

Metronomic Chemotherapy as a New Strategy for End-stage Pediatric Oncology Patients in Iran

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Dear Editor

Metronomic chemotherapy is the continual, systemic administration of non-toxic chemotherapy doses that target proliferating endothelial cells during tumor angiogenesis. This strategy began 40 years ago in adult oncology, but in pediatric settings, experiences are few. At Amir Oncology Hospital, for the first time in Iran, we have systematically reviewed evidence-based documents and extracted chemotherapy protocols from the literature for management of hopeless patients; to actually increase their survival and life expectancy.

What is metronomic chemotherapy?

This type of chemotherapy inhibits tumor progression initially through anti-angiogenesis mechanisms while prominently decreasing undesirable toxic adverse effects. Metronomic chemotherapy can induce tumor responses in oncology patients previously resistant to treatment or in those who have relapsed after classic chemotherapy.

In addition, the clinical advantage duration obtained with metronomic chemotherapy can be longer than the benefit received with more common approaches. Despite the disparity of efficacy reported for metronomic chemotherapy based on the drug combination and tumor type; all clinical trials have proven that this new treatment, alone or in combination with other treatment options, is well tolerated. The highest grade of toxic adverse effects observed include grade 1 nausea, vomiting, grades 1 and 2 anemia, neutropenia, leukopenia and lymphopenia, as well as low-grade fatigue.

We intend to treat a number of patients at Amir Oncology Hospital with this new, unique program which is a first for Iranian pediatric oncology centers.

A potential suggested chemotherapy regimen for Meduloblastoma/cerebral Primitive Neuro-Ectodermal Tumor (PNET), Osteosarcoma, Nephroblastoma, high grade Glioma, Hodgkin's lymphoma,

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Rhabdomyosarcoma, Neuroblastoma and kidney Rhabdoid tumors is listed below. Vinblastine (3 mg/m²) weeks 1-7; Methotrexate (twice weekly, PO, 10 mg/m² for 3 weeks) weeks 5-7; Celecoxib (250 mg/m² PO, B.I.D.) daily days 1-56 or Valproic acid (20 mg/kg/day, daily); Cyclophosphamide (30 mg/m²/day, PO) days 1-21, followed by a two-week chemotherapy break.¹ This treatment protocol is scheduled for period cycles of 56 days (8 weeks).

Another chemotherapeutic regimen consists of the following: The first cycle consists of weekly Vincristine (1.5 mg/m²) on days 1, 8, 15, and 22; daily Cyclophosphamide (25-30 mg/m²) on days 1 to 21; and twice weekly Methotrexate (15 mg/m²) on days 21 to 42, followed by a 1 week break. For subsequent cycles, Vincristine was administered only at weeks 1 and 5 of each cycle.²

Conclusion and future of metronomic chemotherapy

Metronomic chemotherapy is an efficient

intervention for control of disease progression in most types of malignancies. However, the progress of metronomic chemotherapy faces unknown or unexplored territory. It seems that it's impossible to suggest a single metronomic regimen for all of types of refractory malignancies. Determining the most favorable combination regimens of metronomic chemotherapy remain a critical point for any tumor type. Other factors that need to be optimized include the number of agents to be synthesized; doses of each agent to be used, either alone or in combination; and the timing of drug administration and break therapy.³

Currently strategies are being developed in the clinic to combine metronomic chemotherapy with conventional chemotherapy administered at the maximum tolerated dose, radiotherapy, and/or targeted therapy. These strategies are opening the way for an immense number of potential combinations. Kinetics and livability of circulating endothelial cells and progenitor endothelial cells can be powerful predictive instruments for patient stratification and treatment monitoring, but the best

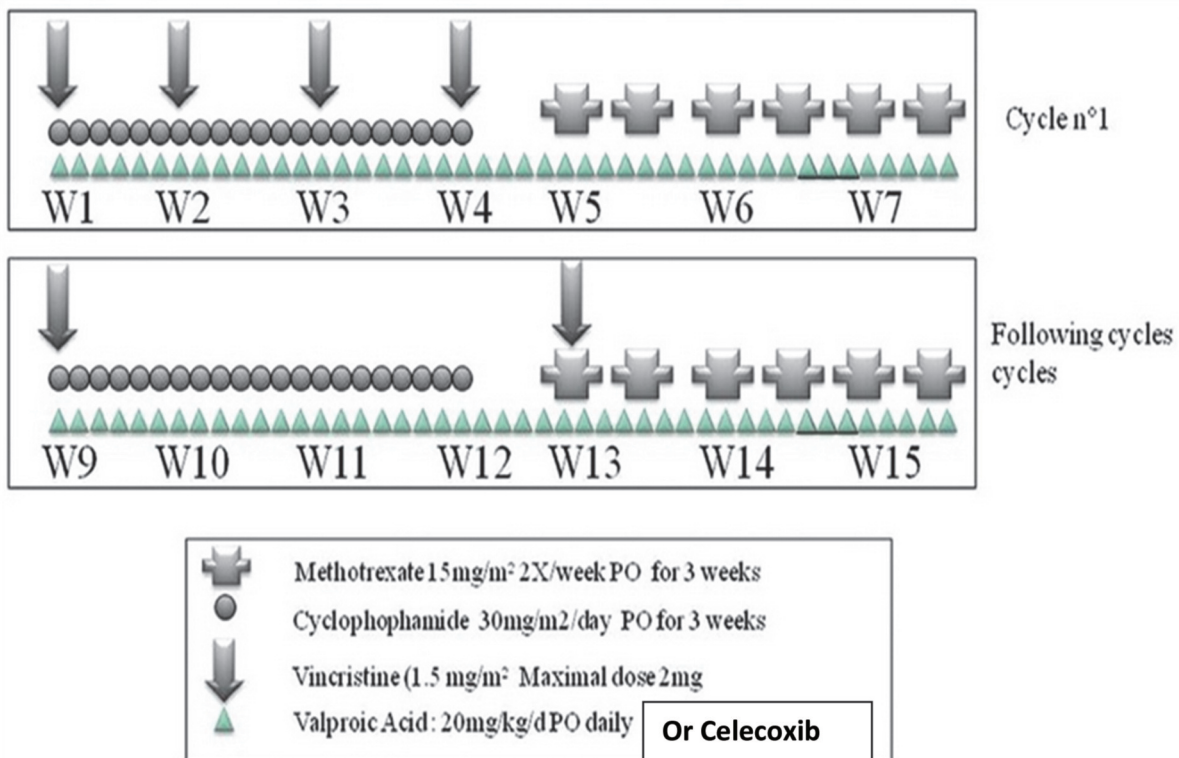


Figure 1. Metronomic chemotherapy protocol for Meduloblastoma/cerebral Primitive Neuro-Ectodermal Tumor (PNET), Osteosarcoma, Nephroblastoma, high grade Glioma, Hodgkin's lymphoma, Rhabdomyosarcoma, Neuroblastoma and kidney Rhabdoid tumors. "W" is substituted for week of treatment.

method of identification and measurement need to be defined in future.⁴

In addition, a primary principal for the expansion of anti-vascular treatment, in particular metronomic chemotherapy, is based on the concept that vascular endothelial cells are genetically stable and presumably are less likely to acquire drug resistance compared to malignant cells. Evidences have suggested that tumor endothelial cells are differentiated from normal endothelial cells. They have tumor-specific genetic abnormalities and acquire drug resistance. Therefore, pharmacogenetic and pharmacoproteomic studies on tumor endothelial cells are necessary in order to recognize their sensitivity to metronomic chemotherapy which will assist in developing drugs for clinical use.⁵

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