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SPECIAL ARTICLE

Metronomic Chemotherapy in Progressive Pediatric Malignancies: Old Drugs in New Package

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Abstract Despite intensive research in the field of cancer, many pediatric cancers are still incurable with current treatment protocols. Repetitive administration of conventional chemotherapy at maximal tolerated dose imposes many side effects that further limits the dosing and therefore decreases the anticancer effects. Usually limited options remain when a malignancy progresses after one or two lines of standard chemotherapy protocol. The goal of an oncologist at this point of time remains mainly palliative with an effort to halt the progression of cancer and improve quality of life. Metronomic chemotherapy is defined as the chronic administration of chemotherapeutic agents at relatively low, minimally toxic doses, and with no prolonged drug-free breaks. It is thought this type of chemotherapy inhibits tumor growth primarily through anti-angiogenic mechanisms, promoting apoptosis and immune- surveillance.

Keywords Metronomic chemotherapy · Drugs · Pediatric malignancy

Introduction

The cure rate in pediatric malignancies has dramatically increased from less than 30 % four to five decades ago to as high as 70–80 % presently [1]. Over the past four decades mortality rates in children with various malignancies have also shown significant declining trends [2]. Despite intensive research and addition of targeted chemotherapy in the existing armamentarium of chemotherapy, many childhood cancers still cannot be cured with current treatments. Overall, up to 30 % of all children diagnosed with all forms of cancer die as a result of the progressive disease [3]. This figure is likely to be higher in India as a lot more patients present with advanced stages of the disease and are thus likely to have more treatment failures.

In progressive cancers after multiple lines of chemotherapy have failed, further treatment with chemotherapy imposes many side effects that limit dosing and hamper the efficacy of anticancer treatment. At this crucial junction of progressive disease and limited options of chemotherapy, declining further treatment for the patient usually gives the patient and their caretakers a feeling of being abandoned. Saying yes to an alternative way of administering chemotherapy drugs may prevent impending doom and provides a ray of hope.

Low dose chemotherapy administered continuously with an antiangiogenic potential is referred to as metronomic chemotherapy and is an option for a vast majority of patients suffering from multiply relapsed or refractory cancer. This review will address the basis of metronomic chemotherapy and the data on the same in pediatric malignancies.

Metronomic Chemotherapy *vs.* Conventional Chemotherapy

Conventional cytotoxic drugs are designed for use at maximum tolerated dose (MTD) to treat cancer directly by inhibiting or killing rapidly dividing tumor cells and are usually administered at defined intervals as determined by the recovery of bone marrow [4]. In the past two decades, progress in our understanding of the molecular basis of tumor cells has highlighted the limits of conventional

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schedules of cytotoxic agents. First, most solid neoplasms are the result of multiple genetic abnormalities and may contain heterogeneous subpopulations of cells with different cell kinetics, angiogenic, invasive, and metastatic properties [5]. Therefore, tumor responses to a chemotherapeutic regimen may differ, even between patients with the same histology. Secondly, after varying periods of sensitivity, tumor cells develop resistance to cytotoxic agents that cause DNA damage or disrupt DNA replication, a phenomenon related to their genomic instability. Thirdly, conventional chemotherapy is, in general, more effective against the primary tumor than against metastasis [6, 7]. Metastasis is the leading cause of cancer-related death. Most cytotoxic agents, even if given in combined schedules at MTD, achieve only palliation in patients with advanced cancer.

The word metronomic is derived from word "metronome", a musical instrument that produces regular, metrical ticks (beats, clicks)—settable in beats per min. These ticks represent a fixed, regular aural pulse. Metronomic chemotherapy is the frequent administration of chemotherapy drugs at doses below the MTD and with no prolonged drug-free break. It thus achieves a sustained low blood level of the drug without significant toxic side effects. It is administered with the aim of achieving cancer control by targeting angiogenesis. Thus metronomic chemotherapy differs from standard cytotoxic chemotherapy in terms of frequency of the dose, pharmacokinetics, target, intent of treatment and host toxicity (Table 1).

The Angiogenesis–Chemotherapy Model

In 1971, Dr. Judah Folkman proposed the tumor angiogenesis hypothesis "In the absence of vascularization, solid tumors remain dormant and 2–3 mm^3 in size, with size being limited by the ability of oxygen and nutrients to diffuse into the tumor" [8]. Like normal endothelial cells, tumor endothelial cells are also thought to be genetically stable. They proliferate under the stimulus of known growth factors like vascular endothelial growth factor (VEGF). Proliferation and migration of endothelial cells are inhibited by naturally occurring angiogenesis inhibitors like endostatin, angiostatin and thrombospondin-1. Till date around 40 antiangiogenic agents are under clinical trials [9, 10]. Besides direct cell kill, conventional chemotherapy drugs also act by altering tumor blood supply *via* inhibition of tumor angiogenesis, a process by which tumors induce their own blood supply [11–14]. However, long gaps in conventional cytotoxic chemotherapy results in regrowth of the endothelial cells and further angiogenesis [15]. Endothelial cells of the tumor vessels are more vulnerable to low dose continuous chemotherapy as compared to endothelial cells of normal (mature) vessels [13]. Additionally, continuous low-dose chemotherapy enhances the antiangiogenic and proapoptotic effects of some cytotoxic agents, in both dividing tumor cells and endothelial cells [13, 14].

Activation of Immunity

Convincing evidence from the literature indicates that both innate and adaptive immune systems make a crucial contribution to the antitumor effects of conventional chemotherapy based cancer treatments [16]. Despite causing neutropenia and lymphocytopenia, certain cytotoxic chemotherapy drugs (anthracyclins, taxanes and alkylating agents) have immunostimulatory properties. Among them, the effect on regulatory T cells (T_{reg}) appears to be relevant in the context of metronomic chemotherapy. T_{reg} are CD4+ CD25+ lymphocytes, enriched in FoxP3, glucocorticoid-induced TNF receptor and cytotoxic T-lymphocyte-associated antigen-4 that can inhibit antigen-specific immune response both in a cytokine dependent and cell contact-dependent manner [17]. T_{reg} can thus inhibit anti-tumor immune response by suppressing the activity of both tumor-specific (CD8+ cytotoxic T lymphocytes and CD4+ T helper cells) and tumor nonspecific effector cells (natural killer [NK] and NK T cells). Increased number of T_{reg} cells is associated with tumor progression and lack of response [18]. Many studies (preclinical and clinical) have documented the role of low dose cyclophosphamide in reducing the number of T_{reg} cells, suppressing the function of the T_{reg} cells and increasing both lymphocyte proliferation and

Table 1 Summary of differences between metronomic chemotherapy and conventional cytotoxic chemotherapy

	Metronomic chemotherapy	Conventional chemotherapy
Dosing frequency	Continuous dosing, *e.g.*, wkly, every other day, daily	At intervals *e.g.*, Three wkly, fortnightly, wkly
Doses used	Lower than in conventional MTD regimens	Dose intense and used at MTD
Pharmacokinetics	Sustained plasma concentration of the drug	Rise and fall of the plasma concentration of the drug
Target	Endothelial cells in the growing vasculature of the tumor	Proliferating tumor cells
Host toxicity	Significantly less toxic and reduced need for supportive therapy	Toxicity is a concern as doses are used at MTD
Intent of treatment	Cancer control	Cancer eradication

MTD Maximally tolerated dose

memory T cells [19–21]. Besides the activity of low dose chemotherapy on T_{reg} cells and subsequent activation of NK cell antitumor activity, this therapy also has immunostimulatory effect by inducing dendritic cell maturation [22]. Tanaka et al. found that some of the chemotherapeutic drugs such as vinblastine, paclitaxel and etoposide that can be used in metronomic chemotherapy regimens could promote dendritic cell maturation at non-toxic concentrations [23].

Induction of Tumor Dormancy

Tumor dormancy occurs at two points during natural course of malignancy: Initially, during the very early phase of cancer, the tumor cells are lying dormant and they start dividing after initiation of angiogenesis. Later, after completion of anticancer treatment during the remission phase, the tumors are dormant and they resume their growth from remaining residual tumor cells later at the time of relapse [24]. Dormancy occurs by either cell cycle arrest or when there occurs equilibrium between tumor cell proliferation and cellular apoptosis. Metronomic chemotherapy induces tumor dormancy by three different methods, namely, by suppressing angiogenesis, causing apoptosis of cancer cells and by immune-surveillance.

Rationale of Various Drugs used in Metronomic Chemotherapy

Metronomic chemotherapy regimen is usually a combination of various drugs of different classes having antiangiogenic, immunostimulatory as well as apoptotic properties. Continuous administration of low dose of a surprisingly wide range of drugs (such as cyclophosphamide, methotrexate, etoposide, vinblastine and paclitaxel) is cytotoxic to both circulating endothelial cells and circulating endothelial progenitor cells but has no effect on non endothelial cells and leucocytes [14]. Because of their relative genetic stability, endothelial cells are inherently less susceptible to the development of drug resistance than are tumor cells [13]. Even when maximally tolerated doses of chemotherapy drugs are no longer effective, significant inhibition of tumor growth and sparing of normal tissue can sometimes be achieved by simply changing to a metronomic dosing regimen.

The selective toxicity of metronomic chemotherapy for Treg has been studied for the alkylating agent cyclophosphamide [25]. In animal models and in humans administration of low dose of cyclophosphamide leads to a profound decrease in the number of circulating Treg and directly inhibits Treg function [21].

Cyclo-oxygenase 2 (COX 2) inhibitors also show antitumor activity, caused partly by inhibition of angiogenesis [26]. These compounds, being orally active, are suitable for long-term administration and cause only moderate side-effects [27]. Preliminary preclinical studies have shown that the antitumor activity of some cytotoxic agents is potentiated when combined with COX 2 inhibitors [28]. Celecoxib (COX-2 inhibitor) treatment of cells in culture has been shown to result in cell cycle arrest [29]. This appears to be due to the down regulation of various cyclin proteins, which are the essential subunits of cyclin-dependent kinases (CDK) that constitute the cell cycle engine and drive the cells through the cell cycle. Loss of CDK activity prevents the phosphorylation of CDK target proteins, most prominent among them is retinoblastoma (Rb) tumor suppressor protein, which remains hypophosphorylated and thus enforces the checkpoint and concomitant growth arrest in G1 phase of the cell cycle.

Thalidomide, an immunomodulator is known to have powerful anti-angiogenic activity. It has well established anticancer activity against multiple myeloma and Kaposi sarcoma and various other tumors. Thalidomide increases the degradation of the mRNA of a number of peptide-signaling molecules such as fibroblast growth factor and tumor necrosis factor- alpha (TNF-α) [30]. The suppression of TNF-α in cancer patients may be of particular palliative benefit since high levels of TNF-α have previously been linked to cachexia and tumor-related malaise [31].

In vitro data have shown that most chemotherapy drugs may induce resistance of tumor cell lines upon long-term drug exposure. Thus, having a break from these drugs prevents the development of resistance [32]. Therefore drugs in metronomic chemotherapy regime should be regularly stopped, constantly creating phases of long exposure to one or more agents and deprivation to others so as to prevent drug resistance.

Metronomic Chemotherapy in Adult Cancers

Till date majority of clinical trials investigating metronomic chemotherapy in adults have been done in patients with breast carcinoma [33]. Many investigators have used various metronomic chemotherapy regimen for patients with advanced and recurrent ovarian carcinoma [34], advanced multiple myeloma, hormone resistant prostate cancer, non hodgkin lymphoma and others [35]. These regimens showed only modest response rate to metronomic chemotherapy and overall clinical benefit. There has been no other randomized clinical study comparing metronomic chemotherapy with conventional chemotherapy in progressive malignancies in adult patients. Patil et al. from India demonstrated clinical benefit rate of 66.67 % with an estimated median progression free survival of 5.2 mo by using metronomic chemotherapy for palliation in advanced oral cancer [36].

Clinical Evaluation of Metronomic Chemotherapy in Pediatric Malignancies

As compared to adult patients the number of clinical trials of metronomic chemotherapy in children are very limited, but few results are quite promising. Sterba et al. reported promising responses to metronomic temozolomide in combination with radiotherapy in children with medulloblastoma [37]. Later they evaluated a four-drug metronomic chemotherapy combination which included celecoxib, 13-cis retinoic acid, temozolamide and etoposide called as COMBAT protocol (combined oral maintenance biodifferentiating and anti-angiogenic therapy) in 22 children administered over a period of 1 y. Nine of the 14 patients assessable for response demonstrated evidence of treatment benefit manifested as prolonged disease stabilization or response. The protocol medication was well tolerated with very good compliance. Only minimal side effects were observed which responded to dose modification or local therapy [38].

Recently Fousseyni et al. conducted a prospective, pilot, single-center study to evaluate the use of metronomic chemotherapy with vincristine, cyclophosphamide and methotrexate in 12 children with refractory cancer (majority were wilms tumor and retinoblastoma) in economic deprived country Mali; no objective response was observed, but 7 patients experienced disease stabilization (58 %) and continued their treatment for 15 to 24 wk. After a median follow-up of 39 wk, 6 patients (50 %) were alive. Most importantly, in 3 patients (25 %), disease remained stable for at least 6 mo after completion of treatment [39]. Various metronomic chemotherapy regimens have been used in pediatric malignancies in variable number of patients and different childhood cancers [38–42] (Table 2).

Toxicity of Metronomic Chemotherapy

Metronomic chemotherapy appears to be safe and convenient based on various clinical trials done in adult as well as pediatric patients. Metronomic chemotherapy also may be a cost effective/cost-saving treatment option as demonstrated in various trials [38, 43].

Table 2 Various metronomic chemotherapy regimens used in pediatric malignancies

Metronomic chemotherapy regimens with dosages and schedule *	Indications	Number of patients	Reference
• Oral Thalidomide 3mg/kg continuously • Oral Celecoxib 100 mg BID continuously • Oral Etoposide 50 mg/m^2/d q 21 d . alternate with • Oral Cyclophosphamide 2.5mg/kg/d q21 d	Various progressive tumors	20	38
• Inj Vincristine 1.5 mg/ m^2 on days 1, 8, 15, and 22 • Oral Cyclophosphamide 25 mg /m2 on days 1 to 21 • Oral Methotrexate 15 mg/m2 on days 21 to 42, followed by a 1-wk break .	Various progressive tumors	12	39
• Inj vinblastine 1 mg/m^2 3 times a wk / wk • Oral Celecoxib 250 mg/m^2 BD continuously • Oral Cyclophosphamide 30 mg/m^2 continuously	Various progressive tumors	33	40
• Oral Celecoxib *100 mg BD for 21 d alternating with combination of Oral Retinoic acid 100mg/m^2 BD for 21 d Oral Etoposide 50 mg/m^2 BD for 21 d Oral Temozolamide 90 mg/m^2 for 21 d Oral Cyclophosphamide 2.5 mg/kg/d for 21 d	Progressive brain tumors	10	41
• Oral Topotecan 0.8 mg/m^2/d for 21 consecutive days repeated every 28 d.	Recurrent childhood brain tumors	26	42

* Regimens are continued till progression of cancer

High-grade toxic effects are rare. The most common toxic effects noted in trials so far includes grade 1 nausea and/or vomiting, grade 1 and 2 anemia, neutropenia, leucopenia and lymphopenia as well as low-grade fatigue. However, data are still limited and definitive conclusions cannot be drawn regarding the tolerance of these combinations. Overall, metronomic chemotherapy is associated with minimal toxicity and can provide significant clinical benefit and improve the quality of life of patients with advanced and/or relapsed cancer. There are two reports wherein prolonged use of metronomic chemotherapy like temozolamide or etoposide resulted in secondary leukemia [44, 45]; however the intent of treatment with metronomic chemotherapy is not curative and long term side effect like secondary leukemia is not a concern.

Conclusions and Future Directions

Future preclinical and clinical studies will need to define the best agents for use according to tumor type, the number of agents to be incorporated, the doses of each agent to be used alone or in combination, and the timing of drug administration. Generally, this type of therapy is continued till progression of the disease. In view of only single arm studies investigating metronomic chemotherapy in children, many such answers will be provided by a well designed randomized controlled trial between metronomic chemotherapy and best supportive care in future. By combining well-known drugs "of the past" with an innovative treatment schedule, these metronomic chemotherapy regimen appears to be well tolerated and associated with possible cancer stabilization for few months.

Conflict of Interest None.

Role of Funding Source None.

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