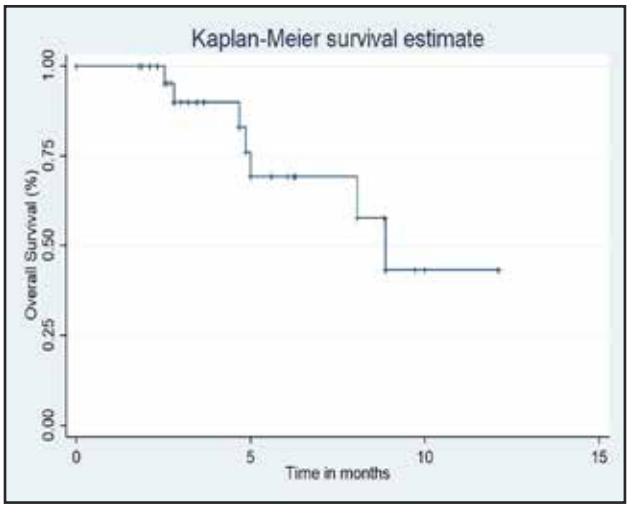

Figure 2: Kaplan–Mier survival estimate graph – Median overall survival of 8.8 months

The compliance with the therapy was 100% and was well tolerated. No dose adjustments were required. Toxicity was reported in only one patient (4%) who had hematemesis (grade III).

At a median follow–up of 4.6 months, seven patients (28%) had died. The median overall survival was 8.8 months. The Kaplan–Mier survival estimate graph is shown in Figure 2. A univariate analysis was performed using the cox proportional hazard model to analyze the influence of smoking tobacco, primary or recurrent tumor, tumor type, skin involvement, bone involvement, and node positivity on the prognosis of patients receiving metronomic therapy with a palliative intent (Table 2). Among these factors, skin involvement showed a significantly better outcome when treated with metronomic therapy in a palliative setting (p–value 0.029; HR: 6.35 with 95% CI: 1.21 – 33.3).

Factors	HR (95% CI)	p– value
Smoking tobacco	0.43 (0.07 – 2.46)	0.344
Presentation: (Primary or recurrent)	0.13 (0.01 – 1.17)	0.070
Tumor type (UIG, UPG or Verrucous)	0.93 (0.26 – 3.2)	0.914
Skin involvement	6.35 (1.21 – 33.3)	0.029
Bone involvement	1.35 (0.30 – 6.07)	0.689
Node positivity	4.03 (0.47 – 33.9)	0.199

Table 2: Univariate analysis of factors influencing prognosis

Discussion

We performed this study to assess the feasibility of using metronomic therapy as an option for palliative therapy in lip and oral cavity cancers in the Eastern Indian population. Using the metronomic therapy regimen, we observed a disease control rate of 84% (partial or stable response) after eight weeks, with a 68% subjective improvement in symptoms. Seven patients (28%) died during the follow–up period, with a median overall survival of 8.8 months.

In India, cancer of the lip and oral cavity is the second most common cause of cancer and cancer–related mortality. [2] Compared to high–income countries, the lack of cancer awareness, the social stigma of cancer, and poor access to quality affordable cancer centers account for the late diagnosis and locally advanced presentation of cancer in low to lower–middle–income countries like India. [4] At this stage, most of the patients are not amenable to curative resections and are subjected to only palliative therapy.

Systemic therapy forms the crux of treatment of unresectable or metastatic oral cavity cancers. Several regimens have been studied in this setting, including conventional cytotoxic chemotherapy, molecular targeted therapy like epithelial growth factor receptor inhibitors, or immunotherapy with PD–L1 checkpoint inhibitors. In patients with no prior exposure to systemic therapy, the KEYNOTE–048 trial established the role of pembrolizumab, with or without chemotherapy, as first–line therapy in metastatic or recurrent cancers of the head and neck due to the improvement in overall survival (Median overall survival: 13 months). [5] The phase III EXTREME trial showed an improvement in overall survival with chemotherapy plus cetuximab compared to chemotherapy alone (Median 10.1 vs 7.4 months). [6] Unlike the KEYNOTE–048 trial, thirty–nine percent of this patient population had received conventional systemic chemotherapy before the study. Based on these studies, cetuximab and pembrolizumab have become an essential component of the systemic therapy regimens for the palliative treatment of head and neck cancers.

Although targeted agents are proven to be beneficial, for a patient coming from a rural or low–income background, the foremost question that comes to mind is affordability and access to treatment. Sometimes, patients even deny treatment based on their inability to afford chemotherapy. Both cetuximab and pembrolizumab have a high cost, and their routine use in low–income countries is not practical. Metronomic therapy has emerged in recent times as an answer to this social issue due to its low cost, easy availability, and safety.

Methotrexate and celecoxib are active agents in head and neck cancers and are economical, readily available, have a well–known pharmacodynamic profile, and a good safety profile. [7,8] Metronomic therapy has been reported to activate anti–tumor immunity and also has a direct anti–cancer effect. [9] Celecoxib inhibits cell proliferation, induces apoptosis, and augments sensitivity to anti–cancer drugs. The dose of methotrexate selected was 15 mg/m^2 as it has been reported to saturate the tumor cell dihydrofolate reductase at this dose, and further augmentation of the dose will be devoid of any benefit. [10]

A Southwest Oncology Group compared single–agent methotrexate with cisplatin plus 5–fluorouracil and carboplatin plus 5–fluorouracil. The response rate was significantly better with cisplatin plus 5–fluorouracil, but the median response duration and survival times were similar in all three groups.[11] Patil et al., in a phase II study, reported significantly better progression–free survival and overall survival with oral metronomic therapy compared to single–agent platinum in a palliative setting in relapsed, metastatic and inoperable cancers of head and neck.[12] The disease control rate in our study was 84% which was higher than what has been reported earlier. This could be due to the good compliance observed in our study.

In the recently published open–label, randomized, phase III study, Patil et al. compared oral metronomic therapy (a combination of methotrexate and celecoxib) with intravenous cisplatin in patients planned to receive palliative therapy for recurrent or newly diagnosed unresectable squamous cell carcinoma of head and neck.[3] They showed a significant improvement in overall survival with metronomic therapy (7.5 vs 6.1 months; p–value 0.026) and paved the way for an alternative treatment for the palliation of head and neck cancers in developing countries like India. Our study included patients with unresectable tumors, advanced, recurrent tumors, metastatic patients, and patients who could not undergo surgical intervention due to severe comorbidities. The median overall survival was 8.8 months, similar to the outcome reported by Patil et al. in their study. The inclusion of medically inoperable patients in early–stage may be a limiting factor in the median overall survival in our study. In a subgroup analysis of clinical factors influencing the prognosis of these patients, we found that the prognosis was similar for smoking status, presentation, tumor type, bone involvement, and node positivity. Skin involvement was found to be a predictor of better prognosis in patients receiving metronomic therapy.

Conclusion

Considering the resource constraints and cost limitations in the low and middle–income countries, oral

metronomic therapy in the form of methotrexate and celecoxib should be regarded as a suitable regimen in the palliative treatment of patients with unresectable, metastatic, or advanced recurrent cancers.

Funding and Conflict of Interest

The authors have no relevant financial or non–financial interests to disclose. The authors have no conflicts of interest to declare that are relevant to the content of this article

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