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# A STUDY ON ADHERENCE PATTERNS, TOXICITIES AND QUALITY OF LIFE OF PATIENTS WITH PROGRESSIVE ADULT MALIGNANCIES ON METRONOMIC CHEMOTHERAPY

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## ABSTRACT

**Objective:** This study was conducted to assess the medication adherence patterns, toxicities and the quality of life of the patients with progressive solid malignancies, receiving metronomic chemotherapy.

**Materials and Methods:** 51 patients of either sex, aged above 18 years, attending the medical oncology unit of a tertiary care teaching hospital were included and data on demographics and cancer chemotherapy was obtained. The overall adherence towards chemotherapy was assessed by 8 itemed Morisky adherence scale, patients' propensity towards adherence was determined by Merck`s Adherence Estimator, quality of life of patients was assessed by European Organization for Research and Treatment of Cancer QLQ-30 and toxicities through Common Toxicity Criteria rating scale.

**Results:** The study identified haematological side effects (25.4%) like neutropenia, anemia and thrombocytopenia as grade-3 and grade-4 toxicities. All other toxicities were of grade-1 and grade-2 type. According to morisky adherence scale 88.2% patients showed medium adherence. By Merck's adherence estimator 55% had a high risk for non-adherence due to sentimental reasons and financial burden of the chemotherapy.

**Conclusion:** Metronomic chemotherapy had less severe ADRs and the requirement for the administration of intravenous drugs was minimized which benefits the patients who are often too sick to travel frequently to the hospitals.

**Key words:** chemotherapy, metronomic, toxicities, adherence, quality of life

## INTRODUCTION

"Metronomic" chemotherapy was coined by Douglas Hanahan as a new modality of drug administration for cancer.[1] The aim of the metronomic therapy is to induce and maintain tumour dormancy (angiogenic dormancy), leading to long term asymptomatic control of the disease. Metronomic chemotherapy (MCT) is defined as chronic administration of comparatively low doses of cytotoxic drugs with no prolonged drug- free interruptions at close, regular intervals. It minimizes resultant need for supportive care treatment and host toxic side effects. It is not always dose-intense i.e., not necessarily designed with the intension of substantially increasing cumulative drug- dose over time; however this is a form of dose- dense chemotherapy.[2]

The metronomic chemotherapy has significant advantages which differ substantially from the traditional paradigm of pulsed administration of the maximum tolerated dose at fixed intervals of chemotherapeutic drugs. MCT shifts the therapeutic

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target from the tumour cells to the tumour vasculature and overcomes drug resistance. Better than standard chemotherapy (SCT), MCT counteracts tumour regrowth due to neoangiogensis and revascularization that may occur between cycles of chemotherapy and is thought to be able to overcome acquired tumour resistance to chemotherapy. Such an effect may be mediated through a cytotoxic effect on endothelial cells using drug doses that have very little or no effect on cancer cells. Selective inhibition of endothelial cell migration, increase in the endogenous angiogenesis inhibitor thrombospondin- 1 expression level, selective inhibition of proliferation and/or induction of apoptosis of activated endothelial cells and a sustained decrease in levels and viability of bone marrow- derived endothelial progenitor cells are the mechanisms of anti-angiogenic activity of the MCT.[3-5] Clinical trials have indicated that MCT shows a significantly more favourable toxicity profile than SCT, with virtually no break three or four adverse events. High grade toxic effects were either rare or not found. Furthermore, MCT is usually thought to improve quality of life and patient compliance through reduced hospitalization and no intravenous drug administration.

The only available anti-neoplastic drugs which can be administered orally or limited to: Cyclophosphamide, Capecitabine/Leucovorin, Etoposide, Thalidomide, Methotrexate, Temozolomide, Dexamethazone, Chlorambucil, Busulfan, 6-mercatopurine, procarbacin, idarubicin, topotecan. The use of some of these drugs is limited because not all are available in such low doses as it would be necessary for daily (Metronomic) treatment, since they were classically defined as MTD and were developed for oral CHT treatments.[2]

## METHODOLOGY

A prospective study was conducted in patients of either sex, aged above 18 years, attending the medical oncology unit of a tertiary care teaching hospital with progressive solid malignancies and treated with metronomic chemotherapy after obtaining their consent of the study patients and the approval of the Institutional Ethics Committee. Patients with metastatic, relapsed, recurrent, progressive, advanced solid tumors, those at high risk for relapse, advanced cancers, not in remission solid tumors receiving metronomic chemotherapy during the course of their disease were included for the study. Patients receiving both conventional and oral chemotherapy, patients diagnosed with other than solid tumors and paediatric population were excluded.

Patients with different types of progressive solid tumours were categorized into 6 groups based on the metronomic chemotherapy regimen they were receiving. Group I were patients with gynecological (ovarian and cervical cancer) receiving tablets Endoxan and Topotecan. Group II were patients with Head and neck cancer (cheek & tongue) receiving tablets Methotrexate, Cyclophosphamide Etoposide and Geftinib. Group III were patients diagnosed with (gastro intestinal cancers) pancreatic, colorectal, stomach, duodenum and gall bladder cancer receiving tablets Luporal, Leucovorin, Etoposide and Endoxan. Group IV were patients with breast and other types of cancers receiving tablets Capecitabine, Cyclophosphamide and Etoposide. Group V were the patients with lung cancer receiving tablets Capecitabine, Etoposide, Endoxan and Erlotinib. Group VI were the patients with Hepato cellular cancers receiving tablets Sorafenib and Capecitabine.

Data collection was done by direct medication history interview of the patients and also from the case records of the patients. The data obtained were documented in a specially designed proforma for the study. Data collected included patient demographics (age, sex, body weight and body surface area), type and stage of cancer, cancer chemotherapy cycle, co-prescribed drugs, co-morbidities, surgical and radiotherapy details, complications of chemotherapeutic drugs prescribed in metronomic doses and also the co-prescribed drugs, follow up status of the patients. Patients were then subjected to the following assessment parameters.

Overall Adherence was assessed by 8 itemed Morisky adherence scale,[6] patients propensity towards adherence was determined by Merck`s Adherence Estimator[7] and Quality of life of patients by European Organization for Research and Treatment of Cancer Q.L.Q-30 (EORTCQLQ-30) [8] and toxicities through Common Toxicity Criteria rating scale.[9] All the questionnaires were used after obtaining approval from the concerned authors.

### Assessment of Overall Medication adherence:

Patients' Adherence to overall medications was measured using the 8-item "Morisky Medication Adherence Questionnaire". The Morisky is a self-report measure of adherence that has good internal

validity. Each of the 8 items assesses specific medication-taking behaviours such as forgetting medications (also when travelling), stopping medications when one perceives one's medical condition to be under good control or stopping medications without Physicians knowledge when ones medical condition has worsened. The responses for question 1 to question 7 were scaled as "Yes (1), No (0)". Question 8 denoting Difficulty in remembering to take all the medications was graded on 5 point scale ranging from "Never/Rarely(0)", "Once in a while(1)", "Sometimes(1)", "Usually(1)", "All of the time(1)". Summary of the scores on the questionnaire was used to classify patients into low adherence groups.

### Assessment of propensity to adherence:

The questions related to medication adherence were preceded by three Merck Adherence Estimator sentimental statements. Statement 1 was: 1. "I worry that my Prescription medication will do more harm than good." The responses obtained for this statement were classified as "Agree Completely(14)", "Agree Mostly(14)", "Agree Somewhat(4)", "Disagree Somewhat(4)", "Disagree Mostly(0)", "Disagree Completely(0)" and each response were scored as mentioned above. Statement 2 was: "I am convinced of the importance of my prescription medication." The final statement was: "I feel financially burdened by my out-of-pocket expenses for my prescription medication." The responses for the second and third statements were same as the first statement but the scores were different.

### Assessment of Quality of Life:

Quality of life (QOL) of the patients on metronomic chemotherapy was assessed using EORTC Q.L.Q -30 questionnaire, which consists of 30 questions of which questions 1 to 5 were related to physical, questions 6 & 7 were related to role and the responses for physical and role were scaled as YES(2) or NO(1); Questions 8 to 19 were related to any side-effects to the chemotherapy such as Dyspnoea, Pain, Fatigue, Insomnia, Appetite Loss, Nausea and Vomiting, Constipation and Diarrhea; Questions 20 and 25 were to cognitive, questions 21 to 24 were related to emotional, question 26 & 27 were related to social and question 28 was related to financial difficulties of the patient. All the above mentioned questions were scaled based on responses categorized and scored as "not at all(1)", "a little(2)"," quite at bit(3)", " very much(4)"; Question 29 denoting physical condition and Question 30 denoting the quality of life of the patient during the past week were graded on 7 point scale ranging from "Very Poor(1)", "Poor(2)", "Below average(3)", "Average(4)", "Good(5)", "Very good(6)", "Excellent (7)".

### Assessment of Toxicities:

Toxicities to chemotherapy in study subjects were assessed using "Common toxicity Criteria" (CTC) for cancer chemotherapeutic drugs. CTC are a set of criteria for the standardized classification of adverse effects of drugs used in cancer therapy, which has a range of grades from 1 to 5. The values or descriptive comment for each level may vary according to specific conditions and symptoms , but the general guideline is: 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life-threatening, 5 – Death. The scores obtained from the assessment scales for patients in study subjects' were evaluated using suitable statistical methods and the results were tabulated.

### Statistical analysis:

The data obtained were analyzed by SPSS 16.0 version and the demographic data of the study population were expressed as descriptive statistics. The association between the toxicities of the study population and their metronomic chemotherapy regimen, the adherence scores and the metronomic chemotherapy regimen and the association between quality of life of the patients and metronomic chemotherapy regimen were assessed by Pearson's chi-square test. A P value of ≤ 0.05 was considered to be statistically significant.

## RESULTS

Of the 51 patients included in the study, 19(37.25%) were males and 32(62.75%) were females. The age range of the study population was

**Table 1: Age Vs. Sex distribution of the study population**

| Age range (years) | Number of Patients (N=51) | | | | Total | |
|---|---|---|---|---|---|---|
| | Males | | Females | | | |
| | N | % | n | % | N | % |
| 21-40 | 1 | 1.96 | 7 | 13.72 | 8 | 15.68 |
| 41-50 | 2 | 3.92 | 12 | 23.50 | 14 | 27.42 |
| 51-60 | 5 | 9.80 | 10 | 19.6 | 15 | 29.40 |
| > 60 | 11 | 21.5 | 3 | 5.8 | 14 | 27.30 |

between 25 years to 84 years (mean age 53.5 ± 12.3 years). The age and sex distribution of the study population is depicted in table 1.

**Table 2 :Toxicities of the study population**

| Toxicities | Severity of Toxicity | Number of patients(n=51) | | | | | | Total n=51 |
|---|---|---|---|---|---|---|---|---|
| | | Group-I (gynaeco-logical) (n=11) | Group-II (head & neck) (n=3) | Group-III (gastroin-testinal) (n=14) | Group-IV (breast & others) (n=16) | Group-V (lung) (n=4) | Group-VI (hepato-cellular) (n=3) | |
| Neutropenia | Grade-3 | 4 | 1 | 3 | 3 | 1 | 1 | 13 |
| Anemia | Grade-3 | 3 | 1 | 3 | 3 | 1 | 1 | 13 |
| Thrombocytopenia | Grade-3 | 4 | 1 | 3 | 3 | 1 | 1 | 13 |
| Hand & foot syndrome | Grade-1 | 0 | 0 | 1 | 1 | 0 | 1 | 2<br>3 |
| Mucositis | Grade-1 | 0 | 0 | 1 | 0 | 0 | 1 | 2 |
| Fever | Grade-1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Dyspnoea | Grade-1 | 0 | 0 | 0 | 2 | 0 | 1 | 8 |
| | Grade-2 | 1 | 0 | 0 | 2 | 0 | 2 | |
| Fatigue | Grade-1 | 4 | 2 | 4 | 4 | 1 | 2 | 24 |
| | Grade-2 | 3 | 0 | 1 | 3 | 0 | 0 | |
| Pain | Grade-1 | 2 | 0 | 0 | 0 | 0 | 0 | 9 |
| | Grade-2 | 2 | 0 | 1 | 3 | 0 | 1 | |
| Anorexia | Grade-1 | 3 | 1 | 1 | 3 | 0 | 1 | 13 |
| | Grade-2 | 3 | 0 | 2 | 3 | 0 | 1 | |
| Nausea | Grade-1 | 1 | 1 | 3 | 1 | 0 | 1 | 18 |
| | Grade-2 | 5 | 0 | 1 | 3 | 2 | 0 | |
| Vomiting | Grade-1 | 0 | 1 | 2 | 1 | 1 | 1 | 15 |
| | Grade-2 | 4 | 0 | 1 | 3 | 1 | 0 | |
| Constipation | Grade-1 | 1 | 0 | 0 | 2 | 0 | 0 | 4 |
| | Grade-2 | 0 | 0 | 1 | 0 | 0 | 0 | |
| Diarrhoea | Grade-1 | 2 | 0 | 0 | 1 | 0 | 0 | 5 |
| | Grade-2 | 1 | 0 | 0 | 1 | 0 | 0 | |
| Dryness | Grade-1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Edema | Grade-2 | 1 | 0 | 1 | 1 | 0 | 0 | |

Table- 2 depicts the toxicity grades of the study population based on Common Toxicity Criteria guidelines. Of the total 51 patients, 13 patients reported to have Grade-III **neutropenia**, which included 4 patients from Group-I, 1 patient from Group-II, 3 patients from Group-III, 3 patients from Group-IV, 1 patient from Group-V and 1 patient from Group-VI. Grade –III Neutropenia was found to be equally experienced by all the group of patients irrespective of the chemotherapy drug regimen. There were 13 patients who experienced **anaemia,** of which 12 had Grade-III anaemia which includes 3 patients from Group-I, 1 patient from Group-II, 3 patients from Group-III, 3 patients from Group-IV,1 patient from Group –V, 1 patient from Group-VI; and 1patient from Group-I had Grade-IV anaemia. Grade-III **Thrombocytopenia** occurred in 13 patients**,** of which 4 patients were from Group-I, 1 patient was from Group-II, 3 patients were from Group-III, 3 patients were from Group-IV, 1 patient was from Group-V and 1 patient was from Group-VI. Other toxicities observed in the study population like dyspnoea, fatigue, nausea, vomiting, diarrhoea, constipation, Hand and Foot syndrome, pain, mucositis, dryness and edema etc. were of Grade I and Grade II type and were described in Table 5. All the toxicities were observed in all the patients irrespective of their metronomic drug regimen.

### Morisky`s adherence scale:

**Table 3 :Morisky Adherence Score of the study population**

| Category | Number of patients (n=51) | | | Total | P |
|---|---|---|---|---|---|
| | Low score | Medi-um Score | High score | | |
| GROUP-I (gyneco-logical) | 0 | 10 | 1 | 11 | 0.257 |
| GROUP-II (head & neck) | 0 | 3 | 0 | 3 | |
| GROUP-III (gastro intestinal) | 1 | 13 | 0 | 14 | |
| GROUP-IV (breast & others) | 2 | 14 | 0 | 16 | |
| GROUP-V (lung) | 1 | 3 | 0 | 4 | |
| GROUP-VI (hepato-cellular) | 0 | 2 | 1 | 3 | |
| TOTAL | 4 | 45 | 2 | 51 | |

*A P value of ≤ 0.05 is considered statistically significant

Table-3 depicts the adherence scores of the study population based on Morisky adherence scale. Of 11(21.6%) patients in group-I, 10(19.6%) patients have scored for medium adherence and 1(2%) had scored for high adherence. Of 3(5.9%) patients in group-II, 3(5.9%) have scored for medium adherence. Of 14(27.5%) patients in group-III, 1(2%) patient had scored for low adherence, 13 (25.5%) have scored for medium adherence. Of 16(31.4%) patients in group-IV, 2(3.9%) have scored for low adherence and 14(27.5%) have scored for medium adherence. Of 4(7.8%) patients in group-V, 1(2%) had scored for low adherence and 3(5.9%) patients have scored for medium adherence. Of 3(5.9%) patients in group-VI, 2(3.9%) patients have scored for medium adherence and 1(2%) patient had scored for high adherence. Totally among 51 patients in the study, 4(7.8%) patients have scored for low adherence, 45(88.2%) patients have scored for medium adherence and 2(3.9%) patients have scored for high adherence. Majority of the patients in all the six groups had a score for medium adherence. There was no statistically significant association (P= 0.257) between the patients in six groups on different metronomic chemotherapy regimen with respect to adherence scores.

### Merck`s adherence estimator:

**Table 4 : Merck's Adherence Estimator Scores of the Study Population**

| Category | Number of patients (n=51) | | | Total | P |
|---|---|---|---|---|---|
| | Low score | Medi-um Score | High score | | |
| GROUP-I (gyneco-logical) | 3 | 2 | 6 | 11 | 0.853 |
| GROUP-II (head & neck) | 1 | 1 | 1 | 3 | |
| GROUP-III (gastro intestinal) | 3 | 4 | 7 | 14 | |
| GROUP-IV (breast & others) | 3 | 4 | 9 | 16 | |
| GROUP-V (lung) | 0 | 2 | 2 | 4 | |
| GROUP-VI (hepato-cellular) | 0 | 0 | 3 | 3 | |
| TOTAL | 10 | 13 | 28 | 51 | |

*A P value of ≤ 0.05 is considered statistically significant

Table-4 depicts the adherence estimator score of the study population based on Merck`s adherence estimator scale. Of 11 (21.6%) patients in group-I, 3 (5.9%) patients have scored a low risk for adherence, 2 (3.9%) have scored medium risk for adherence and 6 (11.8%) have scored high risk for adherence. Of 3 (5.9%) patients in group-II, 1 (2%) had scored low risk for adherence, 1(2%) patient had scored medium risk for adherence and 1 (2%) had scored high risk for adherence. Of 14 (27.5%) patients in group-III, 3 (5.9%) patient have scored low risk for adherence, 4 (7.8%) have scored medium risk for adherence and 7 (13.7%) patients have scored high risk for adherence. Of 16 (31.4%) patients in group-IV, 3 (5.9%) have scored low risk for adherence, 4 (7.8%) had scored medium risk for adherence and 9 (17.6%) patients had scored high risk for adherence. Of 4 (7.8%) patients in group-V, 2 (3.9%) have scored

**Table 5: QOL of the study population**

| QOL indicators | | Number of patients(N=51) | | | | | | Total | P |
|---|---|---|---|---|---|---|---|---|---|
| | | Group-I (gynaeco-logical) | Group-II (head & neck) | Group-III (gastro intestinal) | Group-IV (breast & others) | Group-V (lung) | Group-VI (hepato-cellular) | | |
| Physical Activity | Yes | 4 | 1 | 4 | 5 | 2 | 3 | 19 | 0.30 |
| | No | 7 | 2 | 10 | 11 | 2 | 0 | 32 | |
| Role | Yes | 6 | 1 | 7 | 9 | 3 | 2 | 28 | 0.91 |
| | No | 5 | 2 | 7 | 7 | 1 | 1 | 23 | |
| Dyspnoea | Not at all | 9 | 3 | 14 | 10 | 3 | 0 | 39 | 0.008* |
| | A little | 2 | 0 | 0 | 3 | 0 | 1 | 6 | |
| | Quite a bit | 0 | 0 | 0 | 3 | 1 | 1 | 5 | |
| | Very Much | 0 | 0 | 0 | 0 | 0 | 1 | 1 | |
| Pain | Not At All | 2 | 1 | 5 | 8 | 0 | 0 | 16 | 0.04* |
| | A Little | 4 | 0 | 2 | 4 | 0 | 1 | 11 | |
| | Quite A Bit | 1 | 1 | 5 | 1 | 4 | 1 | 13 | |
| | Very Much | 4 | 1 | 2 | 3 | 0 | 1 | 11 | |
| Fatigue | Not At All | 3 | 0 | 4 | 5 | 0 | 0 | 12 | 0.41 |
| | A Little | 2 | 1 | 5 | 3 | 1 | 1 | 13 | |
| | Quite A Bit | 1 | 1 | 2 | 4 | 3 | 0 | 11 | |
| | Very Much | 5 | 1 | 3 | 4 | 0 | 2 | 15 | |
| Insomnia | Not At All | 6 | 1 | 10 | 10 | 3 | 2 | 32 | 0.56 |
| | A Little | 0 | 0 | 0 | 1 | 1 | 0 | 2 | |
| | Quite A Bit | 4 | 1 | 3 | 2 | 0 | 0 | 10 | |
| | Very Much | 1 | 1 | 1 | 3 | 0 | 1 | 7 | |
| Appetite loss | Not At All | 5 | 2 | 8 | 9 | 3 | 1 | 28 | 0.63 |
| | A Little | 0 | 1 | 0 | 1 | 0 | 0 | 2 | |
| | Quite A Bit | 3 | 0 | 4 | 3 | 0 | 1 | 11 | |
| | Very Much | 3 | 0 | 2 | 3 | 1 | 1 | 10 | |
| Nausea and vomiting | Not At All | 5 | 2 | 7 | 12 | 1 | 2 | 29 | 0.29 |
| | A Little | 1 | 0 | 4 | 0 | 0 | 1 | 6 | |
| | Quite A Bit | 1 | 1 | 2 | 1 | 2 | 0 | 7 | |
| | Very Much | 4 | 0 | 1 | 3 | 1 | 0 | 9 | |
| Constipation | Not At All | 9 | 3 | 12 | 14 | 4 | 3 | 45 | 0.91 |
| | A Little | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Quite A Bit | 2 | 0 | 1 | 2 | 0 | 0 | 5 | |
| | Very Much | 0 | 0 | 1 | 0 | 0 | 0 | 1 | |
| Diarrhoea | Not At All | 8 | 3 | 12 | 13 | 4 | 3 | 43 | 0.86 |
| | A Little | 2 | 0 | 1 | 0 | 0 | 0 | 3 | |
| | Quite A Bit | 0 | 0 | 0 | 2 | 0 | 0 | 2 | |
| | Very Much | 1 | 0 | 1 | 1 | 0 | 0 | 3 | |

*A P value of ≤ 0.05 is considered as statistically significant

medium risk for adherence and 2 (3.9%) patients have scored high risk for adherence. Of 3 (5.9%) patients in group-VI, 3 (5.9%) patients have scored high risk for adherence. Totally among 51 patients of the study population, 10 (19.6%) have scored low adherence risk, 13 (25.5%) patients have scored medium risk for adherence and 28 (54.9%) patients have scored high risk for adherence. There was no

statistically significant association (P=0.853) between the groups with respect to the metronomic chemotherapy regimen and the risk for adherence scores.

## Quality of life:

Table- 5 depicts the quality of life of the study population. Based on the QOL scores of the study population, for questions 1 to 5, 19 patients have responded as 'YES' indicating decreased physical activity and 32 responded as 'NO' indicating that their physical activity was not compromised. The responses for questions 6 & 7 were as follows, 28 patients have responded 'YES' indicating a compromise in their role in house hold activities and 23 patients have responded as 'NO' indicating a normal role in their day to day activities. The response for question 8 was as follows, 12 patients felt 'not at all', 13 patients felt 'a little', 11patients felt 'quite a bit' and 15 patients felt 'very much' for Dyspnoea. The responses for questions 9 & 19 were as follows, 16 patients have felt 'not at all', 11 patients 'felt a little', 13 patients felt 'quite a bit' and 11 patients felt 'very much' for pain. The responses for questions 10, 12& 18 were as follows, 12 patients felt 'not at all', 13 patients 'felt a little', 11 patients

**Table 6: QOL of the study population**

| QOL indicators | | Number of patients(N=51) | | | | | | Total | P |
|---|---|---|---|---|---|---|---|---|---|
| | | Group-I (gynaeco-logical) | Group-II (head & neck) | Group-III (gastro intestinal) | Group-IV (breast & others) | Group-V (lung) | Group-VI (hepato-cellular) | | |
| Cognitive | Not At All | 10 | 3 | 13 | 13 | 4 | 2 | 45 | 0.150 |
| | A Little | 1 | 0 | 0 | 2 | 0 | 1 | 4 | |
| | Quite A Bit | 0 | 0 | 1 | 1 | 0 | 0 | 2 | |
| | Very Much | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Emotional | Not At All | 5 | 1 | 7 | 8 | 2 | 2 | 24 | 0.454 |
| | A Little | 3 | 0 | 6 | 3 | 1 | 1 | 13 | |
| | Quite A Bit | 3 | 2 | 0 | 3 | 1 | 1 | 10 | |
| | Very Much | 0 | 0 | 1 | 2 | 0 | 0 | 4 | |
| Social | Not At All | 4 | 3 | 4 | 6 | 0 | 1 | 18 | 0.543 |
| | A Little | 3 | 0 | 6 | 7 | 2 | 1 | 19 | |
| | Quite A Bit | 3 | 0 | 3 | 2 | 2 | 1 | 11 | |
| | Very Much | 1 | 0 | 1 | 1 | 0 | 0 | 3 | |
| Financial difficulties | Not At All | 3 | 1 | 3 | 2 | 0 | 0 | 9 | 0.919 |
| | A Little | 2 | 0 | 1 | 1 | 0 | 0 | 4 | |
| | Quite A Bit | 1 | 0 | 1 | 2 | 0 | 0 | 4 | |
| | Very Much | 5 | 2 | 9 | 11 | 4 | 3 | 34 | |
| Physical condition | Very Poor | 1 | 0 | 0 | 1 | 0 | 0 | 2 | 0.008* |
| | Poor | 3 | 0 | 0 | 1 | 0 | 0 | 4 | |
| | Below | 0 | 1 | 1 | 0 | 0 | 2 | 4 | |
| | Average | 1 | 0 | 5 | 2 | 4 | 1 | 13 | |
| | Good | 5 | 2 | 7 | 11 | 0 | 0 | 25 | |
| | Very Good | 1 | 0 | 1 | 1 | 0 | 0 | 3 | |
| | Excellent | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Quality of life | Very Poor | 1 | 0 | 0 | 1 | 0 | 0 | 2 | 0.013* |
| | Poor | 2 | 0 | 0 | 1 | 0 | 0 | 3 | |
| | Below | 0 | 1 | 1 | 0 | 0 | 2 | 4 | |
| | Average | 2 | 0 | 5 | 1 | 4 | 1 | 13 | |
| | Good | 5 | 2 | 7 | 12 | 0 | 0 | 26 | |
| | Very Good | 1 | 0 | 1 | 1 | 0 | 0 | 3 | |
| | Excellent | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

*A P value of ≤ 0.05 is considered as statistically significant

felt 'quite a bit' and 15 patients felt 'very much' for fatigue. The response for question 11 was as follows, 32 patients have felt 'not at all', 2 patients felt 'a little', 10 patients felt 'quite a bit' and 7 patients felt 'very much' for insomnia. The response for questions 13 was as follows, 28 patients have felt 'not at all', 2 patients felt 'a little', 11 patients felt 'quite a bit' and 10 patients felt 'very much' for appetite loss. The responses for questions 14 & 15 were as follows, 29 patients have felt 'not at all', 6 patients felt 'a little', 7 patients felt 'quite a bit' and 9 patients felt 'very much' for nausea and vomiting. The response for question 16 was as follows, 45 patients have felt 'not at all', 5 patients felt 'quite a bit' and 1 patient felt 'very much' for constipation. The response for question 17 was as follows, 43 patients have felt 'not at all', 3 patients felt 'a little', 2 patients felt 'quite a bit' and 3 patients felt 'very much' for diarrhoea. There was no statistically significant association between the QOL indicators like physical activity (P= 0.301), role (P= 0.901), fatigue (P= 0.410), insomnia (P= 0.557), appetite loss (P= 0.631), nausea and vomiting (P= 0.297), constipation (P= 0.907) and diarrhoea (P= 0.815) and the metronomic chemotherapy regimen that they were receiving. But QOL indicators like dyspnoea (P= 0.008), pain (P= 0.036) had a statistically significant association with the metronomic chemotherapy regimen of the study patients.

Table- 6 depicts the scores of the cognitive, emotional, social, financial difficulties, overall physical condition and overall quality of life of the study population. Based on the QOL scores the responses for questions 20 & 25 were as follows, 45 patients have responded 'not at all' indicating that their cognitive skills were not impaired, 4 patients have responded 'a little' indicating that their cognitive skills were little impaired and 2 patients responded 'quite a bit' indicating that their cognitive skills were quite a bit compromised.

The responses for questions 21 to 24 were as follows, 24 patients have responded 'not at all' indicating that their emotional status was good, 13 patients have responded 'a little' indicating that their emotional status was little compromised, 10 patients have responded 'quite a bit' indicating that their emotional status was quite a bit impaired and 4 patients have responded 'very much' indicating that their emotional status was very much compromised.

The responses for questions 26 & 27 were as follows, 18 patients have responded as 'not at all' indicating that their social skills were good, 19 patients have responded 'a little' indicating that their social behaviour was a little compromised, 11 patients have responded 'quite a bit' indicating that their social behaviour was quite a bit impaired and 3 patients have responded as 'very much' indicating that their social behaviour is very much diminished.

The responses for question 28 was as follows, 9 patients responded 'not at all' indicating that they do not have any financial difficulties, 4 patients had responded 'a little' indicating that they have a little financial difficulties, 4 patients had responded 'quite bit' indicating that they have quite a bit financial difficulties and 34 patients had responded 'very much' indicating that they have very much financial difficulties.

The response for question 29 was as follows, 2 patients have responded 'very poor' indicating that their overall physical condition was very poor, 4 patients have responded 'poor' indicating that their overall physical condition was poor, 4 patients have responded 'below average' indicating that their overall physical condition was below average, 13 patients have responded 'average' indicating that their overall physical condition was average, 25 patients have responded 'good' indicating that their overall physical condition was good and 3 patients have responded 'very good' indicating that their overall physical condition was very good.

The response for question 30 was as follows, 2 patients have responded 'very poor' indicating that their overall quality of life was very poor, 3 patients have responded 'poor' indicating that their overall quality of life was poor, 4 patients have responded 'below average' indicating that their overall quality of life was below average,13 patients have responded 'average' indicating that their overall quality of life was average, 26 patients have responded 'good' indicating that their overall quality of life was good and 3 patients have responded 'very good' indicating that their overall quality of life was very good.

There was no statistically significant association between the QOL indicators like cognitive (P= 0.150), emotional (P= 0.454), social (P= 0.543) and financial difficulties (P= 0.919) and the metronomic chemotherapy regimen received by the study population. But QOL indicators like overall physical condition (P= 0.008) and overall QOL (P= 0.013) had a statistically significant association with the

metronomic chemotherapy regimen of the study patients.

## DISCUSSION

This study was conducted to assess the toxicities of metronomic chemotherapy in 51 patients (19 males and 32 females) with progressive solid tumors. The medication adherence patterns of the study population towards their chemotherapeutic regimen and their Quality of life were also assessed in this study. Majority of the patients in this study were in the age range of 51- 60 years (29.4 %).

Of the 51 patients, majority of the patients (34 %) were in Group IV with breast and other cancers receiving tablets Capecitabine, Etoposide and Cyclophosphamide. This was followed by 28% of patients in Group III with pancreatic, colorectal, stomach, duodenum and gallbladder cancers (gastro intestinal cancers) receiving tablets Luporal, Leucovorin, Etoposide and Endoxan. There are an increasing number of clinical studies using metronomic chemotherapy schedules being published in the last years.[10,11] The most commonly examined tumor type was breast cancer, followed by colorectal, melanoma, prostate cancer and different histologic types of sarcoma. [12-15]

Oral chemotherapeutic agents like cyclophosphamide, methotrexate, trofosfamide, capecitabine and etoposide are mainly used in metronomic schedules for different cancer types. A study was conducted by Mross et al, in 60 patients, 25% heavily pre treated with three or more prior chemotherapies and 22% had capecitabine previously as palliative treatment with intermit and capecitabine 2000mg/$m^2$ on days 1-14 every three weeks and vinorelbine 60 mg/$m^2$ 1+8 every three weeks. This study demonstrated the safety and efficacy of metronomic capecitabine in the palliative setting with special focus on the quality of life in advanced breast cancer. [16]

The toxicities of the study population towards the metronomic chemotherapy regimen were assessed using CTC guidelines. Most severe toxicities of the study population were grade III neutropenia, anemia and thrombocytopenia in 25 % of patients each. Only one patient had grade IV anemia. Haematological side effects were found to be less in number (18.8%) with Group IV breast cancer patients. Fatigue, anorexia, nausea and vomiting were the other common toxicities found in the study population and all of them were of grade I and Grade II category in severity. Toxicities like pain, hand and foot syndrome, edema, dryness, constipation and diarrhoea were observed in less number of patients and also they were graded as I and II of severity.

Studies reported on the toxicity profile of metronomic chemotherapy have investigated on heterogeneous tumour types and varied drug combinations. In common, metronomic chemotherapy demonstrated a good tolerability when given daily with common side effects like grade 1 to 2 anaemia and neutropenia and grade 1 to 2 fatigue. A meta-analysis of around 61 studies done in 5491 patients who were treated with metronomic chemotherapy reported the most frequent toxicity as neutropenia in 1122 patients (20.6%). Anaemia was the second most frequently observed toxicity documented in 518 patients (9.5%) but none of these toxicities were indication for an interruption or termination of metronomic chemotherapy. [17]

A study conducted in 18 patients with oral cancers on metronomic chemotherapy also reported minimal toxicities. However there was an episode of grade 4 mucositis in one patient that resulted in discontinuation of metronomic chemotherapy. The other episodes of mucositis seen were of grade 1 or 2 in 12 patients. Only one patient reported to have anemia of grade 3and there was no evidence of neutropenia. [18]

The grade 3 and grade 4 toxicities observed in the present study were well managed with supportive therapy; hence no discontinuation of metronomic chemotherapy was done. The medication adherence patterns of the study population was analysed using Morisky adherence scale and Merck's adherence estimator. As per Morisky's Scale, majority of the patients (88 %) had a medium score of 6 to < 8 indicating a medium adherence. A low adherence was observed in 8 % of patients. Only 4% patients had a high adherence score as per Morisky adherence scores.

The medication adherence patterns of the patients as per Merck's adherence estimator showed a little varied result as this questionnaire focused on the sentiments and the financial difficulties of the patients. Based on this questionnaire, 20% of the patients showed a low risk for adherence problems, 25% showed a medium risk for adherence problems and 55% showed a high risk for adherence problems. These results depicts that majority of the patients

were more concerned about financial difficulties, a major threat for low adherence. The adherence patterns of the study population were the same irrespective to the drug regimen.

The quality of life of the study patients was analyzed using EORTC QOL-30 questionnaire. Majority of the patients (62.7%) felt that their physical activity was normal and not limited. However 55% patients expressed that their role in household activities were limited. Majority of the patients (above 60%) did not experience any side effects during the past week. About 47% patients felt that they were emotionally strong to accept the disease and the therapy given. The cognitive skills were found to be good for 88% of patients. But around 67% patients felt that they were financially burdened by the chemotherapy and around 40% felt that they had difficulty with the family life and social activities. The overall quality of the study population was found to be very good for 12 % patients, good for 51% of patients, average for 24% patients, below average for 7% of the patients and poor and very poor for 9% of the patients irrespective of the drug regimen they were receiving.

To our knowledge, there is a paucity of data on medication adherence patterns and quality of life of the patients on metronomic chemotherapy. The present study had emphasized the effects of metronomic chemotherapy in progressive adult malignancies in terms of low toxicity, good adherence and overall good quality of life. However the major limitations of the present study were the limited number of participants and short follow up, hence not warranting for long term toxicities. Larger studies and long follow up are recommended to confirm these results.

## CONCLUSION

The study conducted on 51 patients on metronomic chemotherapy identified hematological side effects like neutropenia, anaemia and thrombocytopenia as grade-3 and grade-4 toxicities. These toxicities were found to be less in Group IV patients with breast cancer receiving metronomic chemotherapy regimen. All other toxicities were of grade-1 and grade-2 type. Majority of patients had a medium to good medication adherence pattern and overall good quality of life due to less severe toxicities. However they had lesser involvement towards social and family activities. 55% had a high risk for non-adherence due to sentimental reasons and financial burden of the chemotherapy.

The study suggests that metronomic chemotherapy could be considered safe, convenient, acceptable, tolerable and cost effective/cost saving treatment option. Furthermore it also minimizes the requirement for the administration of intravenous drugs which benefits the overburdened health care system as well as the patients who are often too sick to travel frequently to the hospitals.

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