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Original Article

Pharmacology Section

# Metronomic Chemotherapy: Seems Prowess to Battle against Cancer in Current Scenario

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## ABSTRACT

**Introduction:** Metronomic chemotherapy is an emerging method of chemotherapy. Metronomic 'lowdose' chemotherapy regimen induces tumour dormancy and reduces cancer resistance against anticancer drugs. It tends to improve overall success rate of cancer chemotherapy than conventional cyclical regimen.

**Aim:** The aim of this systemic review was to provide comprehensive data of metronomic chemotherapy trials, regimens used and it's outcome in cancer therapeutics.

**Materials and Methods:** Fifty chemotherapy trial data were searched sequentially from web. The main sources were official website of Clinical trial forum, USA and Clinical Trial Registry India (CTRI). Evidence on efficacy and safety of such metronomic chemotherapy trials was gathered from various data published in Medline, New England Journal of Medicine (NEJM), Lancet Oncology and other journals with high credentials. As a result of our search, out of 50 trials including breast -15(30%), colon-, 5(10%) ovarian -5(10%), prostate-5(10%) and others including haematologic, soft tissue and nervous system malignancies -20 (50%). Twenty seven trials showed favourable, 20 trials showed equivocal outcome and 3 trials reported unfavourable outcome. Overall comparison showed definitive statistical significance for using metronomic regimen (p-0.05).

**Conclusion:** It can be concluded that metronomic chemotherapy regimen seems convincing beneficial to induce tumour remission and survival at a higher than conventional regimen. More metanalyses are needed to frame common metronomic chemotherapeutic regimen.

**Keywords:** Cancer resistance, Low dose chemotherapy, Maintenance chemotherapy

## INTRODUCTION

Cancer is one among the leading causes of morbidity and mortality worldwide. In 2014-15, 14.1 million new cases of cancer were diagnosed 7.4 million (53%) in male and 6.7 million (47%) females. Nearly eight lac cancer cases are prevalent in India at any point of time and 5,50,000 cancer patients dying every year [1]. Despite thumping advances in cancer therapeutics, from conventional non-targeted therapy to targeted therapy, availability of monoclonal antibodies, immunotherapy and so on, prognosis of cancer in many cases remains unaltered. The main reasons from therapeutics point of view are resistance to cancer drugs and regional spread of disease. Resistance to cancer drugs is a major threat that leads to failure of treatment recurrence of disease among treated population. Metronomic chemotherapy appears to be prowess to address the resistance and regional spread of cancer by many ways [2].

The Scientist, Doughlas Hanahan coined the term 'metronomic chemotherapy'. The basic principles involved behind such chemotherapy regimen are administering anti-cancer drugs in low doses continuously or at regular intervals but more often than the cyclical conventional anti-cancer therapy schedules.

At present, many experimental works are being carried to explore functional mechanisms of metronomic chemotherapy while on the other side of coin, cancer trials comparing conventional and metronomic regimen are progressing [3].

Our specific objectives were focused to provide comprehensive data of trials employing metronomic chemotherapy, pattern of cancer involved in metronomic trials, data regarding drugs employed in metronomic chemotherapy trials and to compare the outcome as favourable, unfavourable or equivocal to between conventional regimen versus metronomic regimen for different tumours.

This comprehensive analysis was carried by Department of Pharmacology, Saveetha Medical College and Haasan Institute of Medical Sciences between January and April 2016. Fifty chemotherapy trial data were taken sequentially from web. The main sources were official website of Clinical Trial Forum, USA and Clinical Trial Registry India (CTRI). Evidence on efficacy and safety of such metronomic chemotherapy trials was gathered from various data published in Medline, New England Journal of Medicine (NEJM), Lancet Oncology and other journals with high credentials.

Regimen considered as favourable when there is increase in survival rate, reduction in surrogate markers or less number of adverse events. Results quoted as unfavourable where cancer trial registry data showed neither reduction morbidity and mortality or reduction in surrogate marker. Increased number of adverse events if mentioned in metronomic regimen is also considered as unfavourable. Results quoted as unequivocal when there is no significant difference between conventional and metronomic regimen in terms of efficacy or safety profile. Descriptive statistics and non-parametric tests were applied to infer the findings.

## RESULTS OF THE LITERATURE SEARCH

As detailed out in [Table/Fig-1], breast -15(30%), colon- 5(10%) ovarian -5(10%), prostate-5(10%) and others including haematologic, soft tissue and nervous system malignancies -20 (50%). Totally 18 drugs were used as single drug and in combinations in 50 trials. They were cyclophosphamide –27 methotrexate – 10, capecitabine – 9 celecoxib – 7 bevacizumab – 4 vinorelbine – 7, etoposide – 5, dacarbazine – 1, docetaxel – 3, temozolamide – 3, cisplatin – 3, gemcitabine – 2, sirolimus – 2, doxorubicin – 1, paclitaxel – 1, irinotecan – 1, sorafenib, tegafur/uracil – 1.

| S. No. | Cancer trial name | Author's name | Drug given | End point | Outcome |
|---|---|---|---|---|---|
| 1 | Metronomic cyclophosphamide and capecitabine combined with bevacizumab in advanced breast cancer | Silvia Dellapasqua, et al., | Cyclophosphamide and capecitabine Bevacizumab | Response rate | Favourable |
| 2 | Trastuzumab in combination with metronomic cyclophosphamide and methotrexate in patients with her-2 positive metastatic breast cancer | Laura Orlando et al., | Trastuzumab Cyclophosphamide and methotrexate | Progression free survival | Favourable |
| 3 | Zd6474 (zactima) and metronomic chemotherapy in advanced breast cancer | Erica Mayer et al., | Vandetanib cyclophosphamide methotrexate | Progression free survival | Favourable |
| 4 | Prolonged clinical benefit with metronomic chemotherapy in patients with metastatic breast cancer | Orlando L et al., | Cyclophosphamide (ctx) and methotrexate (mtx) (cm) | Determine the safety and tolerability of combination therapy | Favourable |
| 5 | Safety and therapeutic effect of metronomic chemotherapy with cyclophosphamide and celecoxib in advanced breast cancer patients | Perroud HA et al., | Cyclophosphamide and celecoxib | Progression free survival | Favourable |
| 6 | Continuous low-dose oral chemotherapy in recurrent and persistent carcinoma of cervix following chemoradiation: A comparative study between prolonged oral cyclophosphamide and oral etoposide | Upasana Baruah et al., | Oral cyclophosphamide and oral etoposide | Progression free survival | Favourable |
| 7 | Cyclophosphamide, methotrexate metronomic chemotherapy for the palliative treatment of breast cancer. A comparative pharmacoeconomic evaluation | Bocci G et al., | Cyclophosphamide, methotrexate | Response rate | Favourable |
| 8 | Capecitabine metronomic chemotherapy plus aromatase inhibitor for postmenopausal hormone receptor positive breast cancer | Guang-yu Liu et al., | Capecitabine Letrozole | Cost saving/ cost effective | Favourable |
| 9 | Low-dose metronomic oral administration of vinorelbine in the first-line treatment of elderly patients with metastatic breast cancer | Addeo R et al., | Vinorelbine | Adverse events Progression free survival | Favourable |
| 10 | Efficacy of capecitabine metronomic chemotherapy to triple-negative breast cancer (sysucc-001) | Yuan Zhong-yu et al., | Capecitabine | Progression-free survival | Equivocal |
| 11 | Vinorelbine metronomic pluslapatinib for overexpressing her-2 metastatic breast cancer | Dimitris Mavrudis et al., | Vinorelbine lapatinib | Disease-free survival | Equivocal |
| 12 | Low-dose/metronomic (ldm) chemotherapy for metastatic breast cancer | | Cyclophosphamide, capecitabine, methotrexate, celecoxib, pamidronate | Overall response rate | Equivocal |
| 13 | Low dose chemotherapy with aspirin in patients with breast cancer after neoadjuvant chemotherapy | Mary Chamberlin et al., | Cyclophosphamide and methotrexate and aspirin | Rate of response (rr) + rate of stable disease (sd) | Equivocal |
| 14 | Maintenance metronomic chemotherapy for metastatic colorectal carcinoma | David L et al., | Capecitabine, celecoxib and methotrexate | Toxicity and safety Biomarker analysis | Equivocal |
| 15 | Low dose metronomic poly-chemotherapy for metastatic crc (ldmchemocrc) | Ofer Purim et al., | Capecitabine cyclophosphamide methotrexate celecoxib | Length of progression free survival (pfs) | Equivocal |
| 16 | Metronomic therapy in patients with metastatic melanoma | Marc S. Ernstoff et al., | Vinblastine cyclophosphamide dacarbazine | The median progression free survival | Equivocal |
| 17 | Study of combination of metronomic oral vinorelbine and sorafenib in patients with advanced non-small cell lung cancer | Eng-Huat Tan et al., | Oral vinorelbine sorafenib | Progression free survival | Equivocal |
| 18 | Metronomic oral vinorelbine in advanced breast cancer and non small cell lung cancer | Cazzaniga ME et al., | Vinorelbine | Response rate | Favourable |
| 19 | Metronomic oral vinorelbine in patients with metastatic tumours | Evangelos Briasoulis et al., | Vinorelbine | Response rate | Favourable |
| 20 | Efficacy, safety, and potential biomarkers of thalidomide plus metronomic chemotherapy for advanced hepatocellular carcinoma. Open- labeled, single-arm, multicentered, investigator-initiated study | Shao YY et al., | tegafur/uracil Thalidomide | Time to treatment failure Progression free survival | Favourable |
| 21 | Metronomic therapy with cyclophosphamide and dexamethasone for prostate carcinoma | Glode LM et al., | Cyclophosphamide Dexamethasone | Response evaluation criteria in solid tumours (recist) | Favourable |
| 22 | Clinical outcome of patients with docetaxel resistant hormone refractory prostate cancer with second line cyclophosphamide based metronomic chemotherapy | Nelius T et al., | Cyclophosphamide | Psa | Favourable |
| 23 | High-dose celecoxib and metronomic “low-dose” cyclophosphamide is an effective and safe therapy in patients with relapsed and refractory aggressive histology non–hodgkin's lymphoma Multicenter phase II prospective study | Buckstein R et al., | Celecoxib and cyclophosphamide | Psa response Survival and toxicity | Favourable |
| 24 | Phase II study of metronomic chemotherapy for recurrent malignant gliomas in adults | Santosh Kesari et al., | Etoposide, cyclophosphamide plus thalidomide Celecoxib | Progression free survival | Equivocal |

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| 25 | Metronomic chemotherapy with daily, oral etoposide plus bevacizumab for recurrent malignant glioma: a phase ii study | Reardon DA et al., | Etoposidebevacizumab | Progression free survival | Unfavourable |
| 26 | Metronomic chemotherapy enhances the efficacy of antivascular therapy in ovarian cancer | Kamat AA et al., | Docetaxel | Progression free survival | Favourable |
| 27 | Phase II clinical trial of bevacizumab and low dose metronomic oral cyclophosphamide in recurrent ovarian cancer a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia | Garcia AA et al., | Cyclophosphamide Bevacizumab | Response rate | Favourable |
| 28 | Phase II trial of low dose continuous (metronomic) treatment of temozolomide for recurrent glioblastoma | Kong DS et al., | Temozolomide | Progression free survival | Favourable |
| 29 | Metronomic capecitabine and docetaxel as second-line chemotherapy for advanced gastric cancer(MICADO) | Vincenzo Catalano et al., | Capecitabine Docetaxel | Progression free survival | Equivocal |
| 30 | Protracted etoposideduring induction therapy for high risk neuroblastoma (PEPI) | Peter Zage et al., | Protracted oral etoposide adriamycin and cyclophosphamide iv cisplatin and iv bolus etoposide | Tumour response | Equivocal |
| 31 | Combining low-dose or metronomic chemotherapy with anticancer vaccines | Stephen R et al., | Cyclophosphamide, gemcitabine, doxorubicin | Response rate | Equivocal |
| 32 | Effect of maximum-tolerated doses and low-dose metronomic chemotherapy on serum vascular endothelial growth factor and thrombospondin-1 levels in patients with advanced nonsmall cell lung cancer | Tas F et al., | Cisplatin Docetaxel | Response rate | Unfavourable |
| 33 | Cyclophosphamide "metronomic" chemotherapy for palliative treatment of a young patient with advanced epithelial ovarian cancer | Samaritani R et al., | Cyclophosphamide | Decrease in biomarker levels | Favourable |
| 34 | Metronomic therapy concepts in the management of adrenocortical carcinoma | Berruti A et al., | Gemcitabine and fluoropyrimidines | Progression-free survival time | Favourable |
| 35 | Metronomic oral vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer: results of a phase ii trial (move trial) | Camerini A et al., | Oral vinorelbine | Response rate | Equivocal |
| 36 | Metronomic chemotherapy in patients with advanced solid tumour with bone metastasis and advanced pretreated osteosarcoma | Maud et al., | Sirolimus combined with cyclophosphamide methotrexate and zoledronate | Overall response rate (ORR), clinical benefit | Equivocal |
| 37 | A pilot study of a metronomic chemotherapy regimen with weekly low-dose docetaxel for previously treated non-small cell lung cancer | Takashi Yokoi et al., | Docetaxel | Response rate | Favourable |
| 38 | Maintenance bevacizumab only or bevacizumab plus metronomic chemotherapy in advanced colorectal cancer | Alberto Z et al., | Bevacizumab Capecitabine Cyclophosphamide | Objective response rate, disease control rate | Equivocal |
| 39 | Sirolimus in combination with metronomic chemotherapy in children with recurrent and/or refractory solid and CNS tumours | Thomas et al., | Sirolimus celecoxib etoposide cyclophosphamide | Progression-free survival | Equivocal |
| 40 | A pilot study of metronomic temozolomide treatment in patients with recurrent temozolomide-refractory glioblastoma | Kong DS et al., | Temozolamide | Change in radiographic response to treatment for solid tumours | Equivocal |
| 41 | Antiangiogenic effect of metronomic paclitaxel treatment in prostate cancer and non-tumour tissue in the same animals: a quantitative study | Lennernäs B et al., | Paclitaxel | Progression-free survival | Favourable |
| 42 | Oral metronomic cyclophosphamide in elderly with metastatic melanoma | Borne E et al., | Cyclophosphamide | Safety Objective response rate and overall survival | Favourable |
| 43 | Phase ii study of metronomic chemotherapy with bevacizumab for recurrent glioblastoma after progression on bevacizumab therapy | David A. Reardon et al., | Etoposide Temozolomide | Progression-free survival | Unfavourable |
| 44 | Capecitabine “metronomic” chemotherapy for palliative treatment of elderly patients with advanced gastric cancer after fluoropyrimidine-based chemotherapy | Shen J et al., | Capecitabine | Progression-free survival | Favourable |
| 45 | Low dose metronomic oral cyclophosphamide for hormone resistant prostate cancer: a phase II study | Lord R et al., | Cyclophosphamide | Safety and toxicity | Favourable |
| 46 | Metronomic therapy for pediatric patients with solid tumours at high risk of recurrence | Ted Zwerdling et al., | Bevacizumab cyclophosphamide valproic acid temsirolimus | 5 year event free survival | Equivocal |
| 47 | Safety and efficacy of metronomic cyclophosphamide, metformin and olaparib in endometrial cancer patients (endola) | Benoit et al., | Olaparib metformin metronomic cyclophosphamide | Progression free survival | Equivocal |
| 48 | A pharmacokinetic and pharmacodynamic study on metronomic irinotecan in metastatic colorectal cancer patients | G Allegrini et al., | Irinotecan | PK/PD profile | Favourable |
| 49 | Metronomic chemotherapy: possible clinical application in advanced hepatocellular carcinoma | Torimura T et al., | Cyclophosphamide Flurouracil | Safety and efficacy | Favourable |

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| 50 | Low-dose metronomic chemotherapy with cisplatin: can it suppress angiogenesis in hepatocarcinoma cells | Fang-Zhen Shen et al., | Cisplatin | Safety and efficacy | Equivocal |

**[Table/Fig-1]:** Showing metronomic trials of various cancers with the regimen used and its outcome [4,5].

As evident from above, cyclophosphaomide and methotrexate were used most often in many tumours and doss employed was 50mg once daily and 2.5mg twice daily respectively. A total of 27 trials showed favourable 20 trials showed equivocal outcome and three trials reported unfavourable outcome. Overall comparison showed definitive statistical significance for using metronomic regimen (p-0.05).

Detailed results of 50 trials with type of cancer, drugs used end points observed by investigator and outcome is depicted in [Table/Fig-1].

## DISCUSSION

Our study was undertaken to analyse and provide comprehensive data of newer metronomic chemotherapy regimen which showed convincing results in various experimental studies and paved to begin cancer trials with metronomic regimen. In our study most commonly employed drugs were alkylating agent, cyclophosphamide and anti-metabolite methotrexate. Our analysis showed breast cancer were commonly employed with metronomic regimen probably due to its more common occurrence and metronomic regiment is highly favolurable in breast cancer. Success of metronomic regimen quoted by us was supported by systematic review of Banys-Paluchowski M et al., among European nations; however the drug employed was capeciabine which is different from our analysis [3].

Colon cancer, prostate cancer and ovarian cancers using metronomic regimen showing favourable outcome in their endpoints. These findings are well supported by similar analysis conducted by investigators worldwide [6-8].

In case of three trials of small cell cancer of lung, metronomic regimen did not produce any additional benefits. The postulated reason was, in cases of small cell or non-small cell lung cancer metronomic drug and dosage regimen is yet to be refined when compared to other protocols used in various malignancies. Elharrar X et al., have discussed the aforesaid reason elaborately the failure of designing successful regimen in lung cancer in his publication BMC cancer 2016 [9].

Glioblastoma and other nervous system tumours including neuroblastoma did not show convincing benefits in either of the regimen. These tumours are aggressive and carries poor prognosis in general remains unaltered by metronomic regimen [10].

Mechanisms involved in administering low dose metronomic regimen than maximum tolerated dose used in regular or cyclical chemotherapy regimen is now adequately elucidated. The mechanisms are low dose daily administration of drugs which reduces cancer drug resistance and induces tumour dormancy. Metronomic regimen reduces interleukins and metallopeoteinases, 'switch off' Vascular Endothelial Growth Factor (VEGF) genes responsible for angiogenesis and hence, metastasis in cancer growth [11,12].

Changing the conventional regimen to metronomic regimen is termed as "chemoswitch" by oncologists and hailed by many. Metronomic regimen are not devoid of adverse effects, shared toxicities of anti-cancer drugs like nausea, vomiting, alopecia are applicable but they are expected and shown to be less in many trials [13,14].

## FUTURE DIRECTIONS

Metronomic regimen with conventional regimens is showing evidenced based information to support their use [15,16]. Future directions should include using newer biologics in metronomic regimen to improve its efficiency with conventional drugs. Cancer therapeutic committee should frame a common metronomic regimen which will be used as reference module in many developed nations. Common consensus if arrived on metronomic regimen, it will help to policy decision in monetary benefits and resource allocation at institutional to national level. As many of the cancer drugs has propensity to induce second tumour effect, long term administration of metronomic regimen should be guarded with the risk involved. Pooling of many meta-analysis outcome from trials conducted from various ethnicities is a need to see any variation in response.

Our analysis provides the preliminary success trend of metronomic regimen versus cyclical chemotherapy trial and hence, systematic review of a particular malignancy was not mentioned as each of it has to be with meticulous inclusion and exclusion of various cancer using metronomic regimen.

## CONCLUSION

Metronomic regimens often employ cyclophosphamide (50mg/d) and methotrexate (5mg/d) to treat various malignancies and convincingly effective in many cases. Breast, colon, ovarian and prostate cancer have shown favourable outcome with metronomic regimen whereas small cell lung cancer and nervous system malignancies are not yielding any additional benefits with metronomic regimen.

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