EDITORIAL

Slow and Steady Keeps Them in the Race: Metronomic Therapy in Children With Cancer

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Survival in childhood cancer has improved to approximately 80% in high-income countries (HIC) [1]. This success story is attributable to advances in diagnosis and risk stratification, and the protocolized administration of cytotoxic therapy [1,2]. However, the survival lags by 50% in low-income and low-and middle-income countries (LMIC) [1]. The road blocks faced by children with cancer in LMIC include resource constraints, a delayed presentation with advanced disease, treatment abandonment, malnutrition, and increased treatment-related toxicity. Treatment protocols that have been established and validated in HIC are not designed to address the challenges prevalent in LMICs [2]. Malignancy accounts for approximately 1% of deaths in children aged 5-14 years in India [3]. Novel Cost-effective strategies to treat children with cancer are of immense importance in LMICs such as India.

Conventionally, oncological trials have focused on the eradication of the malignancy and the reduction of relapse. With the best of infrastructure, a realistic possibility of a cure in every child with cancer is not conceivable. Five-year overall survival reported in high-risk malignancies such as acute myeloid leukamia, soft tissue/bone sarcomas and neuroblastoma; is markedly lesser when compared to malignancies such as Hodgkin lymphoma, Wilms tumor and germ cell tumors [4]. Survival is notably inferior in metastatic cancers and cancers that are refractory to therapy, or relapse following completion of therapy. Salvage treatment for such cancers is resource-intensive and toxic, and therefore often impractical in LMICs [5].

Metronomic therapy is an alternative paradigm in the management of children with cancer [5]. The approach involves the prolonged administration of chemotherapeutic agents in low, minimally toxic doses with no prolonged drug-free breaks [6]. Further, repurposed non-cytotoxic drugs, *e.g.* celecoxib, thalidomide and valproate, are incorporated into metronomic protocols [7]. In comparison, standard chemotherapy regimens utilize maximally tolerated doses (MTD) of cytotoxic drugs administered over a definite time [6]. Chemotherapy at MTD directly targets the cancer cells, which have an inherent tendency to develop mechanisms of resistance (akin to bacteria treated with antibiotics) [8]. Therapy at MTD necessitates breaks to allow recovery from toxicity, which further facilitates tumor cell proliferation [6]. Alternatively, metronomic therapy attempts to collapse the house by breaking the scaffold. That is, it targets the endothelial cells in the tumor microenvironment by anti-angiogenic mechanisms [6,8]. Additionally, metronomic therapy attempts to switch on the natural immune surveillance mechanisms against the malignant clone and induce tumor cell dormancy [6,8]. The prolonged oral maintenance therapy in acute lymphoblastic leukemia and the recent evidence favoring maintenance therapy in high-risk rhabdomyo-sarcoma stand testimony to the impact of a metronomic approach on outcome in pediatric malignancies [9,10]. ***Web Table* I** lists recent Indian studies which have demonstrated the feasibility and utility of metronomic therapy in children with high-risk cancers. Low cost, minimal toxicity, home-based intake of oral drugs, and a reduction in the need to travel to the hospital and admission comprise the self-evident benefits of metronomic therapy in LMICs [5,6].

Although metronomic therapy appears simple and attractive, there are caveats which need to be addressed. Standard chemotherapy regimens are ratified by randomized trials. Phase III trials, response criteria such as radiological remission in solid malignancies and lymphomas, minimal residual disease assessment in leukemia and outcomes such as disease-free survival may not be relevant in patients on a metronomic regimen [5,11]. Pharmacokinetic studies to optimize drug doses, identification of beneficiary disease subgroups and biological markers for response assessment constitute areas that merit research in the metronomic field [11]. This issue of *Indian Pediatrics* carries an important study in this regard. Pramanik, *et al.* [12] performed a placebo-controlled randomized trial of metronomic therapy in children with progressive extracranial solid malignancies.

The clinical aspects of the study were published previously and are briefly described in **Web Table I** [12]. The current study evaluated specific biomarkers in the same patient cohort. The authors examined the baseline and subsequent levels of vascular endothelial growth factor (VEGF) a pro-angiogenic cytokine, and thrombospondin-1 (TSP-1), an anti-angiogenic cytokine [13]. Although the study concluded that these were not reliable biomarkers for assessment of response to metronomic chemotherapy, some interesting trends were illustrated. The baseline VEGF levels were lower in responders. TSP-1 decreased in responders and increased in non-responders in the metronomic arm.A similar finding was not observed in the placebo arm. The results reaffirm the influence of metronomic treatment on angiogenesis. The study opens new vistas for research in metronomics. For instance, biomarkers such as VEGF levels may show promise as surrogates for identifying patients who would benefit with a metronomic approach. Since the effects of metronomic therapy encompass multiple pathways, the authors rightly state in their discussion that a broader spectrum of circulating biomarkers needs to be studied to yield clinically relevant indicators [13].

A survey of pediatric oncology physicians working in LMIC revealed a strong belief that the use of metronomic therapy is likely to increase with time [14]. An overwhelming majority expressed interest to participate in international studies and registries [14]. Research in metronomic therapy can fill many lacunae, if not all, in the treatment armamentarium for children with cancer.

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Web Table I Indian Studies on Metronomic Therapy in Childhood Cancer

Authors, place, year	*Subjects*	*Treatment regimen**	*Salient results*
Banavali, *et al.* [15], Mumbai, 2019	87 children with non M3-Acute myeloid leukaemia; median age 11 y	6 cycles of 6-thioguanine (40 mg/m^2) and etoposide (50 mg/m^2) days 1 to 20 given q 28 d	Overall survival of 64% at 28 mo
Pramanik, *et al.*[12], Delhi, 2017	Randomized trial comparing 52 patients on metronomic therapy and 56 patients on placebo, with extra-cranial solid malignancies failing 2 lines of treatment; age range 5-18 y	Thalidomide 3 mg/kg OD; celecoxib (100, 200 or 400 mg BD if weight <20 kg, 20-50 kg or >50 kg, respectively); etoposide 50 mg/m2/d alternating with cyclophosphamide 2.5 mg/kg (max. 100 mg) every 3 wk	Patients without bone sarcoma and those able to tolerate therapy for more than 3 cycles (9 wk) benefited. Overall, no improvement in 6-mo progression free survival
Devdas, *et al.* [16], Mumbai, 2019	49 children with relapsed, refractory or metastatic soft tissue sarcomas; age range 3-46 y	Each 28-d cycle: Tamoxifen 40 mg/m^2/d daily, cyclophosphamide and etoposide each 50 mg/m^2/d for 21 d	Clinical benefit (stable disease or response) in 79% of patients

**All the drugs mentioned were orally administered.*