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METRONOMIC CHEMOTHERAPY

Dr. Kapil Kumar Garg*

Department of Medical Oncology, Max Super Specialty Hospital, New Delhi, India.

***Corresponding Author: Dr. Kapil Kumar Garg**

Department of Medical Oncology, Max Super Specialty Hospital, New Delhi, India.

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ABSTRACT

Conventional chemotherapy protocols include administration of chemotherapy drugs on certain specific days with period of rest in between to reduce their side effects and toxicity. The rest period also allows body tissues including bone marrow to recover from damage inflicted by these drugs. Downside of this practice is that it gives tumour cells enough time to regrow and develop drug resistance. To address this issue, a novel way of administering conventional chemotherapy drugs in a frequent low dose protocol was introduced. This strategy called metronomic chemotherapy (MCT) leads to reduction in tumour growth by inhibiting angiogenesis and has changed the traditional approach of treatment in the field of oncology.

KEYWORDS: Metronomic Administration, Chemotherapy, Angiogenesis.

INTRODUCTION

Since the inception of conventional chemotherapy, the dilemma of using high drug dose chemotherapy for better tumour killing vis-à-vis increasing toxicity has existed. Chemotherapy protocols were introduced to address these issues which allowed rest periods between drug dosages for bone marrow to recover from the toxicity. Unfortunately, this allows tumour cells to grow and develop drug resistance genes. This leads to poor therapeutic response in subsequent chemotherapy cycles which prompts clinician to either increase the drug dosage or introduce second line agents which are more toxic and usually less efficacious. Hence a poor clinical response with significant morbidity and mortality ensues.

BACKGROUND

Metronomic chemotherapy (MCT) term was coined by Doughlas Hanahan as he did exhaustive work in this field.[1] Detailed research was done by Folkman et al and they concluded that a chemotherapy drug if given in chronic low dose fashion acts as an anti-angiogenic agent.[2] This effect is attributed to a cell target switch present on tumour endothelial cells which is affected by MCT. The dosage of drug should be below the maximum tolerated dose. Angiogenesis is one of the main factors responsible for the spread of tumour and multiple experimental animal studies have been done in this field.[3] In one study, administration of low dose thrice weekly cyclophophamide eradicated lymphomas and sarcomas in rats. The dosage used was 10 mg/kg and 5mg/kg body weight respectively without any reported incidence of significant toxicity.[4]

PATHOPHYSIOLOGY

Apart from direct toxic effects on tumour cell, MCT has certain novel mechanism of actions. Angiogenesis is a physiological process involved in growth and development which involves mature endothelial cell dependent generation of new blood vessels. The same process is pathological in neoplastic conditions which help in growth and extension of tumour cells. Vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) are pro-angiogenic factors where as thrombospondin-1 is an angiogenic inhibitor.[5] Angiogenesis inhibitor drugs like bevacizumab and sunitinib are being used successfully utilising the same principle.[6] Conventional chemotherapy drugs such as cyclophosphamide, methotrexate and taxanes have anti-angiogenic effect when administered in metronomic fashion.

Vasculogenesis is a progenitor endothelial cell dependent generation of new blood vessels and is different from angiogenesis. The circulating progenitor endothelial cells are the alternative source for tumour blood vessel generation. They are found in patients with neoplastic conditions and are sensitive to various chemotherapy drugs in metronomic proportions. Levels of these circulating endothelial cells could be used as marker of vasculogenesis although further studies are required for their clinical validation.[7] MCT enhances immune response against the tumour antigens by suppression of regulatory T cell activity.[8] Hence, MCT is a multi-targeted therapy which leads to tumour dormancy.[9]

CURRENT CLINICAL SCENARIO

The first clinical study of MCT was done in patients with breast cancer by Colleoni et al in 2002. Overall clinical benefit of 31.7% was reported with minimal toxicity using cyclophophamide plus methotrexate combination therapy.[10] Apart from breast cancer, MCT has been studied in patients with lymphomas, melanomas, prostate and ovarian tumours with largely positive results.[11]

Reduced toxic profile and drug resistance makes MCT use very suitable in neoplastic processes. One health-economic study showed MCT to significantly reduce healthcare expenditure and need for valuable resources.[12] But despite the given advantages, MCT has not been in widespread clinical use as expected. One main reason is lack of defined MCT protocols for each tumour type, specific drug combinations and dosages. MCT is well tolerated except for nausea and vomiting. Due to the frequent dosing protocol in MCT, there is a potential risk of cumulative drug toxicity. The anti-angiogenic effect of MCT may be harmful for normal growth and development in paediatric population and needs to be studied. Monitoring of angiogenic processes to predict clinical response and prognosis is another challenge due to lack acceptable biomarker. Although VEGF and thrombospondin-1 may act as surrogate markers but the validation for their clinical use is limited.[13] Table 1 summarises some of the commonly used MCT regimens. It is interesting to note that most of these regimens involve chemotherapy drugs to be administered orally.

Table: 1

Malignancy	MCT regimen used
Refractory non-Hodgkin's lymphoma[14]	Daily oral cyclophosphamide plus celecoxib
Recurrent ovarian carcinoma[15]	Daily oral cyclophosphamide plus two weekly bevacizumab
Breast carcinoma[16]	Daily oral cyclophosphamide plus twice weekly oral methotrexate
Metastatic breast carcinoma[10]	Daily oral cyclophosphamide and twice weekly oral methotrexate
Hormone refractory prostate carcinoma[17]	Daily oral cyclophosphamide and daily oral dexamethasone
Refractory paediatric tumours of different types[18]	Daily oral etoposide plus daily oral Cyclophosphamide plus daily oral celecoxib plus daily oral thalidomide

THE ROAD AHEAD

Several pre-clinical and clinical studies have been carried out in the field of MCT till date and certain phase 2 trials have been done with encouraging results. Further studies targeted at designing specific treatment regimens with drug dosages, combinations, timing etc are required to facilitate its use in specific neoplastic conditions.

CONCLUSION

The goal of chemotherapy is complete tumour suppression and MCT represents a novel way of utilising the already existing chemotherapy arsenal in achieving this. Although complete tumour eradication is not necessary for clinical response, MCT has great potential in reducing morbidity and mortality associated with tumour burden.

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