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Metro-SMHOP 01: Metronomics combination with cyclophosphamide-etoposide and valproic acid for refractory and relapsing pediatric malignancies

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Abstract

Background: In low- and middle-income countries, therapeutic options for advanced, refractory, or relapsing malignancies are limited due to local constraints such as cost of drugs, distance from oncology centers, and lack of availability of new anticancer drugs. Metronomics, which combines metronomic chemotherapy (MC) and drug repositioning, allows for the provision of new therapeutic options for patients in this setting.

Aim of the study: To evaluate the activity and toxicity of a metronomic regimen in Moroccan pediatric patients with refractory or relapsing malignancies.

Patients and methods: From July 2014 to January 2018, patients with refractory/relapsing solid tumors treated in five pediatric oncology centers were consecutively enrolled. The metronomic regimen consisted of 28-day cycles with daily oral administration of cyclophosphamide (30 mg/m^2) from days 1 to 21, together with oral etoposide (25 mg/m^2) from days 1 to 21 followed by break of one week and daily valproic acid (20 mg/kg) from days 1 to 28.

Abbreviations: LMIC, low- and middle-income countries; MC, metronomic chemotherapy; MTD, maximum tolerated dose; OS, overall survival; PFS, progression-free survival; SMHOP, Moroccan Society of Paediatric Haematology and Oncology

Results: Ninety-eight children (median age, 8 years) were included. Underlying malignancies were neuroblastoma (24 patients), Ewing sarcoma (18), osteosarcoma (14), rhabdomyosarcoma (14), and miscellaneous tumors (28). A total of 557 cycles were given (median: 6; range, 1-18 cycles). One-year progression-free survival of our patients was 19%, and one-year overall survival was 22%. Complete response was obtained in three cases (3%), partial response in 11 cases (11%), and tumor stabilization for more than six months in 28 cases (28%).

Conclusion: This three-drug metronomic combination was well tolerated and associated with tumor response and disease stabilization in 42 patients even for a long period.

KEYWORDS
angiogenesis, cancer, chemotherapy, drug repositioning, immune system, metronomic, pediatric, pharmacology

1 | INTRODUCTION

Over the past few decades, researchers have established that angiogenesis is crucial for the local and metastatic growth of cancer. Pioneering research on angiogenesis carried out by Judah Folkman established the tumor vascular endothelium as a clinically validated therapeutic target.[1] The discovery of the antiangiogenic properties of anticancer agents led to the development of a new modality of chemotherapy drug administration called "metronomic chemotherapy" (MC), which was discovered by teams of both Judah Folkman and Robert Kerbel.[1,2]

This novel approach refers to the frequent, even daily, administration of cytotoxic drugs of doses significantly less than the maximum tolerated dose (MTD), with no prolonged drug-free breaks.[3] MC is frequently combined with drug repositioning to generate a metronomic combination.[4] Drug repositioning consists of using non-anticancer agents for which anticancer properties have been identified.[5]

Many clinical trials in both adult and pediatric populations confirm the potential and efficacy of MC in terms of clinical benefit and survival prolongation.[6-13]

For the first time in Morocco we tested the concept of MC for children with cancer. We reported the results of the multicenter prospective phase II trial of a multiagent oral metronomic "three-drug" regimen for children with recurrent or refractory cancer.

The objective of this work is to evaluate the efficacy and safety of a metronomic combination with cyclophosphamide-etoposide and valproic acid in pediatric patients. This project was conducted by The Moroccan Society of Paediatric Haematology and Oncology (SMHOP).

2 | PATIENTS AND METHODS

Over a period of 42 months from July 2014 to January 2018, patients under 18 years of age, with relapsing or refractory tumors or a very advanced disease were included in a prospective multicenter metronomic phase II trial in five Moroccan pediatric hematology/oncology centers of the SMHOP.

The protocol was approved by our institutional ethics committee (CERB N/R: 65/16). Informed consent was obtained from parents and children when applicable.

The metronomic protocol consisted of the combination of oral chemotherapy with cyclophosphamide, etoposide, and valproic acid. The MC protocol consisted of 28-day cycles with daily oral administration of cyclophosphamide (30 mg/m^2) from days 1 to 21, together with oral etoposide (25 mg/m^2) from days 1 to 21 followed by break of one week and daily valproic acid (20 mg/kg) from days 1 to 28. Etoposide and cyclophosphamide were chosen because both drugs have antiangiogenic and proimmune anticancer properties.[14] Their anticancer activity when given as single agents or in combination when given in a metronomic manner is well documented in a wide spectrum of pediatric tumors.[14] Valproic acid has been added to produce antihistone deacetylase (HDAC) and multidrug resistance (MDR) reversal properties. Traore et al. have already demonstrated that valproic acid can be safely added to the metronomic regimen.[15]

Because the oral formulation of etoposide is not available in Morocco, the i.v. formulation was repackaged to oral formulation in syringes by the pharmacists as described by Demoré et al.[16]

The primary objective was the evaluation of progression-free survival (PFS). Secondary objectives were the impact of treatment on the quality of life, the consumption of analgesia, and transfusion needs. Further evaluation of antitumoural activity was performed by overall survival (OS), the clinical benefit was defined as complete remission, partial remission, and stable disease more than six months.

The baseline evaluation included medical history and physical examination, complete blood count, hepatic and renal function tests. Patient assessment was performed clinically after every cycle. Disease was evaluated every four cycles by imaging or earlier in the case of clinical progression. Quality of life was assessed at baseline and at

every four cycles using Lansky scale for under 12 years and Karnofsky scale for children over 12 years. Toxicity was evaluated using the WHO Common Toxicity Criteria version 4.0. The collected data were based on the following criteria: age, sex, diagnosis, time between initial management and inclusion in the metronomic regimen, previous line of chemotherapy, type of surgical treatment, previous radiotherapy, histological diagnosis, tumor volume, Karnofsky or Lansky evaluation, biological toxicity, and imaging.

2.1 | Statistical analysis

Patient baseline characteristics were summarized as number (percentage) of patients for categorical endpoints and median (range) for continuous endpoints. Secondary endpoints of the study included objective response rate, OS, PFS, safety assessments, and quality of life. OS was defined as time from the date of treatment initiation to date of death from any cause, and PFS was defined as time from the date of treatment initiation to date of either death from any cause or disease progression. The Kaplan-Meier method was used to estimate time-to-event endpoints. Statistical analyses were performed using SPSS 13.0 software.

TABLE 1 Patient characteristics

Characteristic	Frequency (%)
Gender	
Male	64 (65%)
Female	34 (35%)
Age (years)	
Median	8
Range	(2-18 years)
Disease strata/diagnosis	
Neuroblastoma	24 (24%)
Rhabdomyosarcoma	14 (14%)
Bone tumor	32 (32%)
Osteosarcoma	14 (14%)
Ewing sarcoma	18 (18%)
Malignant germ-cell tumors	4 (4%)
Hodgkin lymphoma	4 (4%)
Wilms tumor	4 (4%)
Retinoblastoma	4 (4%)
Medulloblastoma	3 (3%)
Miscellaneous tumors	9 (9%)

3 | RESULTS

From July 2014 to January 2018, 98 patients were enrolled in the trial. Sixty-four were males and 34 were females, giving a sex ratio of 1.8. The median age at the initiation of treatment was eight years (range, 2-18 years). The median time between initial management and inclusion in this protocol was 12 months (range, 1 month-12 years).

The MC regimen was used in relapse in 36 cases, progression in 41 cases, resistance in 15 cases, 3 cases for very advanced disease at diagnosis and standard treatment refusal in 3 cases.

Diagnoses included neuroblastoma (24), Ewing sarcoma (18), osteosarcoma (14), rhabdomyosarcoma (14), and other miscellaneous diseases (28 cases). Sixty-two patients were metastatic at diagnosis (63%). Patient characteristics are summarized in Table 1.

A total of 557 cycles of MC were given to 98 patients with a median of six cycles per patient (range, 1-18 cycles).

Treatment was well tolerated overall in the majority of patients with no toxicity or maximum grade 1 toxicities in 529 cycles of MC (95%). The most common toxicities were hematologic: grade 3-4 anemia (hemoglobin < 8 g/dL) was observed in 28 cycles (5%), and grade 4 thrombocytopenia (platelets $< 20 \times 10^9$/L) occurred in 11 cycles (2%). In 28 cycles of MC, transfusion was needed (5%) especially in metastatic neuroblastoma. No other grade 3 or 4 toxicities were observed. Analgesic treatment was used in 107 cycles of metronomic treatment (19%). There was no dose reduction for toxicity.

The six-month OS was 40% (95% CI). Complete response was obtained in three cases (3%), partial response in 11 cases (11%), and stable disease for more than six months in 28 cases (28%). One-year PFS of our series was 19% and one-year OS was 22%. In Figure 1, we report the PFS and the OS. No relapse was observed 18 months after treatment was stopped; for four patients, no relapse was observed at 54 months.

Patients with Ewing sarcoma, rhabdomyosarcoma, neuroblastoma, and Hodgkin lymphoma were more likely to benefit from the metronomic approach. Conversely, no response or disease stabilization was seen in patients with osteosarcoma and Wilms tumor. Table 2 shows the major tumors types, number of previous lines of chemotherapy, and response to MC.

Quality of life was assessed after cycles of MC using Karnofsky/Lansky scores. The median percentage of the initial Karnofsky/Lansky evaluation was 50% (range, 40%-100%) versus 70% (range, 50%-100%) in the final evaluation. In 15 patients, an increase in the Karnofsky/Lansky evaluation was noted (15%).

4 | DISCUSSION

We present the Moroccan experience with a three-drug all oral metronomic protocol (etoposide-cyclophosphamide-valproic acid) for pediatric patients with refractory/relapsing malignancies in SMHOP centers. We found that this regimen could lead to sustained responses and stable disease in 14% and 28%, respectively, of the cases for a clinical benefit rate of over 40%. In some cases, MC was offered to patients initially presenting with very advanced tumors or in some cases of standard treatment refusal.

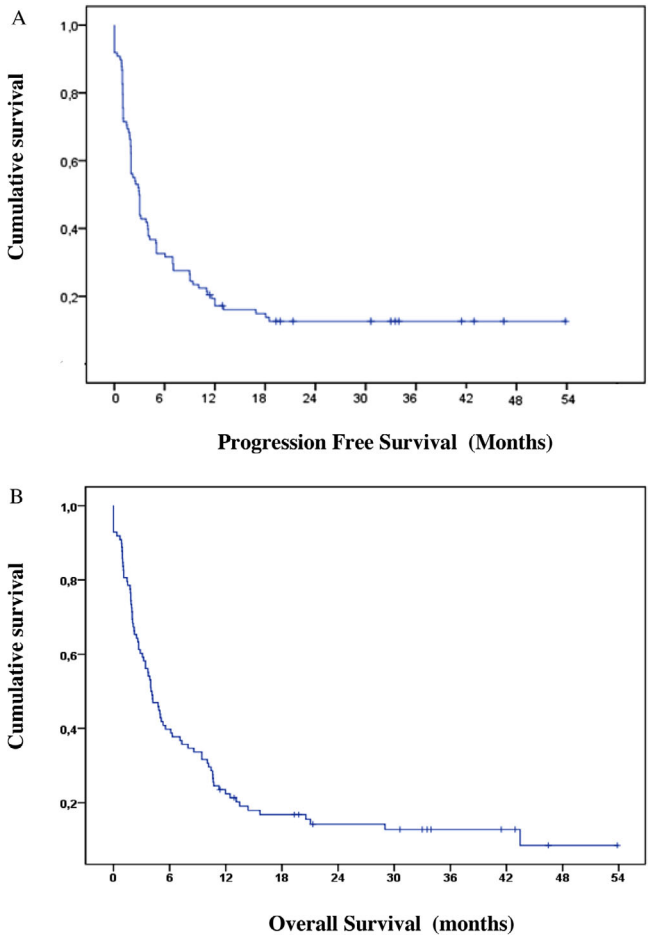

FIGURE 1 A: PFS for all patients. PFS after six months was 32%, after 12 months 19%, and after 24 months 12%. B: OS for all patients. OS after six months was 40%, after 12 months 22%, and after 24 months 14%

In our study, the median PFS was three months and depended on the diagnosis, in line with previous studies on metronomics in palliative care settings.[11,17-19] Although the number of patients treated in this study is higher than in most metronomic pediatric trials,[9,10,15,17,23,26] the design of the study with the lack of cohort of patients with different type of diseases and phase 2 design (i.e., Simon 2 steps) does not allow us to formally demonstrate its activity or absence of activity in specific tumors. Nevertheless, as reported in previous studies, our osteosarcoma patients were not good responders to metronomic chemotherapy.[11,17] Therefore, we do not believe that patients with osteosarcoma should be treated with this MC protocol. Conversely, some tumors such as neuroblastoma or lymphoma or low-grade glioma are good candidates for MC.[11,18-21] Berthold et al. concluded that a metronomic protocol using celecoxib, cyclophosphamide, vinblastine, and etoposide has low toxicity and is as effective as a current standard treatment for recurrent high-risk neuroblastoma.[19] The phase II study of a multiagent oral metronomic regimen, conducted by Robison et al., showed that clinical benefit was evident in patients with low-grade glioma and ependymoma.[11]

No relapse was observed after 18 months once the treatment had stopped, suggesting that, as observed in some studies, reinduction of neoplasm dormancy might be achieved in some patients.[9,14,26]

We also observed that this regimen was well tolerated with very little hematological toxicity, frequently observed when using a more intense metronomic protocol.[17,22,23] Quality of life during metronomic therapy has rarely been reported. Porkholm et al. have reported that the Karnofsky-Lansky scores increased significantly during MC in 17 children, with 35% of the patients having a transient improvement in their clinical status.[23] In this trial, quality of life was maintained during treatment, which suggests that the low toxicity of the treatment did not impede the benefit induced by MC.

Metronomics combines MC and drug repositioning.[4] In this study, we used valproic acid as already described by Traore et al. in Metro-Mali 02.[15] Valproic acid may act through histone deacetylase (HDAC) inhibition and/or inhibition of proline-glycine-proline. No dose levels of valproic acid were checked, so dose levels were likely not to be optimal for all patients. The design of the study does not allow us to conclude with regard to the value of adding valproic acid to the metronomic backbone. A randomized trial would be mandatory to answer this question. Alternative repurposed drugs could be used to further strengthen and widen the spectrum of action of a metronomic combination or be selected on the biomolecular profiling of the tumor,[24,25] with the advantages of usually mild toxicity and low cost while trying to tailor a metronomic regimen.[14]

TABLE 2 Outcomes by tumors types and number of previous lines of chemotherapy

Stratum	*N*	Treatment lines prior to MC	CR	Response PR	SD	PD
Neuroblastome	24	1 (1-2)	-	1	4	19
Ewing sarcoma	18	1 (1-2)	1	4	3	10
Osteosarcoma	14	1	-	-	-	14
Rhabdomyosarcoma	14	1(1-3)	1	2	4	7
MGT	4	1	-	-	1	3
Hodgkin lymphoma	4	1 (1-3)	-	1	1	2
Wilms tumor	4	1 (1-2)	-	-	-	4

CR, complete response; MGT, malignant germ-cell tumors; PD, progressive disease, PR, partial response; SD, stable disease.

For low- and middle-income countries, metronomics has been foreseen as a potential way to overcome many barriers to anticancer treatment such as cost and toxicities.[4] Over the last few years, a growing number of publications have investigated the potential role of metronomics for children in LMIC,[4,14,20,24,26-28] and a recent international survey has confirmed the interest of pediatric oncologists working in LMIC for this approach, especially for palliative care or as a maintenance for patients with high-risk disease.[29] Indeed, access to newer therapies such as targeted therapies or immunotherapies is very limited in LMIC. Consequently, for these patients, metronomics represents a way to respond to patients' unmet needs and to families who want something to be done for their children.[30] The hope that can be generated must of course be balanced and integrated in a palliative approach.

5 | CONCLUSION

We report the activity and toxicity of a three-drug metronomic regimen in patients with refractory/relapsing/advanced pediatric malignancies. We believe this regimen can be further used in patients. International cooperation is required to explore stronger evidence for metronomics in children and tailor treatment to underlying disease and setting.

CONFLICTS OF INTEREST

The authors report no conflict of interests.

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An anonymized copy of the data reported here will be made available to readers" in ScholarOne system.

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