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Metronomic Chemotherapy in Low- and Middle-Income Country; is a New Concept in Pediatric Oncology

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Abstract:-

- ***Background:***

Metronomic chemotherapy (MC) is defined as the frequent administration of chemotherapy at doses below the maximal tolerated dose (MTD) and with no prolonged drug-free break or simply "lower doses, longer times". MC well adapted to low- and middle-income countries.

- ***Objective:***

The aim of this study was to describe the use of MC and assess the safety of MC drugs given to children with refractory, relapse and advance cancer of various tumor types.

- ***Methods*:**

This prospective observational study was conducted in the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from January 2016 to January 2019. This study evaluated the outcome and safety of MC with orally available cytotoxic drugs, Cyclophosphamide (50mg/m^2/dose) and Etoposide (50mg/m^2/dose) daily for 21days followed by 1-week break, Sodium Valproate (Valproic acid)- 10-15mg/kg/day for 21 days followed by 1-week break. This treatment was given to children with advance stage diseases (stage-IV), relapse cases and refractory cancer following treatments with the standard protocols available in our institution. Adverse events were determined through laboratory analyses and investigator observations.

- ***Results:***

Total 21 children (median age- 4y; range, 6 m to14y) were included. Among 21 patients 2 patients lost to follow-up. 19 patients included in this study. The most frequent diagnoses were Neuroblastoma (14). At 8 weeks 13(68.42%) patients experienced disease stabilization and progressive disease 06(31.57%). 11(57.89%) patients achieved partial remission. Complete remission achieved 9(47.36%) patients at 28 weeks and 2(10.52%) patients up to last follow-up at 150weeks and continued their treatment for 37.5 months. After a median follow-up of 24 weeks (range:2-96wk) 8 patients (42%) were alive. During treatment period there were no significant complication only one patient developed mild neutropenia. No other moderate to severe toxicities were noted.

- ***Conclusion:***

The MC that we used was safe, well tolerated and represents good value for patients with advance diseases that are eligible for palliative care. Children achieved disease stabilization, partial and complete remission without any complication. The use of MC in children in low and middle-income countries is safe and effect.

***Keywords*:-** *Metronomic Chemotherapy, Low and Middle Income, Advanced Cancer, Children.*

I. INTRODUCTION

Metronomic chemotherapy is a new concept in oncology compared to conventional chemotherapy. 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 (MTD) imposes many side effects that further limits the dosing and therefore decreases the anticancer effects.[1]

Conventional chemotherapy is, in general, more effective against the primary tumor than against metastasis. 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[1].

Overall, up to 30 % of all children diagnosed with all forms of cancer die as a result of the progressive disease. 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.[1,2]

The term "metronomic chemotherapy" (MTC) is currently used for frequent and regular administration of lower doses of chemotherapeutic drugs with minimal drug free time intervals, or simply "lower doses, longer times", in order to establish a prolonged and lower albeit an active range of plasma concentration enabling a favorable side-effect profle.[3,4] According to NCI (National Cancer

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Institute) Dictionary of Cancer Terms, metronomic chemotherapy: treatment in which low doses of anticancer drugs are given on a continuous or frequent, regular schedule (such as daily or weekly), usually over a long time. Metronomic chemotherapy causes less severe side effects than standard chemotherapy. Giving low doses of chemotherapy may stop the growth of new blood vessels that tumors need to grow.

The introduction of the maximum tolerated dose (MTD) in usual treatment protocols made necessary the imposition of rest periods between cycles of therapy—a practice that not only involves re-growth of tumor cells, but also growth of selected clones resistant to the therapy[5].

The novel therapeutic approach of MCT is emerging in the era of targeted cancer treatment[5]. In the past 5 years, multiple clinical trials have investigated the safety and efficacy of metronomic chemotherapy. Numerous types of high-risk tumors, including brain tumors (i.e., high-grade glioma, ependymoma, and medulloblastoma), neuroblastoma and sarcomas, hepatoblastoma, nephroblastoma could potentially benefit from these treatments. The common utilization of daily oral therapy for the maintenance phase of leukemia may represent an old example of metronomic chemotherapy. Drugs with anti-angiogenic property usually used as metronomic therapy. The recent studies have suggested that frequent administration of low doses (1/10th-1/3rd of the maximum tolerated dose, MTD) of some anti-neoplastic drugs known as 'metronomic' chemotherapy which shows the anti-angiogenic property of the drugs[6].

II. MATERIALS AND METHODS

➢ *Study Design and Patient Material*

In this study, 21 patients with advanced stage disease included. Among 21 patients 2 patients lost to follow-up. 19 patients continued their treatment up to last follow-up. This prospective observational study was conducted in the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from January 2016 to January 2019. This study evaluated the outcome and safety of metronomic chemotherapy. The patients started treatment with low dose orally available cytotoxic drugs, Cyclophosphamide (50mg/m^2/dose) and Etoposide (50mg/m^2/dose) daily for 21days followed by 1-week break, Sodium Valproate (Valproic acid)- 10-15mg/kg/day for 21 days followed by 1-week break. This treatment was given to children with advance stage diseases (stage-IV), relapse cases and refractory cancer following treatments with the standard protocols available in our institution. Adverse events were determined through laboratory analyses and investigator observations. Children were followed-up every eighth week by radiological evaluation and every fourth week by clinical examination, including laboratory (hematological and biochemical) results. Assessment of tumor response was performed according to standard RECIST criteria[7] (Table-1).

➢ *Patient Data*

Clinical data were obtained from a structured questioner. Variables recorded were age at diagnosis, date of diagnosis, date of recurrence, site of primary tumor, side effects, previous treatment, date of death, cause of death (cancer-related or other), treatment duration, indication for treatment, response of the treatment and last date of follow-up for survivals. Side effects were classified according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.

➢ *Operational Definition*

- *Overall Survival (OS):*

OS was defined as the time from diagnosis to date of death (cancer-related or other causes) or date of last follow-up for patients who were alive at the time of analysis.

Table 1 RECIST criteria for evaluation of tumor response

Response	RECIST
Complete response	Disappearance of all target lesions, all nodal lesions have short axis <10mm
Partial response	≥30% decrease in the sum of diameters from baseline sum diameters
Progressive disease	≥20% increase in the smallest sum of diameters as reference with an absolute increase of ≥5mm
Stable disease	Dose not meet the above criteria

RECIST, Response Evaluation Criteria in Solid Tumors

III. RESULTS

Total 21 children (median age- 4y; range, 6 m to14y) were included. Among 21 patients 2 patients lost to follow-up. 19 patients included in this study. The most frequent diagnoses were Neuroblastoma (14). At 8 weeks 13(68.42%) patients experienced disease stabilization and progressive disease 06(31.57%). 11(57.89%) patients achieved partial remission. Complete remission achieved 9(47.36%) patients at 28 weeks and 2(10.52%) patients up to last follow-up at 150weeks and continued their treatment for 37.5 months. After a median follow-up of 24 weeks (range: 2-96wk) 8 patients (42%) were alive. During treatment period there was no significant complication only one patient developed mild neutropenia. No other moderate to severe toxicities were noted.

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Table 2 Distribution of patients by age

Age(year)	Number of patient(n)	Percentage (%)
≤5	13	68.43
≥5	06	31.57
Total	19	100.00
Median age	4(0.6-14)	

Table 2 Among 19 patients aged <5 years groups were 68.43% (13), >5yrs group were 31.57% (06) Median age: 4 years (range was 0.6-14)

Table 3 Gender distribution of patients

Gender	Number of patient(n)	Percentage (%)
	09	47.37
	10	52.63
	19	100.00

Table 3 In this study 47% were male and the remaining 52% were female and M: F ratio was 1:1.1

Table 4 Diagnosis of diseases at presentation

Diagnosis	Number of patient(n)	Percentage (%)
Neuroblastoma	14	73.68
Medulloblastoma	02	10.52
Hepatoblastoma	01	05.26
Hepatocellular carcinoma	01	05.26
Nephroblastoma	01	05.26
Total	19	100.00

Table 4 At presentation most, frequent diagnosis was Neuroblastoma 14(73.68%) and medulloblastoma (10.52%)

Table 5 Evaluation of tumors according to RECIST criteria

Evaluation criteria	n/%
Stable disease (SD)	13(68.42%)
Progressive disease (PD)	06(31.57%)
Partial remission (PR)	11(57%)
Complete remission (CR)	02(10.52%)

Table 5 This table shows 13(68.42%) patients experienced stable disease (SD) and Progressive disease (PD) 06(31.57%) at 8 weeks of follow-up. Patients achieved partial remission (PR) 11(57%) at 12 weeks and complete remission (CR) 02(10.52%) at 28 weeks.

IV. DISCUSSION

Despite in last three decades survival rate of childhood cancer improved in developed country as well as low- and middle-income country although it is a challenging issue for physicians worldwide[8]. In developed country cure rate is high 80% but in low- and middle-income country (LMICs) only 10%, mostly due to delayed diagnosis[8]. In our institute 40-50% (although this is not actual data because of lack of proper registry system) children with cancer come at advanced stage and this group of children needs palliative care.

According to Traore Fousseyni at all. Metronomic chemotherapy (MC) is defined as the frequent administration of chemotherapy at doses below the maximal tolerated dose and with no prolonged drug-free break[9]. In our study we also frequently use orally available chemotherapy having anti-angiogenic effect at a dose below the maximal tolerated dose.

In METRO-MALI-01 study median age, 3.7 y (range, 2 to 7 y)[9] and in our study Median age: 4 years and female were more. Children in this study were relapse, refractory disease and advanced stage disease like METRO-MALI-01 study.[9] metronomic chemotherapy (MC) is one step forward treatment strategy for advanced stage of disease in low- and middle-income country. At presentation most common diagnosis was Neuroblastoma like in METRO-MALI-01 study where Nephroblastoma was common. According to RECIST criteria for evaluation of tumor response at eight weeks of MCT 13 patient's tumor were stable but in metro-Mali study where 6 stabilizations of disease were observed[9]. In our study we used orally available anticancer drugs which have antiangiogenic property e.g. Cyclophosphamide and Etoposide.

D. Zapletalova et al, also use Cyclophosphamide and Etoposide, temozolomide, celecoxib, fenofibrate as metronomic chemotherapy in their study[10]. MC (with anti-angiogenic property) may be used as maintenance therapy in

selected very-high-risk subsets, or it can be used for overt relapses or also in palliative care setting[10,11]. Valproic Acid also use as a MC in metro mali-1 study.[9, 10, 12]

During treatment period and after completion of therapy there are no major toxicity seen in this study like other study in pediatric group of patients and disease stabilization shows after discontinuation of therapy.[9,12,13,14] The children suffering with some debilitating diseases who may turn to long-term survivors with MC. Therefore, metronomic regimens used in children could be more efficient and safer and less toxic and cost effective for advanced disease LMICs.

V. CONCLUSION

The MC that we used was safe, well tolerated and represents good value for patients with advance diseases that are eligible for palliative care. Children achieved disease stabilization, partial and complete remission without any complication. The use of MC in children in low-income countries warrants further studies.

STRENGTHS AND LIMITATIONS

The strength of our study is that it is the first prospective observational study to our knowledge, of pediatric metronomic chemotherapy. Sample size is small and single center study.

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