DOI: 10.7860/JCDR/2023/66994.18783

Case Report

Oncology Section

Impact of Oral Metronomic Chemotherapy in Locally Advanced Carcinoma of the Laryngopharynx: A Case Report

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ABSTRACT

Oral cancer continues to be a significant health concern in Southeast Asia. The primary treatment involves surgical resection with or without reconstruction, along with adjuvant therapy. However, the survival rates for patients with stage I-II oral cancer range from 70% to 80%, whereas in more advanced stage III-IV cancers, these rates drop significantly to 40%-50%. Unresectable oral cancers are primarily managed with palliative intent, utilising systemic therapy and/or radiotherapy. Unfortunately, a substantial portion of these cases (around 60%-80%) are diagnosed at an advanced stage due to delayed diagnosis, limited access to definitive treatment, and financial constraints. These challenges underscore the critical need for therapies that can effectively halt cancer progression, promote regression, and maintain the disease in an operable state while awaiting definitive treatment, typically involving surgery. In this context, Oral Metronomic Chemotherapy (OMCT) emerges as a promising alternative. OMCT offers cost-effectiveness and involves the regular administration of chemotherapeutic drugs at low doses without interruption. The concept of "metronomic" chemotherapy draws inspiration from a metronome, which produces regular ticks representing a constant pulse. Herein, the authors presented case report of a 55-year-old male patient to compile evidence-based data on the use of OMCT in treating locally advanced carcinoma of the laryngopharynx. It explores the mechanism of action, utility, and potential future directions of OMCT. By analysing a real-world case, it seeks to highlight the effectiveness and advantages of OMCT as a treatment option for oral squamous cell carcinoma.

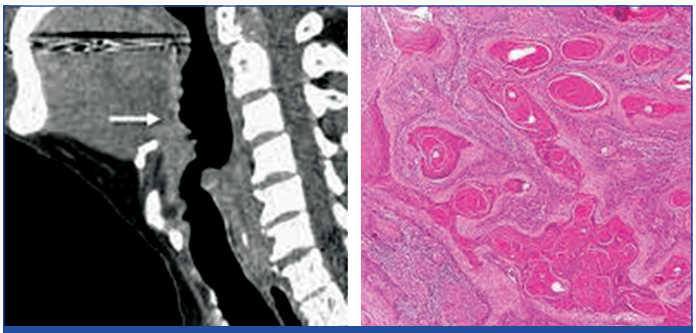
Keywords: Cyclophosphamide, Head and neck cancer, Methotrexate, Radiation oncology

CASE REPORT

The case report involves a 55-year-old male patient who presented to the OPD of Radiation Oncology with a history of hoarseness of voice for four months and painful swallowing for two months. The patient appeared thin with an Eastern Cooperative Oncology Group Physical Status (ECOG PS) of III. Oral examination revealed poor oral hygiene, normal mouth opening, nicotine-stained teeth, and an ulceroproliferative growth involving the left tonsil and the left side of the base of the tongue, crossing the midline with restricted tongue movement. Additionally, a 2.5×2.5 cm left cervical lymph node at level II was palpated.

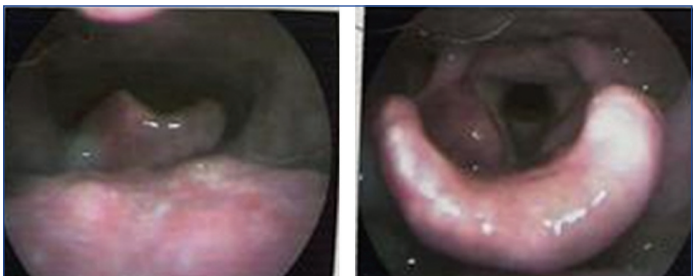
The Contrast-enhanced Computed Tomography (CECT) of the face and neck revealed a soft tissue density lesion measuring 1.9×1.9×7.6 cm involving the base of the tongue, the left side of the oral part of the pharynx, the epiglottis, the glossoepiglottic fold, the vallecula, the pyriform sinus, and the aryepiglottic fold. Several enlarged left level II cervical lymph nodes with central necrosis were also observed, the largest measuring 2.0×2.1 cm, as shown in [Table/Fig-1]. Biopsy of the oropharyngeal growth showed nests of squamous epithelial cells with abundant eosinophilic cytoplasm, large vesicular nucleus, and keratin pearls, confirming keratinising squamous cell carcinoma [Table/Fig-2]. Laryngeal endoscopy revealed an ulceroproliferative growth over the left tonsil, involving the left vallecula, the left side of the epiglottis, the left aryepiglottic fold, and the pyriform sinus.

Given the patient's poor general condition, palliative weekly chemotherapy followed by radiotherapy was initially advised. However, the patient's attendants were reluctant and preferred home-based treatment only. After a comprehensive multidisciplinary tumour board discussion, the patient was planned for OMCT, consisting of tablet methotrexate 20 mg once a week and tablet celecoxib 200 mg twice daily. The patient was asked to follow-up in the OPD after four weeks of the course of OMCT. During each follow-up, the patient underwent haematogram analysis, including



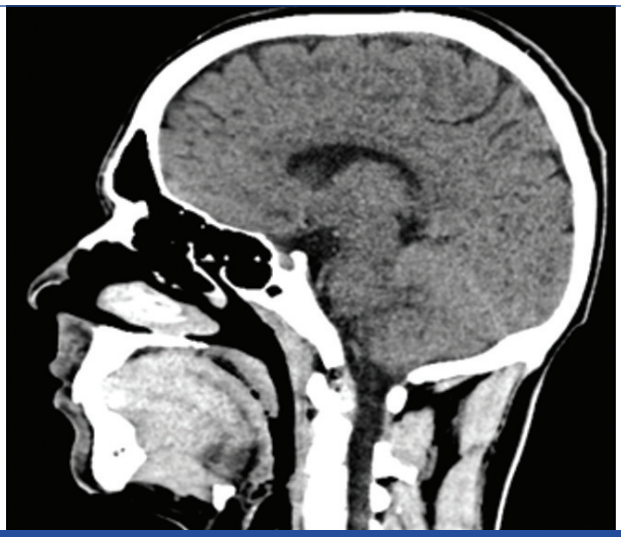
[Table/Fig-1]: Representing the Contrast-enhanced Computed Tomography (CECT) scan face and neck of 55-year-old male, showing a soft tissue lesion measuring 1.9×1.9×7.6 cm involving the base of the tongue, left-side of the oral part of the pharynx, epiglottis, glossoepiglottic fold, vallecula, pyriform sinus, and aryepiglottic fold. **[Table/Fig-2]:** Showing well differentiated squamous cell carcinoma. Tumour islands have a visible basal layer and there is prominent central keratinisation with formation of 'keratin pearls' (H&E, 10x). (Images from left to right)

Complete Blood Count (CBC), platelet counts, Total Leukocyte Count (TLC), and neutrophil counts, along with serum creatinine assessment. After three months of OMCT, laryngeal endoscopy showed a complete response with no evidence of growth [Table/Fig-3]. The patient's general condition improved significantly, no



[Table/Fig-3]: Shows laryngeal endoscopy image after three months of Oral Metronomic Chemotherapy (OMCT) with tablet methotrexate 20 mg once a week and tablet celecoxib 200 mg twice daily. The laryngeal endoscopy reveals a complete response to OMCT, with no growth seen and no evidence of malignancy.

growth was palpable on physical examination, and there were no palpable cervical lymph nodes. A follow-up CECT of the face and neck showed no evidence of disease [Table/Fig-4]. The improved general condition of the patient with no adverse effects and normal clinical examination with no growth palpable on the base of the tongue and on the tonsils, was observed [Table/Fig-5].



[Table/Fig-4]: Shows Contrast-enhanced Computed Tomography (CECT) scan face and neck of 55-year-old male, after three months of OMCT with tablet methotrexate 20 mg once a week and tablet celecoxib 200 mg twice daily. The CECT face and neck reveals a complete response to OMCT, with no evidence of malignancy.

[Table/Fig-5]: Represents the improved general condition of the patient from ECOG PS III to ECOGPS I, no adverse effects and normal clinical examination of the patient with no growth palpable in the base of tongue or on tonsils.
ECOG: Eastern cooperative oncology group; PS: Performance status

DISCUSSION

Oral cancer remains a significant health concern in Southeast Asia, affecting a diverse group of cancers in various anatomical sites within the oral cavity, each with distinct histologies [1]. While surgical resection with or without reconstruction and adjuvant therapy is the primary treatment for resectable cases, the survival rates for stage I-II oral cancer patients range between 70% and 80%. However, in more advanced stage III-IV cancers, these outcomes dramatically decline to 40%-50%. Managing unresectable oral cancers predominantly relies on palliative intent, involving systemic therapy and/or radiotherapy [2]. Head and Neck Squamous Cell Carcinoma (HNSCC) is a prevalent malignancy in Asian subcontinents, particularly in India, where it ranks as the third most common cancer, with males being more affected [3]. Unfortunately, a substantial number of these cases (approximately 60%-80%) present at an advanced stage, often due to delays in diagnosis and access to definitive treatment, exacerbated by limited tertiary cancer centres and financial burdens. These challenges underscore the critical need for therapies that can effectively halt cancer progression, promote regression, and maintain the disease in an operable state while awaiting definitive treatment, which typically involves surgery. Moreover, these therapies should be easily deliverable, safe, and cost-effective. Conventional chemotherapy, with its potential for significant toxicity and the need for rest periods between cycles, leading to tumour cell repopulation, may not be ideal for meeting these requirements.

In this context, OMCT emerges as a promising alternative that fulfills the mentioned criteria, offering cost-effectiveness and low-dose administration at regular intervals without interruption. The term “metronomic” draws inspiration from the musical device “metronomic”, producing regular short ticks representing a constant aural pulse. Similarly, metronomic chemotherapy involves the regular administration of chemotherapeutic drugs, maintaining a constant low blood level of the drug. The typical drugs used in OMCT include a daily dose of celecoxib (200 mg twice a day) and oral low-dose methotrexate (15 mg/m^2 weekly). Treatment with OMCT is typically continued until surgery in advanced cancer or until disease progression in metastatic cases, intolerable side-effects, or life-threatening complications [4].

Mechanism of action of Oral Metronomic Chemotherapy (OMCT)

One of the attractive features of OMCT is its low incidence of grade 3 and above adverse events, making it a safer option compared to single-agent intravenous cisplatin. Additionally, OMCT is cost-effective, with therapy costing less than rupees 300 per month [5]. OMCT works through multiple mechanisms, including antiangiogenesis, modulation of immune response, and induction of tumour cell inactivity. The drugs used in OMCT target angiogenic pathways, inducing hypoxia and nutrient starvation in tumour cells. It also affects tumour endothelial cells and promotes the induction of the antiangiogenic protein Thrombospondin-1, which inhibits angiogenic Hypoxia-inducible Factor (HIF)-1α and reduces circulating Vascular Endothelial Growth Factor (VEGF) levels. The immune system plays a vital role in cancer, and OMCT has shown to have an impact on immune responses. OMCT may inhibit regulatory T cells (Tregs), which are known to suppress antitumour immune responses. By inhibiting Tregs, OMCT can restore the activities of immune-specific cytotoxic T cells and Natural Killer (NK) cells, enhancing the body’s ability to fight against cancer. Overall, OMCT presents a promising therapeutic approach in head and neck cancer treatment, offering improved efficacy, reduced toxicity, and cost-effectiveness. Further research and investigation in this area hold potential for enhancing cancer immunity and optimising drug interactions in cancer therapy [6].

Oral Metronomic Chemotherapy (OMCT) Drugs

Celecoxib and methotrexate are the two main drugs utilised in OMCT. Celecoxib exerts its action as a Cyclooxygenase-2 (COX-2) inhibitor. In head and neck cancer, most malignant tumours exhibit an overexpression of COX-2. Studies suggest that COX-2 overexpression contributes to tumourigenesis and lymph node metastasis in these patients, leading to lower survival rates [7]. The abnormal COX-2/Prostaglandin E2 (PGE2) overexpression interferes with cell adhesion, including cell-cell junctions and interactions with the Extracellular Matrix (ECM). This disruption is associated with changes in E-cadherin and N-cadherin, key proteins involved in maintaining the organised structure of epithelial tissues. Prostaglandin treatment has been found to upregulate Snail and Zinc finger E-box Binding homeobox 1 (ZEB1) while downregulating E-cadherin, indicating the involvement of abnormal COX-2/PGE2 overexpression in cancer development [8].

Methotrexate, the other essential drug in OMCT, is a 4-amino 10-methyl analog of folic acid. It acts by binding to and inhibiting dihydrofolate reductase, a critical enzyme that maintains intracellular folates in their reduced form. This reduced state is crucial for nucleic acid synthesis, and its deficiency results in Deoxyribonucleic

Acid (DNA) strand breaks [9]. Methotrexate also directly inhibits folate-dependent enzymes and incorporates abnormal nucleotides into DNA, further inhibiting DNA synthesis [10]. These mechanisms contribute to the efficacy of methotrexate in OMCT for treating head and neck cancer.

The OMCT has gained attention in the treatment of HNSCC, but there is still a scarcity of studies with strong evidence supporting its use. However, OMCT has shown promise in palliative settings, recurrent, and metastatic HNSCC. In palliative chemotherapy, the addition of targeted therapy, such as cetuximab, has improved survival rates for non responders to platinum-based chemotherapy [11]. The OMCT has been studied in comparison to single-agent platinum therapy in palliative settings, and it demonstrated significantly longer progression-free survival and overall survival. OMCT has been evaluated for efficacy and toxicity in patients with advanced or recurrent HNSCC. It has shown effectiveness in terms of clinical benefit rate, pain control, and improved quality of life with minimal toxicity [11]. Factors influencing the outcome of OMCT include the time of failure and the site of primary tumour, with better results seen in patients with time to failure of over six months and in pharyngeal and laryngeal primaries. In the absence of randomised studies, OMCT has been considered a potential approach in adjuvant and neoadjuvant settings. Although there is no definitive evidence yet, studies have suggested that OMCT as a neoadjuvant therapy may prevent progression and improve disease-free survival during the waiting period before definitive surgical treatment [12].

While OMCT holds promise as a viable treatment option, further research and robust clinical trials are needed to establish its role in HNSCC treatment and to better understand its impact on different subsets of patients with varying primary tumour locations. Despite the current challenges and limitations, OMCT has shown potential in improving outcomes and quality of life for HNSCC patients, particularly in resource-constrained situations.

CONCLUSION(S)

The present report highlights the role of OMCT in treating oral cavity squamous cell carcinoma. Current studies emphasise clinical outcomes, necessitating further research on the precise role of immunity in OMCT. Biochemical interactions between OMCT drugs and the tumour microenvironment need exploration to understand the molecular pathways involved in drug-tumour cell interactions. Chemotherapeutic agents, especially cisplatin, sensitise tumour cells to radiotherapy, but it is unclear if similar interactions occur in OMCT combined with radiotherapy. Thorough exploration at the clinical and molecular levels is crucial for a comprehensive understanding.

OMCT offers a promising treatment avenue for oral squamous cell carcinoma, especially for patients unable to tolerate standard palliative chemotherapy or surgery. Its enhanced efficacy, lower toxicity, and cost-effectiveness make it a viable choice, necessitating further research through robust clinical trials. Understanding OMCT's role in head and neck cancer treatment and its impact on diverse patient subsets and primary tumour locations is essential for optimised treatment strategies and improved outcomes in this challenging condition.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 18, 2023
- Manual Googling: Sep 12, 2023
- iThenticate Software: Oct 27, 2023 (14%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Aug 16, 2023**
Date of Peer Review: **Sep 01, 2023**
Date of Acceptance: **Nov 01, 2023**
Date of Publishing: **Dec 01, 2023**