

Metronomic Chemotherapy: Low Dose Less Toxic Anticancer Strategy

Anjan Khadka^{*1} and Neha Akhoon²

¹Department of Pharmacology, Nepalese Army Institute of Health Sciences (NAIHS), Sanovaryang, Kathmandu, Nepal

²Department of Pharmacology, Armed Forces Medical College (AFMC), Pune-40, India

Corresponding author*

Dr. Anjan Khadka,

Department of Pharmacology,

Nepalese Army Institute of Health Sciences (NAIHS),

Sanovaryang, Kathmandu, Nepal

E-mail: anjankhadka14@yahoo.com

Abstract

Metronomic chemotherapy is the frequent administration of chemotherapeutic drugs at doses below the maximum tolerated dose and with no prolonged drug-free break. It thus achieves a sustained low blood level of the drug without significant side effects; hence there is reduced need for supportive therapy. However in case of conventional therapy toxicity is a concern. Metronomic chemotherapy exerts both direct and indirect effects on tumor cells and their microenvironment. It can inhibit tumor angiogenesis, stimulate anticancer immune response and also induces tumor dormancy. Optimizing a metronomic anticancer therapy is still a challenging task. New strategies are being developed to combine metronomic chemotherapy with conventional chemotherapy, radiotherapy and/or targeted therapy. An important disadvantage of this type of regimen is the empiricism in finding the optimal 'low-dose' and in monitoring therapeutic efficacy during the course of treatment.

Keywords: Cancer, Chemotherapy, Antimicrobials, Metronomic.

1. Introduction

Metronomic chemotherapy deals with administration of chemotherapeutic agents at doses below the maximum tolerated dose (MTD).[1,2] The aim of therapy is to achieve a sustained low blood level of the drug without toxic effects [2,3] The drug is given frequently at low dose (1/10th-1/3rd of the maximum tolerated dose, MTD) without drug window period.[1] It is derived from the word "metronome", meaning musical instrument that produces fixed and regular aural pulse, and metrical ticks.[1,2] It has emerged as a newer strategy to improve response rates and reduce toxicities. Changes in the understanding of cancer biology, evolution and metastasis have boosted the interest in metronomic chemotherapy. [4] The important features of metronomic chemotherapy includes: [1,5,6]

- Regular administration of chemotherapy without any interruptions using an optimized dose
- Preference for oral drugs
- Low incidence of side effects
- Low risk of developing resistance

Table 1: Metronomic chemotherapy vs. Conventional Chemotherapy [2-7]

	Metronomic chemotherapy	Conventional Chemotherapy
Dose	Uses dose lower than maximum tolerated dose (MTD)	Uses MTD
Frequency	Continuous (weekly, daily or every alternate day)	Various larger intervals (fortnightly, monthly or 3 weekly, etc.)
Plasma concentration	Sustained level	Variable (Rise and fall)
Target	Endothelial cells in the growing vasculature of the tumor	Proliferating tumor cells
Objective	To achieve cancer control by targeting angiogenesis	To treat cancer directly by inhibiting or killing rapidly dividing tumor
Effectiveness	Effective against both primary and metastatic tumors	More effective against the primary tumor than against metastasis
Toxic effects	Minimal or nil toxic effect	Maximum (main concern, need for supportive adjunctive therapy)

Metronomic chemotherapy is an effective modality with clinical advantages such as reduction in toxic effects thereby allowing for safe and long-term use. There are studies conducted to test the benefits of metronomic chemotherapy regimens when these are given along with anti-angiogenic drug which demonstrates that this strategy has potential promise in the treatment of breast cancer and tumors of central nervous system. [8] Combination of anti-angiogenic drugs like bevacizumab with metronomic chemotherapy produce significant responses with prolonged tumor regression in advanced breast cancer. [8,9]

Vascular endothelium growth factor (VEGF) can be regarded as predictive marker of response of metronomic chemotherapy. Human VEGF concentration found to be significantly reduced after combining anti-angiogenic agents with metronomic chemotherapy. The anti-cancer effects of low dose metronomic chemotherapy involves inhibition of tumor blood vessel formation in addition to inhibition of growth of endothelial cells and reduction of circulating endothelial progenitors mobilization and viability.[10]

2. Mechanism of Action

Being a multi-targeted therapy metronomic chemotherapy elicits effects on tumor cells and their microenvironment both directly and indirectly. Angiogenesis is responsible for tumor growth and metastasis. Metronomic chemotherapy has potential to inhibit tumor angiogenesis, stimulate immune response against cancer and also induces tumor dormancy as well as induction of ageing (senescence) in tumors by acting in caspase cascades.[3,11-14]

The action of metronomic chemotherapy as anti-angiogenic includes [7,14,16]:

- i. Selective inhibition of proliferation and/or induction of apoptosis of activated endothelial cells and endothelial cell migration.
- ii. Increase in the expression of thrombospondin-1, an endogenous inhibitor of angiogenesis
- iii. Sustained reduction of bone marrow-derived endothelial progenitor cells (CEPs) levels and their viability

3. Role of Metronomic Chemotherapy

Anti-angiogenic dose of a drug which is higher than cytotoxic dose should not be considered anti-angiogenic. Anticancer agents to be termed metronomic when they produce significant difference between the dose that produce cytotoxicity and endothelial cell toxicity, and should inhibit angiogenesis both *in-vivo* and *in-vitro*. [7,11,16,17]

Various immunomodulatory and anti-cancer drugs demonstrate anti-angiogenic, immune-stimulatory and apoptotic properties. Commonly used drugs for metronomic chemotherapy are cyclophosphamide, methotrexate, etoposide, vinblastine, paclitaxel, gemcitabine, temozolomide, capecitabine, sorafenib, everolimus etc. [16-17] Metronomic drugs are used singly or in combination as different regimens against several types of previously treated or untreated tumors. [2,6,21] Metronomic schedule has been proposed for many solid tumors as well as in multiple myeloma. [17] Metronomic chemotherapy initially was thought to inhibit tumor angiogenesis by targeting activated endothelial cells but now its spectrum has broaden to multi targets like activation of immunity, effect on tumor initiating cells and induction of tumor dormancy. [22] It has lead new direction in treatment of advanced non-small cell lung cancer, advanced stage breast cancer, treatment resistant oral cancers, metastatic colorectal cancer, metastatic uterine carcinosarcoma, etc. [22-24]

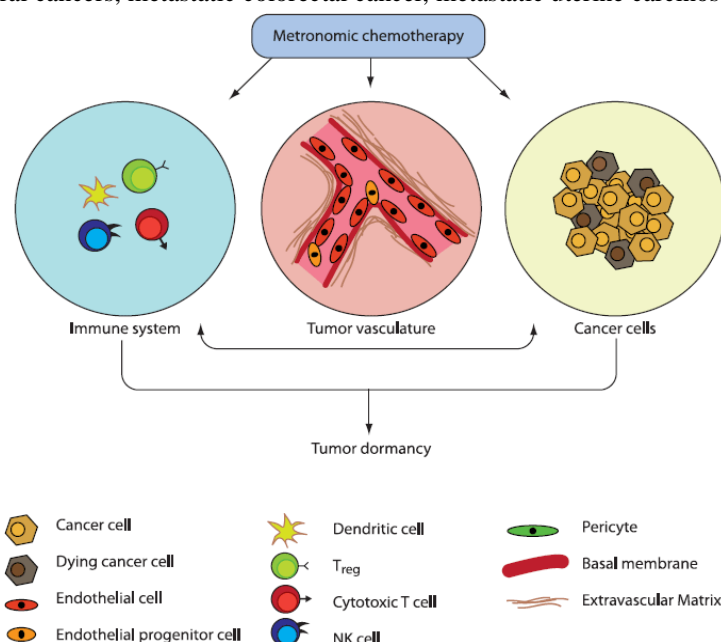


Figure 1: Action of Metronomic Chemotherapy [6, 25]

4. Clinical trials

Phase I study of metronomic chemotherapy in advanced refractory solid tumors showed that there was no dose-limiting toxicity in 30 patients taking low dose vinorelbine, cyclophosphamide and interferon alpha, and suggested for further exploration regarding efficacy as drugs were well-tolerated. [26]

Phase II study of temozolomide, thalidomide, and celecoxib for newly diagnosed glioblastoma in adults suggested that the addition of thalidomide and celecoxib to adjuvant temozolomide was well tolerated but did not meet the primary endpoint i.e. four month progression free survival. [27] Phase II study of metronomic chemotherapy for recurrent malignant gliomas in adults studied the feasibility of antiangiogenic chemotherapy and recommended for further studies using metronomic chemotherapy combined with one or more potent antiangiogenic agents. [28]

A multicentric phase II study in Asian patients with advanced hepatocellular carcinoma showed that bevacizumab (5 mg/kg i.v every 2 weeks) with erlotinib (150 mg/day orally) elicit good tolerability and modest activity in the Asian cohort of advanced hepatocellular carcinoma. The study also suggested further research to identify predictive biomarkers of this drug combination. [29]

Studies with metronomic chemotherapy involve different schedules for different cancer types. Oral drugs such as cyclophosphamide, methotrexate, trofosfamide, etoposide, capecitabine, and 5-fluorouracil are the main chemotherapeutic agents used in trials. The responses of these agents are measured in terms of tumor stabilization or prolonged progression free survival. [6]

A phase 3 multicentric randomized trial (IMPRESS) in patients with advanced non-small-cell lung cancer with acquired resistance to EGFR tyrosine-kinase inhibitors reported that the platinum-base doublet chemotherapy remains the standard of care in the disease because gefitinib did not prolong progression-free survival when combined with platinum based chemotherapy. [30]

Phase II trial of metronomic chemotherapy as salvage therapy for patients with metastatic breast cancer shows that efficacy of continuous low dose metronomic chemotherapy regimens can be improved when they are combined with anti-angiogenic, endothelial specific, drugs such as neutralizing monoclonal antibodies to receptors for vascular endothelial cell growth factor (VEGF), which are highly expressed by the activated endothelial cells of newly tumor vasculature. Such combination can induce remarkable responses including sustained tumor regression, even of drug resistant tumors, as well as marked prolongation of survival with no serious toxicity. In addition, the regimen of cyclophosphamide (CTX) and methotrexate (MTX) shows a clear cut financial cost-saving benefit compared to a number of other novel regimens like taxanes in metastatic breast cancer.[31]

Phase II study of metronomic capecitabine in triple negative breast cancer evaluate the tolerability and efficacy as extended adjuvant treatment. Forty-one patients with median age of 50 years were enrolled and treated. Adverse effects were found to be palmar–plantar erythrodysesthesia in 13 patients (31.7%); diarrhea in five patients (12.2%); and vomiting in two patients (4.9%). Estimated median follow-up duration was 34 months and estimated mean disease-free survival (DFS) was 42.4 months (95% CI, 39.02–45.79), while median DFS was not reached. Estimated mean overall survival was 44.34 months (95% CI 41.9–46.9). Extended adjuvant metronomic capecitabine is well tolerated with patient compliance and need to be compared in a study with control arm, larger sample, as well as longer follow-up.[32]

5. Examples of Metronomic regimens

- For breast cancer → Cyclophosphamide (oral, daily) and Methotrexate (oral, twice weekly) or Cyclophosphamide (oral, daily), Methotrexate (oral, twice weekly) and Thalidomide (oral, daily)[18, 20, 23]
- For recurrent ovarian cancer → Cyclophosphamide (oral, daily) and Bevacizumab (every 2 weeks)[33]
- For metastatic colorectal cancer → Capecitabine[24]
- For newly diagnosed glioblastoma → Temzolomode, Thalidomide and Celecoxib[26]
- For advanced non-small cell-lung cancer → Gefitinib and platinum compounds[27]

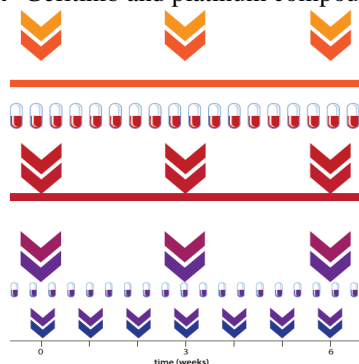


Figure 2: Dosing Schedules in Metronomic Chemotherapy [34]

6. Toxicity of Metronomic Chemotherapy

Most common toxic effects are nausea, vomiting, anemia, neutropenia, leucopenia, lymphopenia and fatigue. [4] Metronomic chemotherapy for prolonged duration may lead to cumulative toxicity that can lead to secondary diseases. E.g. secondary leukemia may be due to cumulative dose of etoposide or temozolomide; bilateral subdural hematoma in a child with meningeal carcinomatosis, etc. [31,33-35]

7. Issues with Metronomic Chemotherapy

The common issue in metronomic chemotherapy is endothelial cell toxicity. [7,8,13,14] Other issues are as follows:

- Tumor cells can undergo complex evolution, leading to resistant metronomic chemotherapy. [36, 37]
- Inadequate data regarding safety of conventional and metronomic chemotherapy. [7, 38]
- Therapeutic drug monitoring is necessary to rule out various cumulative toxicities. [5,39]
- Lack of pharmacogenetic research which leads to difficulty in choosing correct metronomic chemotherapy to resistant tumors. [2,13]
- Need for appropriate prognostic and surrogate biomarkers for metronomic regimens and their combination with other therapies. [40-41]

8. Conclusion

Cancer research aims to identify the effective agents to use according to the type and activity of tumor. New strategies should include combination of metronomic chemotherapy with conventional chemotherapy. Metronomic chemotherapy is a potential newer strategy for cancer treatment. Dose adjustment and tumor activity are the main tasks for metronomic chemotherapy. Low-dose regimens offer advantages like superior efficacy, low adverse effect profile and wide spectrum of activity against tumor cells.

Conflicts of Interest: None

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