

## Metronomic Chemotherapy for Head-and-neck Cancers in Coronavirus Disease 2019 Pandemic

Sir,

By April 24, 2020, the new coronavirus disease 2019 (COVID-19) patients account for 2,718,699 cases with 190,654 deaths (<https://www.worldometers.info/coronavirus>). Billions of people across the world are under home quarantine and following the lockdown policies of their native countries necessary to contain the pandemic outbreak. This global pandemic has shown its impact in diverse ways upon different populations. Cancer patients are at high risk for becoming seriously ill from COVID-19 infection because of the compromised immune status due to cancer as well as ongoing treatment involving chemotherapy, immunotherapy, and targeted therapy.

The active cancer patient population constituted 20% of the mortality figures from COVID-19 in March 2020 in Italy.<sup>[1]</sup> Head-and-neck cancer patients and their oncologists both are susceptible to COVID-19 infection while undergoing or performing diagnostic and therapeutic procedures as these are frequently associated with aerosol generation. Given the severity of the COVID-19 global crisis, the government and health caregivers have turned their undivided attention to this disease. However, other diseases such as cancer, cardiac diseases, and chronic kidney diseases also impact human health significantly. As per the World Health Organization, there are approximately 657,000 new cases of cancers of the oral cavity and pharynx each year, with more than 330,000 deaths per year (<https://www.who.int/cancer/prevention/diagnosis-screening/oral-cancer/en/>). Most of these patients (60%–70%) in developing nations present in locally advanced stages.<sup>[2]</sup> Curative treatment modalities for these cancers include a combination of surgery, radiation, and/or chemotherapy.

The selection of appropriate treatment protocols needs triaging the patients into the surgically operable and inoperable group. Detection in the early stage by cancer screening may reduce morbidity and mortality.<sup>[3]</sup> In the pandemic period, however, the cancer screening for head-and-neck squamous cell cancer (HNSCC) should be compulsively postponed/rescheduled because of the highly contagious nature of the COVID-19 virus<sup>[4]</sup> and high viral load in the oral secretions of presymptomatic and paucisymptomatic patients.<sup>[5]</sup> Unfortunately, the treatment of premalignant, verrucous, and early-stage oral lesions must be deferred or delayed in the outbreak period.

Metronomic chemotherapy (MCT) is a relatively new treatment modality coined by Hanahan.<sup>[6]</sup> It aims at causing dormancy of angiogenesis within the tumor, leading to symptomatic relief. MCT is a low-dose chemotherapy,

being used as a substitute for conventional chemotherapy with better toxicity profile, easier use, and lower cost.<sup>[7]</sup> HNSCCs have increased cyclooxygenase (COX) enzyme expression, which helps in tumor angiogenesis and metastasis.<sup>[8,9]</sup> Methotrexate has shown a variable tumor response in HNSCC by interfering with the deoxyribonucleic acid repair process.<sup>[6]</sup> Celecoxib (200 mg twice daily), anti-COX inhibitor with methotrexate (15 mg/m<sup>2</sup> body surface area, weekly), is commonly used in MCT<sup>[10]</sup> for HNSCC.

In countries like India, where the burden of oral cancers is predominantly borne by the lower economic strata with the majority of them present with advanced-stage disease, the oral MCT may be a suitable option.<sup>[9,11]</sup> In the time of COVID-19 pandemic, the needs of daycare admission with regular follow-up for chemotherapy may present significant risks to the healthcare workers. These considerations have also led to elective surgeries being suspended by hospitals worldwide. Prolonged head-and-neck cancer surgeries performed under personal protective equipment are proving to be substantially inconvenient for the surgeons, anesthesiologists, and other assisting healthcare workers, which might adversely affect the oncological outcomes of procedures performed during the epidemic. Various guidelines have also been introduced for triaging the patients.

The result of low-dose methotrexate plus celecoxib seems beneficial as adjuvant or neoadjuvant in the curative setting for HNSCC.<sup>[10]</sup> MCT has shown promising results even in palliative settings in metastatic HNSCC patients.<sup>[8]</sup> It helps in pain relief, improves speech and food intake, and decreases the analgesic dependence. Palliation of symptoms understandably makes a significant positive impact on psychosocial performance status. Furthermore, the malignant cells of the oral cavity have an intrinsically variable response to methotrexate, which might help in the development of individualized treatment.<sup>[12]</sup>

Although MCT is a safe and effective treatment modality for preventing disease progression in HNSCC, the patients should be counseled about the possible adverse events. Follow-up with tele-consultation should be sought following the requirements of social distancing directives. The safety of patients and healthcare staff is of paramount importance. The decision of MCT should be always taken after the multidisciplinary tumor board discussion, which may be organized online. The documentation of MCT should always be rigorous. Any pandemic is a dynamic phenomenon; we should always be vigilant for the welfare of patients and healthcare workers. Simultaneously, we

must also preserve our medical resources to meet the surge of patients when the epidemic wanes and the travel restrictions are relaxed.

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### Conflicts of interest

There are no conflicts of interest.

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