World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

A REVIEW ON METRONOMIC CHEMOTHERAPY

S. D. Labhade* and J. S. Jagtap

India.

***Corresponding Author: Dr. S. D. Labhade**
India.

Article Received on 09/12/2019 **Article Revised on 29/12/2019** **Article Accepted on 19/01/2020**

ABSTRACT

The introduction of the "Maximum Tolerable Dose" (MTD) in normal treatment protocols (and its concurrent over toxicity) made vital the burden of rest periods between cycles of treatment—a training that includes re-development of tumor cells, yet in addition development of chose clones impervious to the treatment. So as to avoid the problems caused by traditional chemotherapeutic regimens, a new modality of drug administration called "metronomic chemotherapy" has been proposed. It refers to the chronic, equally spaced administration of (generally) low doses of various chemotherapeutic drugs without extended rest periods. The curiosity of this treatment methodology lies not just in its anti- tumor efficacy with exceptionally low adverse effect, yet additionally in a cell target switch. With plenty of experimental work, beginning with the pioneering work in the Folkman and Kerbel labs, Metronomic chemotherapy (MCT) has built its foundations. Browder and colleagues demonstrated that standard chemotherapeutic drugs such as cyclophosphamide can also be used as anti-angiogenic agents. The administration of cyclophosphamide in doses lower than the MTD, at shorter intervals and without extended rest periods, showed results better than those obtained with the MTD schedule in the treatment of two cyclophosphamide-resistant tumours, Lewis lung carcinoma and the murine mammary carcinoma cell line EMT-6.

KEYWORDS: Metronomic chemotherapy, angiogenesis, optimal biologic dose, circulating endothelial progenitors (CEPs), tissue dormancy.

INTRODUCTION

The therapeutic concept of administering agents (cytotoxic/-static, non-cytotoxic and/or targeted drugs) continuously at lower doses - relative to MTDs in the case of cytostatic and cytotoxic drugs or continuously at tolerable doses as in the case of targeted drugs without drug-free breaks over extended periods - known as 'metronomic therapy' (MT).

More importantly, several phase II trials have shown that metronomic therapies showed anti-cancer activity in different cancer types with different drugs. The mechanism of metronomic therapy using cytotoxic/ static drugs is either by direct killing or inhibiting endothelial cells (ECs) in the tumor vasculature, killing bone-marrow-derived endothelial progenitor cells, stimulating the immune system, directly affecting tumor cells through a drug-driven effect as well as specifically inhibiting a target when targeting drugs were used in additional to metronomic therapy.[1]

Characteristics of metronomic chemotherapy[3]

- Frequent (dose-dense) CHT administration without any interruptions.
- Not using the maximal tolerated dose (MTD) include a biological optimized dose (BOD).
- No application of hematopoetic growth factors.
- Preference for oral drugs.
- Low incidence of treatment related side effects.
- Potential for delayed development of resistance.

Criteria for an anti-angiogenic approach of metronomic chemotherapy[4]

- Strong differential cytotoxicity between cancer cells and endothelial cells
- Altered function of endothelial cells shown in dynamic contrast enhanced magnetic resonance imaging (DCEMRI) or contrast enhanced ultrasonic examinations (CEUS) by changes in the permeability and blood-flow in tumors.
- Changes of mechanistic effects (e.g. biomarker changes: IL-1 &6, uPA, VEGF, VEGFR1&2, bFGF, Ang 1&2, MMP-2&9, vessel density etc.)
- Inhibition of angiogenesis *in vivo* & *in vitro* (*in vivo* models at best only with spontaneous, slow growing tumors).

Metronomic chemotherapy a new therapeutic option in clinical oncology[2]
Metronomic Chemotherapy and Conventional Cytotoxic Chemotherapy
Table 1: Summary of Differences between Metronomic Chemotherapy and Conventional Cytotoxic Chemotherapy.[2]

Sr. No.		Metronomic chemotherapy	Conventional chemotherapy
1	Dosing frequency	Continuous dosing, e.g., wkly, every other day, daily	At intervals e.g., Three wkly, fortnightly, wkly
2	Doses used	Lower than in conventional MTD regimens	Dose intense and used at MTD
3	Pharmacokinetics	Sustained plasma concentration of the drug	Rise and fall of the plasma concentration of the drug
4	Target	Endothelial cells in the growing vasculature of the tumor	Proliferating tumor cells
5	Host toxicity	Significantly less toxic and reduced need for supportive therapy	Toxicity is a concern as doses are used at MTD
6	Intent of treatment	Cancer control	Cancer eradication

Possible mechanisms of the anti-angiogenic basis of metronomic chemotherapy

Two pathways are there by which metronomic chemotherapy could lead to growth arrest or apoptosis of endothelial cells in the tumour neovasculature. A '**direct'** pathway assumes that activated, differentiated endothelial cells are intrinsically sensitive to low-dose chemotherapy, for which there is some evidence 80–85; the same might be true for circulating endothelial progenitor cells. The '**indirect'** pathway (right) assumes that the levels of metronomically administered drugs are too low to induce growth arrest or apoptosis of endothelial cells. Instead, an endogenous inhibitor of angiogenesis such as thrombospondin, is induced in certain cells by low-dose chemotherapy.[5] This inhibits tumour angiogenesis and vasculogenesis, leading to a reduction in tumour neovascularization in the absence of side effects such as myelosuppression, hair loss, and nausea or vomiting.

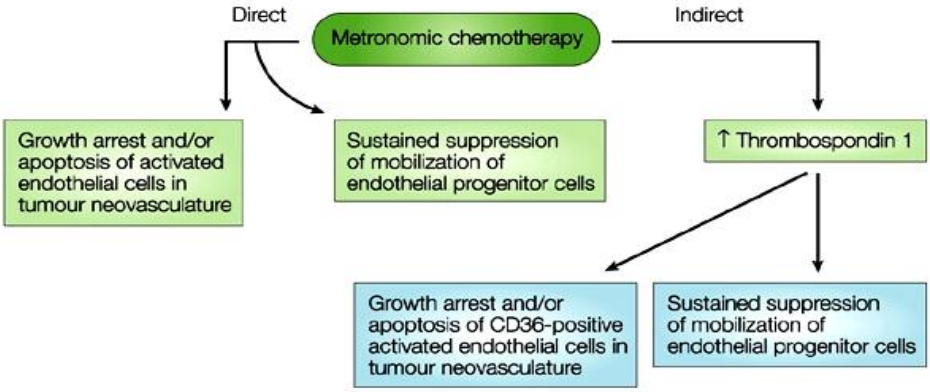

Figure 2: Direct and indirect mechanisms of metronomic chemotherapy.

Anti-Angiogenic Mechanisms

The 'activated' endothelial cells of newly forming blood-vessel capillaries are highly and selectively sensitive to very low doses of various chemotherapeutic drugs. For example.

To test the anti-proliferative, migration-inhibitory and sometimes cytotoxic effects of picomolar concentrations of chemotherapeutic drugs on various human cell types, including fibroblasts, lymphocytes, tumour cells, epithelial cells from various tissues, and microvascular or macrovascular endothelial cells.[7]

Four-dimensional effect

Drug driven dependency/deprivation or a 4-D phenomenon has been hypothesized by André and Pasquier to explain the efficacy of the drug regimens using intermittent drug interruptions. According to this postulation, tumor cells become dependent on chemotherapeutic agents during long exposures and sudden withdrawal or replacement therapy may lead to cell death.[8,9] This hypothesis may be used to explain the situations where multiple drugs are used with differing periods of administration.

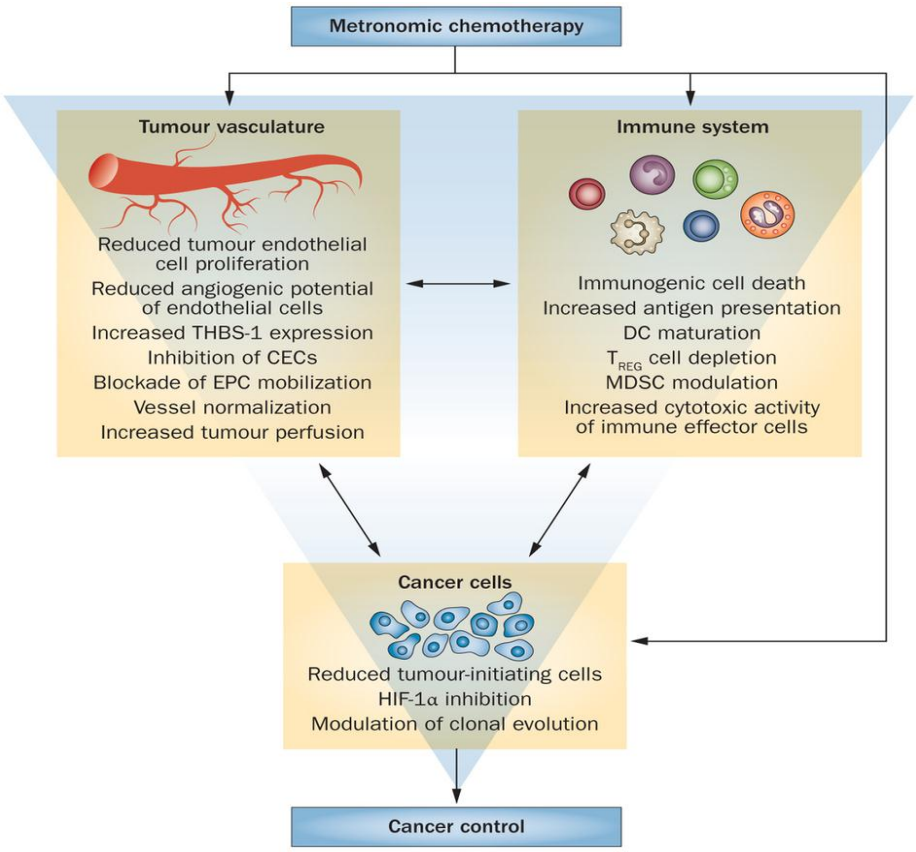

Figure 3: Control of cancer by 4D effect.

Drugs used in metronomic chemotherapy

Metronomic chemotherapy regimen is usually a combination of various drugs of different classes having anti-angiogenic, immune-stimulatory and apoptotic properties. Frequent and repetitive administration of low dose of some anti-neoplastic drugs (CPA, methotrexate, etoposide, vinblastine, paclitaxel) is cytotoxic to both circulating endothelial cells and circulating CEPs but has no effect on non-endothelial cells and leucocytes.[10,11]

Metronomic Chemotherapy In Pediatric Patients

Metronomic chemotherapy has the potential to improve survival and quality of life of pediatric cancer patients by reducing the burden of adverse effects number of clinical trials of metronomic chemotherapy in pediatric population is limited in number but some of the results are very promising.[12,13,14]

Table 2: Metronomic Chemotherapy Regimens Used In Pediatric Age Group.

Patient Profile	Metronomic chemotherapy regimen
Refractory, relapsing or "high risk" of relapse tumors of various types	Etoposide (orally, daily, 3 weeks) alternating with temozolomide(oral, daily, 6 weeks) Celecoxib (Oral, daily) Retinoic acid(Oral, daily, 2 weeks)
Refractory or relapsing tumors of various types	Etoposide (orally, daily, 3 weeks) alternating with cyclophosphamide (oral, daily, 3 weeks) Thalidomide (oral, daily) Celecoxib (oral, daily)
Refractory relapsing tumors of various types	Vinblastine (i.v., 3 ties/ week) Celecoxib (oral, daily) Or Cyclophosphamide (oral, daily) Celecoxib (oral, daily)

Metronomic Chemotherapy In Adults

Most of clinical trials on metronomic chemotherapy in adults have been conducted in patients with breast carcinoma. Many investigators have used various metronomic chemotherapy regimens for patients with advanced and recurrent ovarian carcinoma, advanced multiple myeloma, hormone resistant prostate cancer, non-Hodgkin lymphoma and others. Some well-studied

metronomic regimens for adults have been listed in [Table 3] and most of these studies have showed modest response rate to metronomic chemotherapy and overall clinical benefit.

Table 3: Metronomic Chemotherapy Regimens Used In Adults.

Patient profile	Metronomic chemotherapy regimen
Metastatic breast cancer previously treated with conventional chemotherapy Untreated or previously treated breast cancer with conventional chemotherapy	Cyclophosphamide (oral. daily) Methotrexate (oral, twice weekly) Cyclophosphamide (oral. daily) Methotrexate (oral. twice weekly) (or) Cyclophosphamide (oral. daily) Methotrexate (oral. twice weekly) Thalidomide (oral. daily)
HER2+metastatic breast cancer. previously treated with trastuzumab and conventional chemotherapy Recurrent ovarian cancer previously treated with conventional chemotherapy Hormone- refractory prostate cancer, previously treated by androgen deprivation	Cyclophosphamide (oral. daily) Methotrexate (oral. twice weekly) Trastuzumab (every 3 weeks) Cyclophosphamide (oral. daily) Bevacizumab (every 2 weeks) Cyclophosphamide (oral. daily) Dexamethasone (oral. daily) Or Dexamethasone(orally ,daily) Celecoxib (Oral, twice daily)
Aggressive relapsed or refractory non-Hodgkin's lymphoma Progressive multiple myeloma. previously treated with conventional chemotherapy Metastatic or locally advanced neuroendocrine carcinoma	Cyclophosphamide (oral. daily) Celecoxib (oral, twice daily) Cyclophosphamide (oral. daily) Prednisone (oral, daily) 5-fluorouracil (i.v..daily) Long-acting release octreotide (monthly)

❖ **Toxicity of metronomic chemotherapy**

In total, metronomic CHT alone or in combination demonstrated a good tolerability when daily given, so this is obligatory. Most common side effects were grade 1 nausea and grade 1 to 2 anaemia and neutropenia as well as grade 1 to 2 fatigue. The number of treated patients with sampled toxicity data is low. Overall, metronomic CHT has often been described with minimal toxicity offering a significant benefit for the patients including quality of life. Theoretically high cumulation over time of etoposide, temozolomide and cyclophosphamide can lead to secondary leukemia, myelodysplastic syndromes (MDS) or resistance.

Most common toxic effects were mild nausea and/or vomiting, mild to moderate anemia, neutropenia, leucopoenia and Lymphopenia as well as low-grade fatigue. High-grade toxic effects were either rare or not found. Prolonged metronomic chemotherapy may lead cumulative toxicity of anticancer agents, which can lead to secondary diseases. For example, cumulative dose of etoposide or temozolomide can lead to secondary leukemia.[15,16]

Pharmacogenetics

Gene expression profiling and comprehensive gene expression analysis of the resistant tumors can guide in choosing correct metronomic therapy. Gene expression of resistant tumors clearly differs from non-resistant tumors and to investigate the molecular basis of in-vivo resistance mechanism genome-wide microarray studies are required. Some studies revealed that expression of resistance-related genes in vivo differs from gene expression in vitro, indicating an involvement of micro-environmental factors leading to the observed in vivo resistance.[16]

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