Original Article

Study of Metronomic Chemotherapy in Cancer Patients at a Tertiary Care Center in South India

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Abstract

Background and Objectives: Metronomic chemotherapy is a treatment regimen which involves the administration of low-dose chemotherapy frequently with shorter drug-free intervals. In India, a majority of the patients diagnosed with cancer present to the health-care providers at an advanced stage. Moreover, they are often from the lower socioeconomic strata with limited access to health care. Metronomic chemotherapy is a convenient, minimally toxic, and economically viable treatment option whose potential should be explored. **Materials and Methods:** We retrospectively reviewed the data of 100 patients diagnosed with cancer who received metronomic chemotherapy in a tertiary cancer care center. The records of all the patients who visited the cancer care center between September 2015 and February 2017 were reviewed. Data on age, sex, address, diagnosis with staging, sequence of prior treatment received, and duration of metronomic chemotherapy, reasons for discontinuing metronomic chemotherapy, response, toxicity profile, and outcome were collected and analyzed. The statistical analysis was performed using SPSS statistics software, version 23.0. The survival analysis was done using the Kaplan–Meier survival analysis. **Results:** The mean age of patients was 53.75 years (32–92 years). About 60% were in Stage 4. With therapy, 79% improved, 16% deteriorated, and 5% were stable in their symptom profile. The mean disease progression-free survival was 232 days, while the overall survival was 310 days. **Interpretation and Conclusion:** Metronomic therapy is a feasible option in the palliative care setting. It does not require stringent monitoring, as it has a well-tolerated side effect profile when compared to conventional chemotherapy. Its utility in patients being treated with curative intent and the criteria for response assessment with low-cost imaging has to be explored.

Keywords: *Cancer, chemotherapy, metronomic*

Introduction

Ever since cancer chemotherapy was introduced, and there have been remarkable advances in the field.[1] Maximum tolerated dose (MTD) chemotherapy has been shown to achieve good remission rates in the setting of hematological malignancies but has failed to show consistent results in advanced solid tumors. Studies have shown that cancer cells sensitive to MTD chemotherapy, if not treated, proliferate at the expense of resistant clones. When such cancer populations are treated with MTD chemotherapy, the resistant cancer cell populations proliferate unchecked. Further, therapeutic strategies developed to maintain a stable tumor mass rather than aggressive therapies designed to cure may have better survival rates, i.e., control cancer rather than cure it.[2]

There has been a significant increase in the incidence of cancer and consequently in cancer-associated morbidity and mortality in India. Carcinoma of the lip and oral cavity along with lung cancer constitute the top two causes of cancer in males. Carcinoma breast and carcinoma of lip and oral cavity constitute the top two causes of cancer in females.[3]

Breast cancer is a major cause of morbidity and mortality in the female population. Inadequate access to screening programs, diagnostic aids, illiteracy, and financial constraints lead to presentation to the clinic at an advanced stage. It is important to keep circumstances in mind when formulating cancer control strategies.

Metronomic chemotherapy is defined as administration of low-dose chemotherapy at frequent intervals without prolonged drug-free periods. The aim of this therapy is to achieve sustained blood levels of the chemotherapeutic drug, without the severe toxicity profile or the prolonged drug-free breaks as seen in case of MTD chemotherapy.[4] This concept was borne

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out of pioneering studies conducted by Klement *et al*. and Browder *et al*., on the antiangiogenic scheduling of cancer chemotherapeutic agents on tumors.[5,6]

Angiogenesis is a must for cancer survival and growth. Tumor endothelial cells have been shown to proliferate at a lower rate as compared to tumor cells. Tumor models have shown that MTD drug regimens with prolonged drug-free intervals are more specific to tumor cells and have a sparing effect on tumor endothelial cells. Studies by Klement *et al*. and Browder *et al*. showed that cytotoxic drugs when administered frequently, and at low doses, affected these endothelial cells. This variation in specificity was primarily due to the shortened drug-free intervals. It was found to induce aging (senescence) in tumors by acting on caspase cascades.[5,6] Metronomic chemotherapy acts through various mechanisms which include selective inhibition of proliferation and/or induction of apoptosis of activated endothelial cells[7] and endothelial cell migration; increased induction of gene expression of thrombospondin-1, an endogenous inhibitor of angiogenesis;[8] and by causing a sustained reduction of bone marrow-derived circulating endothelial progenitor cells levels and decreased viability.

In this study, we assessed the response to metronomic chemotherapy in solid as well as hematological cancers. As there are no clearly defined criteria to assess the response to metronomic chemotherapy, we look into separate guidelines for response assessment unlike Response Evaluation Criteria in Solid Tumors which requires radiological imaging like computed tomography (CT) scan.

Materials and Methods

We did a retrospective analysis of 100 patients diagnosed with cancer who received metronomic chemotherapy in a tertiary cancer care center between September 2015 and February 2017. The study was conducted after it was approved by the institutional review board.

Patients who were at least 18 years and who had received metronomic chemotherapy for a minimum period of 3 months in neoadjuvant, maintenance adjuvant, or palliative settings were included in the study.

Patients who received metronomic therapy for a period <3 months and in patients where targeted therapy was used as the standard first line of treatment were excluded from the study.

The data collected was as follows: age, sex, address, diagnosis with staging, sequence of prior treatment received, duration of metronomic chemotherapy, reason for discontinuing metronomic chemotherapy, response, toxicity profile, and outcome. Degree of toxicity was assessed using the Common Terminology Criteria for Adverse Events, version 4.0.

The subjective response was assessed based on the patient's symptom profile and clinical examination. Objective response assessment using radiological modalities such as CT or magnetic resonance imaging was not done.

The subjective response was interpreted based on the increase or decrease in symptoms as perceived by the patient. No objective scale was used.

The main end point of the study was to assess the response to treatment based on symptoms, signs, and clinical examination.

Minor end points of the study were to calculate the disease progression-free survival and the overall survival of the patients in the curative and the palliative setting separately.

The statistical analysis was performed using SPSS statistics software, version 23.0 (IBM corporation, New York, United States of America).

The patients included in the study were broadly categorized based on intent into curative and palliative groups. The survival analysis was done for each of the subgroups using the Kaplan–Meier survival analysis.

Results

A total of 100 patients diagnosed with cancer, on metronomic chemotherapy, who had visited a tertiary cancer care center, were included in the study. The mean age of patients was 53.75 ± 11.85 years (32–92 years) with 43 males and 57 females as mentioned in Table 1. About 60% were in Stage 4 among solid tumors.

Out of the patients included in the study, 79% improved symptomatically, 16% deteriorated, and 5% were stable in their symptom profile as shown in Table 2. At the time of analysis, 58% were alive and 42% of patients had died. Of the patients in our study, 21% were being treated with curative intent, but majority (78%) with palliative intent as represented in Table 1.

In our study, 30 (30%) were found to have experienced some form of toxicity. Some commonly recorded side effects were mucositis (9%), leukopenia (6%), nausea and vomiting (4%), diarrhea (2%), rash (3%), neutropenia (4%), thrombocytopenia (3%), and hand-foot syndrome (2%) [Table 3].

The mean disease progression-free survival in all patients was 232 days (curative – 257 days, palliative – 225 days), while the overall survival in all patients was 310 days (curative – 354 days, palliative – 297 days) [Figure 1].

Discussion

Metronomic chemotherapy is a treatment option that has not been explored adequately. Although it has been in use for more than a decade, guidelines on the indications for institution of metronomic therapy and the treatment protocols to be followed are unavailable as there is a dearth of randomized clinical trials comparing its use to MTD chemotherapy. Multiple studies are now underway that aim to determine the optimum regimen, dosage, and treatment duration based on the type of malignancy.

Table 1: Patient profile

Age (years)	53.75 (32-92)	
Sex		
Male	43	
Female	57	
Site of cancer	**Stage**	**Indication for metronomic chemotherapy**
Head-and-neck Carcinoma (46)	Stage 1: 1 Stage 2: 2 Stage 3: 11 Stage 4: 9 Stage 4a: 16 Stage 4b: 5 Not available: 2	Neoadjuvant chemotherapy:[9] 4 Adjuvant: 3 Palliative: 39
Carcinoma ovary (27)	Stage 1: 3 Stage 3: 6 Stage 3c: 9 Stage 4: 9	Adjuvant: 6 Palliative: 21
Sarcoma (4)	Stage 4: 4	Palliative: 4
Hematological Carcinoma (2)	AML - Intermediate-risk AML - M2	Curative[10,11] FLT 3 ITD positive
Metastasis of unknown origin (2)	Stage 4: 2	Palliative: 2
Carcinoma Endometrium (2)	Stage 4: 2	Palliative: 2
Colorectal carcinoma (2)	Stage 4: 2	Palliative: 2
Carcinoma stomach (2)	Stage 4: 2	Palliative: 2
Carcinoma breast (13)	Stage 2a: 2 Stage 2b: 2 Stage 3a: 2 Stage 4: 6 Stage 4c: 1	Palliative: 7 Adjuvant: 6

AML: Acute myeloid leukemia, ITD: Internal tandem duplication

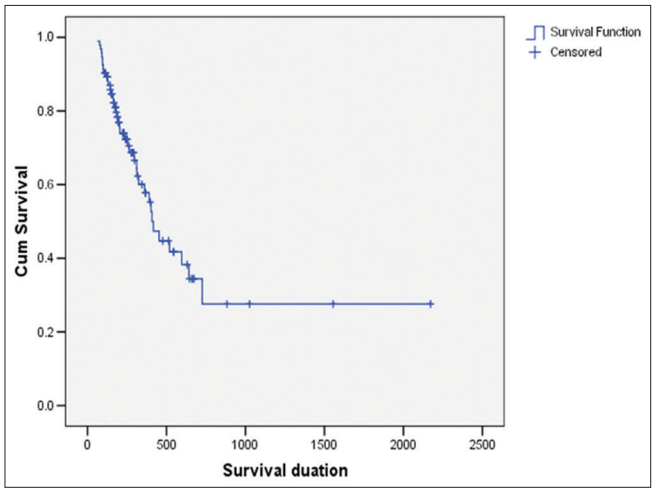

Figure 1: Survival function curve of patients in the study

Another alternative which is available to clinicians is drug repurposing, which involves the application of anticancer effects of drugs such as aspirin and metformin, which have been approved for use in other clinical settings.[12]

A Phase 2 randomized control trial compared the effectiveness of metronomic chemotherapy with single-agent MTD (Cisplatin) chemotherapy in patients with metastatic, inoperable, or relapsed squamous cell head-and-neck cancers. The group receiving metronomic chemotherapy had a significantly longer disease progression-free survival (median 101 days, 95% confidence interval [CI]: 58.2–143.7 days) as compared to MTD chemotherapy group (median 66 days, 95% CI; 55.8–76.1 days). The overall survival was also found to be significantly higher in the metronomic chemotherapy arm (median 249 days, 95% CI: 222.5–275.5 days) compared to the MTD chemotherapy arm (median 152 days, 95% CI: 104.2–199.8 days). Furthermore, there were fewer Grade 3/4 adverse effects reported in the metronomic chemotherapy group.[13] In our study as well, patients had a good survival rate, especially in palliative intent group which had survival rates comparable to conventional chemotherapy, as shown in Figure 1. The side effect profile was also well tolerated as depicted in Table 3. Although studies have questioned the efficacy of metronomic therapy in some poorly responsive cancers,[14] it has been shown to be relatively well tolerated with majority having mild side effects such as Grade 1/ Grade 2 cytopenias and Grade 1/Grade 2 nausea, vomiting, and fatigue. Although data on tolerance to metronomic chemotherapy is still limited, it has been shown to have substantial clinical benefit with minimal side effects, even in patients with advanced cancer.[15,16]

Metronomic chemotherapy is a cost-effective option as compared to MTD chemotherapy. In a comparative

Table 2: Outcomes of metronomic therapy

Site of cancer	Response	Symptomatic benefit	Reason for stoppage
Head-and-neck carcinoma (46)	Progressive disease: 10 Partial response: 18 Complete response: 0 No response: 1 Stable disease: 10 Not applicable**: 7	Better: 34 Worse: 8 Stable: 4	Disease progression: 18 Defaulted: 17 No response: 2 Expired : 3 Not applicable*: 6
Carcinoma ovary (27)	Disease progression: 5 Partial response: 8 Complete response: 1 No response: 0 Stable disease: 7 Not applicable**: 6	Better: 22 Worse: 4 Stable: 1	Disease progression: 12 Defaulted: 2 Not applicable*: 13
Sarcoma (4)	Disease progression: 2 Partial response: 1 Stable disease: 1	Better: 4	Disease progression: 2 Defaulted: 1 Not Applicable*: 1
Hematological Carcinoma (2)	Stable disease: 1 (1) Complete response: 1 (2)	Better: 2	Changed to azacytidine Not applicable *
Metastasis of unknown origin (2)	Stable: 1 (1) Disease progression: 1 (2)	Better: 2	Disease progression: 2
Carcinoma Endometrium (2)	Partial response: 1 (1) Complete response: 1 (2)	Better: 2	Adverse effect (hematuria): 1 Not applicable*: 1
Colorectal carcinoma (2)	Disease progression: 1 (1) Stable disease: 1 (2)	Better: 2	Disease progression: 1 Not applicable *: 1
Carcinoma stomach (2)	Disease progression: 1 (1) Stable disease: 1 (2)	Better: 2	Disease progression: 2

*Refers patients who are continuing with metronomic chemotherapy at the time recording of the last follow-up, **Refers to patients who were started on metronomic chemotherapy as an adjuvant

study evaluating the costs of administering metronomic chemotherapy versus conventional chemotherapy, in patients with metastatic breast cancer, it was found that low-dose metronomic chemotherapy significantly brought down the cost of treatment, especially in those receiving additional targeted therapy.[17] In our study, majority of the patients were below the poverty line and were started on oral drugs. The positives of metronomic chemotherapy include the lower cost and better compliance with treatment, especially among the patients on palliative care.

Cancer has a bearing on the physical, mental, social, and emotional health of its victims. These factors can then hamper their quality of life (Qol), especially among elderly individuals who are likely to have multiple comorbidities, making them poor candidates for surgery, chemotherapy, or radiotherapy. Metronomic chemotherapy has been found to be tolerable, effective, and to have a positive impact on Qol. In a study involving 41 elderly individuals suffering from advanced nonsmall cell lung carcinoma on metronomic chemotherapy, the progression-free survival was found to be 6 months and the overall survival 15 months without any Grade 3 or 4 toxicities. A Functional Assessment of Cancer Therapy-Lung test was used to assess the Qol at baseline and at 4 months, and it suggested a significant improvement in physical, mental, social, and emotional health of the patient, indicating Qol improvement.[18] In our study, Qol was not assessed.

Most of the literature on metronomic chemotherapy is in the setting of malignancies that have known metastases. However, its use in the adjuvant setting is also being explored, especially in triple-negative breast cancer.[19] In our study, metronomic chemotherapy was used in the adjuvant setting in triple-negative breast, ovarian, and head-and-neck cancers (in cases with risk factors for higher recurrence). However, the results were not analyzed separately as the number was small.

The limitations of our study include the fact that it was a retrospective study which may introduce a selection bias. Further, a heterogeneous group of diagnoses which when taken into analysis may interfere with the findings of the study from being generalized. In addition, we did not utilize any advanced imaging modalities to analyze the response to metronomic chemotherapy, as it was financially unviable for our patients and resorted to clinical examination, subjective changes in the symptom profile, and basic imaging modalities like chest X-ray and ultrasound.

Conclusion

The goal of metronomic chemotherapy is to provide symptomatic relief and disease control. Combined with its low costs, shorter hospital stay, and tolerable side effect profile, it is an appropriate option in economically

Table 3: Treatment regimens used

Site of cancer	Regimen	Toxicity
Head-and-neck carcinoma (46)	Injection methotrexate 50 mg weekly: 34	Mucositis: 6 Leukopenia: 3 Vomiting: 1 Diarrhea: 1 Fatigue: 1
	Tablet methotrexate 15 mg/m^2 + Tablet celecoxib 200 mg twice daily: 4	Mucositis: 2 Nausea: 1 leukopenia: 1 Constipation: 1
	3) Tablet gefitinib 250 mg once daily: 9	Skin rash: 2
	4) Tablet Methotrexate 15 mg/m^2 + Tablet endoxan 50 mg once daily (Day 1-Day 14 every 21 days): 1	Nil
	Tablet methotrexate 15 mg/m^2 + Tablet gefitinib 250 mg Once daily: 1	Diarrhoea: 1
Carcinoma ovary (27)	Tablet endoxan 50 mg once daily (Day 1-Day 14 every 21 days) + Tablet methotrexate 5 to 7.5 mg weekly once × 3 weeks + Tablet tamoxifen 20 mg twice daily × 21 days: 17	Vomiting: 2 Mucositis: 1 Neutropenia: 1 Thombocytopenia: 1 Altered taste sensation: 1
	Tablet tamoxifen 20 mg twice daily: 5	Nil
	Tablet letrozole 2.5 mg Once daily: 2	Nil
	Tablet letrozole 2.5 mg once daily+Tablet methotrexate 5 mg weekly once: 2	Nil
	Tablet endoxan 50mg (Day 1 to Day 14) every 21 days + Tablet etoposide 50 mg (Day 1-Day 14) every 21 days + Tablet tamoxifen 20 mg twice daily (Day 1-Day 21) every 21 days: 5	Neutropenia: 1
Sarcoma (4)	Tablet endoxan 50 mg (Day 1 to Day 14) every 21 days + Tablet etoposide 50 mg (Day 1-Day 14) every 21 days + Tablet tamoxifen 20 mg twice daily (Day 1-Day 21): 4	Nil
Hematological Caarcinoma (2)	6-Thioguanine 40 mg once daily (Day 1- Day 14) every 21 days + etoposide 50 mg once daily (Day 1-Day 14) every 21 days + prednisolone 20 mg once daily (Day 1- Day 21) every 21 days: 1	Nil
	Soranib 200 mg once Daily: 1	Nil
Metastasis of unknown origin (2)	Tab gefitinib 250 mg Once Daily: 1	Rash over the abdomen and Bilateral upper limbs
	Tablet capecitabine 500 mg 2-0-2 (Day 1 - Day 14) every 21 days: 1	Grade 1 HFS
Carcinoma endometrium (2)	Tablet etoposide 50 mg (Day 1 - Day 14) every 21 days + Tablet tamoxifen 20 mg twice daily (Day 1- Day 21) every 21 days	Leukopenia
	Tablet endoxan 50 mg once daily (Day 1- Day 14) every 21 days + Tablet methotrexate 5 mg weekly + Tablet tamoxifen 20 mg twice daily (Day 1- Day 21) every 21 days	Nil
	Tablet endoxan 50 mg once daily (Day 1- Day 14) every 21 days + Tablet methotrexate 5 mg weekly	Leukopenia
Colorectal carcinoma (2)	Tablet capecitabine 500 mg 2-0-2 (Day 1 - Day 14)	Grade 3 HFS
	Tablet capecitabine 500 mg 2-0-2 + Tablet metformin 500 mg once daily + Tablet aspirin 75 mg once daily	Nil
Carcinoma stomach (2)	Capecitabine 1000 mg/m^2 bd, D1-D14	Neutropenia Thrombocytopenia
	Capecitabine 1000 mg/m^2 bd, D1-D14	Nil
Carcinoma breast (13)	Tablet endoxan 50 mg once daily (Day 1- Day 14) every 21 days + Tablet methotrexate 2.5 mg once weekly: 8	Grade 3 thrombocytopenia: 2 Grade 3 neutropenia: 1
	Tablet endoxan 50 mg once daily (Day 1- Day 14) every 21 days + Tablet etoposide 50 mg (Day 1 - Day 14) every 21 days + Tablet tamoxifen 20 mg once daily (Day 1- Day 21) every 21 days: 1	Nil
	Tablet endoxan 50 mg once daily (Day 1- Day 14) every 21 days + Tablet methotrexate 5-7.5 mg weekly + Tablet tamoxifen 20 mg once daily (Day 1- Day 21) every 21 days: 4	Nil

HFS: Hand-foot syndrome

backward countries, especially in individuals with advanced cancers or in those who are poor candidates for conventional chemotherapy.

Metronomic therapy is a viable option for palliative care patients with fewer side effects and lower cost. The utility of metronomic chemotherapy in patients being treated with

curative intent and the criteria for response assessment with low-cost imaging has to be explored.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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