

## METRONOMIC CHEMOTHERAPY: ROLE IN DEVELOPING COUNTRIES FOR HEAD AND NECK CANCER

Head and neck squamous cell carcinoma (HNSCC) is one of the countries.<sup>[1]</sup> More than half of the patients present in advanced stage.<sup>[2,3]</sup> The number of institutes providing cancer care is highly inadequate in developing countries. A cross-sectional study on head and neck cancers (HNC) showed that various beliefs ('cancer is a curse'), non-availability of transport, believing mouth ulcer to be self-limiting and prolonged treatment resulting in family stress are important factors in treatment delay.<sup>[4]</sup> Other reasons included poor socioeconomic status of the patient, cost of care and high rate of illiteracy.<sup>[5]</sup> The current pricing system of chemotherapy drugs is unsustainable and not affordable for many patients on palliative care. There is an enormous financial pressure on the society, especially in developing countries due to the skyrocketing costs.<sup>[6]</sup> In these patients, already in advanced stage of cancer, poor access to the specialized cancer centres is further compounded with increasingly long waiting lists for treatment. A prospective observational study on 201 HNC patients showed that there was a delay of 6 months from the onset of symptoms to final treatment.<sup>[7]</sup> Thus, there was a need to initiate a therapy that might inhibit progression of tumour and keep patients operable during this delay. The therapy should have minimal toxicity, economical and easy to administer which becomes very important for low- to middle-income developing Asian countries.

Metronomic chemotherapy (MC) is one such emerging therapeutic option in clinical oncology. The term 'metronomic' is derived from the musical device 'metronome' that produces an audible beat - a click or other sound - at regular intervals. In the same way, MC is the regular administration of low-dose chemotherapy ( $1/10^{\text{th}}$ – $1/3^{\text{rd}}$  of the maximum tolerated dose) that results in a constant low blood level of the drug.<sup>[8]</sup>

MC exerts its anticancer activity by inhibiting tumour angiogenesis, stimulating anticancer immune response

and inducing tumour dormancy.<sup>[8]</sup> The MC antiangiogenic effect was demonstrated by Browder (cyclophosphamide-based MC) and Klement (vinblastine-based MC).<sup>[9,10]</sup> MC also acts on the innate and adaptive immunity. It has been shown that MC selectively induced reduction of circulating regulatory T-cells and subsequent reduction of their inhibitory functions on antigen-specific immune response.<sup>[11]</sup> Tumour dormancy is mainly due to angiogenic dormancy (inability of tumour cells to recruit blood vessels), cellular dormancy (tumour cells in G0–G1 arrest) and immune surveillance (prevent residual tumour cells expansion).<sup>[8]</sup> MC has been used mainly in the palliative settings; however, it can also be tried in the adjuvant and neoadjuvant settings.

### MC in Palliative Settings

Prospective studies have shown that MC as compared to single-agent cisplatin chemotherapy, in patients with metastatic, relapsed or inoperable HNC<sup>[12,13]</sup> may be beneficial. Results showed a significant better progression-free survival (PFS) (249 days vs. 152 days,  $P = 0.02$ ) and overall survival (OS) (101 days vs. 66 days,  $P = 0.014$ ) in MC than cisplatin-based chemotherapy with better pain control. A retrospective study evaluated the role of MC maxillary sinus cancer patients on palliative treatment. It showed that the estimated median survival in patients with an event-free period after the last therapy of <6 months was 45 days, whereas it was 409 days in patients with an event-free period post last therapy >6 months ( $P = 0.063$ ).<sup>[14]</sup>

However, no head-to-head studies have been done comparing MC to the standard of care drug regimen of TPF/cetuximab in this setting. A retrospective study of 60 patients with metastatic/recurrent head and neck squamous cell cancer treated with weekly paclitaxel (80 mg/m<sup>2</sup>) and cetuximab were matched with 60 patients treated with oral MC. The median OS was 191 days in metronomic cohort and 256 days in cetuximab cohort. The hazard ratio was 0.58 in favour of cetuximab cohort ( $P = 0.031$ ).<sup>[15]</sup> However, cetuximab, being a significantly more expensive therapy, may not be feasible routinely

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in low- and middle-resource countries such as India and Pakistan. Complete remission was seen in two patients, partial remission in seven patients, stable disease in four patients, and progressive disease in two patients in a single-arm prospective observational study of 15 patients who received MC in the form of oral methotrexate (15 mg/m<sup>2</sup>/week), oral celecoxib (200 mg twice daily) and erlotinib (150 mg once daily). The median estimated PFS was 148 days. Six patients (40%) showed Grade III/IV toxicity. Thus, addition of erlotinib showed promising results in improving PFS, but proper selection of patients is essential as 40% had Grade III/IV toxicity.<sup>[16]</sup> Mateen *et al.*<sup>[17]</sup> presented their experience with MC in recurrent HNSCC. A total of 72 patients were enrolled and were prescribed oral methotrexate 2.5 mg twice in a week and capecitabine 500 mg twice a day, for at least 6 months. 2-year PFS and OS were 18% and 40%, respectively. Partial response was seen in 17 (29%) patients while 31 (54%) patients showed stable disease at 6-month follow-up. However, this is preliminary data and the complete article is yet to be published.

### MC in the Adjuvant Setting for HNC

The use of MC in the adjuvant setting is still investigational. Pandey *et al.*<sup>[18]</sup> published a retrospective study of 225 patients with locally advanced operable oral cavity carcinoma (Stage III/IVA) where adjuvant MC {oral methotrexate (15 mg/m<sup>2</sup>) once a week and celecoxib (200 mg twice a day) daily} was given in 130/225 (58%) patients after completion of the standard treatment for a duration of 18 months. The use of MC improved OS (14 months vs. 26 months,  $P = 0.04$ ) and disease-free survival (DFS) (8 months vs. 4 months,  $P = 0.22$ ). None of the patients discontinued MC due to toxicity. Lam *et al.* reported that the first prospective randomized trial in which a trend of better control of the distant metastasis was observed in the adjuvant MC (29 patients: Levamisole/uracil-tegafur [UFT] therapy) group (10% vs. 32% for the control group [34 patients]). However, 5-year disease-free actuarial survival rates for patients with and without adjuvant MC were 57% and 39%, respectively ( $P = 0.207$ ).<sup>[19]</sup> Fujii *et al.*<sup>[20]</sup> also reported that adjuvant chemotherapy with UFT was efficacious for treating maxillary sinus carcinoma. The 5-year survival was 76.2% for the UFT group and 17.9% for the control group. An on-going non-randomized Phase II study in

Taiwan (NCT00855881) will look into the effect of 1-year maintenance treatment of metronomic tegafur-uracil in HNSCC.

### MC in Neoadjuvant Setting

Studies have shown that MC strategy was associated with a reasonable response rate in neoadjuvant settings for breast cancers.<sup>[21]</sup> However, the role of MC in neoadjuvant setting for HNC is yet to be studied. A randomized controlled trial assessing addition of neoadjuvant and maintenance oral MC to standard surgery and adjuvant therapy in Stage III/IV operable oral cancers is ongoing (CTRI no. CTRI/2015/01/005405). The primary endpoint of this study is disease-free survival at 3 years. The secondary endpoint is to assess the safety, toxicity and tumour response to neoadjuvant MC.

Thus, clinical studies have shown that MC is a promising strategy in the management of locally advanced head-neck cancers. It may be especially relevant to patients in the developing countries as it is economical, easy to administer without the need for dedicated oncology setups or day-care centres. Patients with advanced head-neck cancers, especially oral cancers tend to be nutritionally deprived, cachectic and may not tolerate conventional chemotherapy easily. Treatment with MC is an attractive option in these patients who would otherwise have been deemed only for symptomatic, palliative care. Overall, in unresectable or recurrent or metastatic HNC, MC has shown good disease control rates with good quality of life outcomes. It should be considered, especially when standard chemotherapy (TPF/cetuximab) may not be feasible due to fitness, logistic or economic issues.

The role of MC in adjuvant setting has shown promising results in clinical trials and can be considered for maintenance therapy. Combination of MC with other therapies might help in improving response rates. The role of maintenance MC in patients who undergo salvage surgery also needs validation. Several clinical trials under design or in progress will clarify the best dose, schedule, optimal sequence and timing of administration. There is a number of MC regimen available which need further standardization. Nevertheless, there is no unanimous consensus for the use of one MC regimen over the other, due to the small study population studies. The role of

MC in sensitizing the tissue to radiation is also yet to be studied.

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