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

Deepa Nair, Manish Mair, Pankaj Chaturvedi,
Head and Neck Oncology, Tata Memorial Centre, Mumbai, India

Received: 3 March 2017 / Accepted: 14 March 2017

Head and neck squamous cell carcinoma (HNSCC) is one of the common cancers in South East Asian countries [1]. More than half of the patients present in advanced stage [2,3]. The number of institutes providing cancer care is highly inadequate in developing countries. A cross-sectional study on head and neck cancers 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 [4]. Other reasons included poor socio-economic status of the patient, cost of care, and high rate of illiteracy [5]. 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 [6]. 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 head and neck cancer patients, showed that there was a delay of 6 months from the onset of symptoms to final treatment [7]. 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 (1/10th–1/3rd of the maximum tolerated dose) that results in a constant low blood level of the drug [8].

MC exerts its anti-cancer activity by inhibiting tumour angiogenesis, stimulating anticancer immune response and inducing tumour dormancy [8]. The MC antiangiogenic effect was demonstrated by Browder (cyclophosphamide based MC) and Klement (vinblastine based MC)[9,10]. 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 [11]. 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) [8]. Metronomic chemotherapy has been used mainly in the palliative settings, however, it can also been 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 [12,13] may be beneficial. Results showed a significant better Progression free survival (PFS) (249 days versus 152 days, p-0.02) and Overall survival (OS) (101 days versus 66 days, p-0.014) in MC than cisplatin-based chemotherapy with better pain control. A retrospective study evaluated the role of MC in 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 above 6 months (P = 0.063)[14].

Corresponding author: Dr Deepa Nair. Head and Neck Oncology, Tata Memorial Centre, Mumbai, India
Email: drdeepanair@hotmail.com
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/m2) and cetuximab were matched with 60 patients treated with oral metronomic chemotherapy was performed. 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) [15]. However, cetuximab, being a significantly more expensive therapy may not be feasible routinely in low and middle resource countries like 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(2)/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 [16]. Mateen et al (17) 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 capcitabine 500 mg twice a day, for at least 6 months. Two-year progression free survival and overall survival were 18% and 40 % respectively. Partial response was seen in 17 (29%) patients while 31 (54%) of patients showed stable disease at six month follow up. But this is preliminary data and the complete article is yet to be published.

**MC in the adjuvant setting for Head and Neck cancers**

The use of Metronomic chemotherapy in the adjuvant setting is still investigational. Pandey et al [18] published a retrospective study of 225 patients with locally advanced operable oral cavity carcinoma (stage III/IVA) where adjuvant MC (oral methotrexate (15 mg/m2) 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 versus 26 months, p = 0.04) and disease free survival ([DFS] 8 months versus 14 months, p = 0.22). None of the patients discontinued MC due to toxicity. Lam et al. reported the first prospective randomized trial in which a trend of better control of distant metastasis was observed in the adjuvant MC (29 patients: levamisole/Uracil-tegafur (UFT) therapy) group (10 % versus 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)([19]. Masato Fujii [20] 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 one-year maintenance treatment of metronomic tegafur-uracil in HNSCC.

**MC in Neoadjuvant setting**

Studies have shown that metronomic chemotherapy strategy was associated with a reasonable response rate in neoadjuvant settings for breast cancers [21]. However, the role of MC in neoadjuvant setting for head and neck cancers is yet to be studied. A randomized controlled trial assessing addition of neoadjuvant and maintenance Oral Metronomic Chemotherapy 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 metronomic chemotherapy 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 are 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 populations studies. The role of MC in sensitizing the tissue to radiation is also yet to be studied.

References:


