Original Article

Preliminary evaluation of children treated with metronomic chemotherapy and valproic acid in a low-income country: Metro-Mali-02

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Abstract

BACKGROUND: Metronomics is defined by the combination of metronomic chemotherapy and drug repositioning. Since off-patent chemotherapeutic drugs can be used and given the low toxicity profile of this approach, metronomics appears to be an invaluable alternative to bring affordable targeted therapies in low-income countries. **OBJECTIVE:** The aim of this study was to report on the preliminary efficacy and safety of a metronomic vincristine/cyclophosphamide/methotrexate/valproic acid regimen given to children with refractory cancer of various tumor types or with a very advanced disease. **MATERIALS AND METHODS:** This prospective, single-center study evaluated the use of a metronomics protocol, consisting of a first cycle of weekly vincristine 1.5 mg/m^2 (days: 1, 8, 15 and 22), daily cyclophosphamide 25 mg/m^2 (days: 1-21), twice weekly methotrexate 15 mg/m^2 (days: 21-42) and daily valproic acid (30 mg/kg/d) followed by a 1-week break. For the following cycles, vincristine was administrated only at week 1 and 5 of the cycle. This treatment was proposed to children with refractory disease and patients who were not eligible for the protocols available in the hospital. Adverse events were determined through laboratory analyses and investigator observations. **RESULTS:** From January 2010 to January 2011, 7 children (mean age: 5.4 ± 3 years old) were treated. Most frequent diagnosis was retinoblastoma. Two partial responses were observed in patients with neuroblastoma and retinoblastoma. These two patients are alive with stable disease at last follow-up (6 and 26 months, respectively) after stopping treatment. **CONCLUSION:** Metronomics allows treating patients with advanced or refractory or relapsing disease and the introduction of targeted treatments in low-income countries. The potential of metronomics in children and young adults living in middle- and low-income countries warrants further larger studies.

Key Words: Angiogenesis, developing country, metronomic chemotherapy, pediatric oncology, tumor dormancy

Introduction

In high-income countries, approximately 75% of the 50,000 children diagnosed with cancer each year survive.[1] Yet cancer remains the leading cause of disease-related deaths in children. In low- and middle-income countries (LMICs), where 80% of all children live, the 200,000 children diagnosed with cancer each year have only very limited access to curative treatments and only about 25% will survive.[2,3] Little is known about the epidemiology of pediatric cancers in LMICs and data suffer from many sources of error such as inaccurate death certificates, misdiagnosis and under-reporting.

Many hurdles prevent the development of efficient management of children with cancer in developing countries: The availability of drugs and treatment facilities, cost, distance to pediatric oncology unit, compliance with treatment, delayed diagnosis, lack of follow-up especially in children who have surgery as the primary mode of treatment, prior consultation of traditional practitioners and cultural barrier.[2-4] In Mali, as in many African

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countries, cancer is still regarded as a disease induced by supernatural forces and/or an incurable disease.

One of the major problems relies in the management of children with relapsed, progressive and/or very advanced disease (AD). For these patients, there is no curative option in LMICs.[3] The treatment of these patients with second line intensive or experimental treatments with new expensive drugs as it is done in Europe or in the USA, is a totally unfeasible option in Africa.

Metronomics[4] is defined by the combination of metronomic chemotherapy (MC)[5] and drug repositioning.[6] MC (i.e., the frequent administrative of chemotherapy at relatively low dose, without extended drug-free break) may be effective through the targeting of cancer cells, tumor-associated angiogenesis and stimulation of anticancer immunity[5] and when combined with drug repositioning (i.e., the use of already approved drugs for new medical indications), it allows the introduction of targeted therapies for patients living in LMICs at a low cost.[4]

Meanwhile, MC has also been reported to significantly reduce the adverse events usually associated with chemotherapy. Although clinical data of MC in pediatric oncology still remains somewhat limited,[5] this approach may be well-suited and represents a real alternative solution for children with cancer in general and in LMICs in particular.[4,7]

We previously reported about the use of a multidrug metronomic combination that was able to induce stabilization of the refractory cancer in children[8] and re-induction of tumor dormancy.[5,9] Valroic acid is an antiepileptic agent, whose anticancer properties have recently been unveiled.[10] Indeed, valproic acid can be used as an HDAC inhibitor in the treatment of many malignancies. Here, we report the assessment of safety and efficacy of a metronomics regimen combining MC (vincristine/cyclophosphamide/methotrexate) and drug repositioning (valproic acid) in children with refractory cancer or very AD who could not tolerate conventional chemotherapy.

Materials and Methods

This prospective, pilot, single-center study evaluated the use of MC with cycles consisting of weekly vincristine 1.5 mg/m² (days: 1, 8, 15 and 22), daily cyclophosphamide 25 mg/m² (days: 1-21) and twice-weekly methotrexate 15 mg/m² (days: 21-42), followed by a 1-week break. For the following cycles, vincristine was administrated only at week 1 and 5 of the cycle [Figure 1]. Our institutional ethics committee approved the protocol. All families gave consent before enrolment of the patients in the study. This treatment was proposed to children, aged from 3 to 21 years of age at study entry, with refractory cancer following treatment protocol available in our institution or to patients who were not eligible for the appropriate protocol. Patients had to have recovered from all acute toxic effects of prior therapy with an absolute neutrophil count ≥1.0 × 109/L and absolute platelet count ≥75 × 109/L. Patients were also required to have an age-adjusted normal serum creatinine or a creatinine clearance ≥60 mL/min/1.73 m², serum bilirubin ≤1.5 times the upper limit of normal (ULN) and the serum alanine transaminase ≤5 times the ULN.

To be included in the study, patients also needed to respect scheduled follow-up and management of

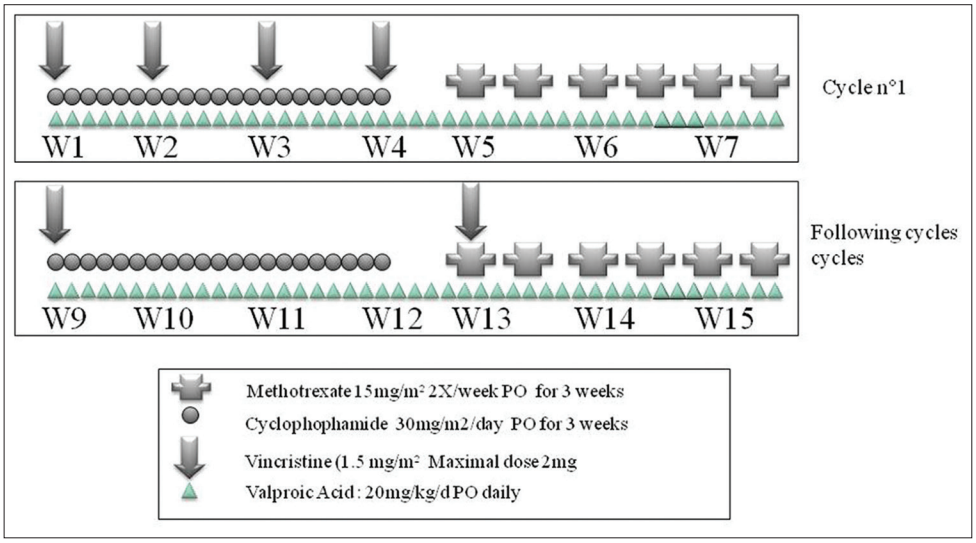

Figure 1: The Metro-Mali-02/03 metronomic regimen

toxicity. Adverse events were determined through laboratory analyses and investigator observations. All patients with an uncontrolled concurrent illness or active infection, human immunodeficiency virus positive, unable to swallow oral medication or pregnant and breast-feeding were excluded from the study. Treatment was terminated upon tumor progression or following physician's decision, according to parent's will or due to unacceptable toxicity.

From January 2010 to January 2011, 7 children were included in this study, with a mean age of 5.4 ± 3 years old. There were five boys and two girls. Of note, malnutrition was found in about 30% of the children. None had medical insurance. 5/7 patients came from a rural area and 6/7 had a low socio-economic status. Details of the population and outcomes are reported in Table 1.

Results

At the end of the observation period, the mean duration of treatment was 34 ± 31 weeks with 2 patients alive with a mean follow-up of 9 ± 11 weeks. Details of treatments outcome are given in the Table 1. Two partial responses, which respectively lasted more than 2 years, were obtained. The first of these two patients had a metastatic neuroblastoma and complete response of medullar metastasis was obtained. These two patients did not display any progression of their disease even after stopping the metronomic treatment. Besides, one patient with a metastatic osteosarcoma received treatment for more than a year before dying quickly of progression. One patient was lost of follow-up after less than 2 month of the treatment and two progressed while receiving treatment.

Most importantly, according to the National Cancer Institute Common Toxicity Criteria, the tolerability was acceptable. The following adverse events were noted: One grade IV anemia and 1 grade IV non-febrile neutropenia. No other grade III or IV toxicities were observed. No patient contracted malaria while on treatment.

Discussion

The population reported here is mainly composed of children with refractory or advanced retinoblastoma and include a very limited number of patients so that extrapolation of the results should be done very carefully.

In line with results published with the Metro-Mali-01 regimen,[8] our results indicate that this metronomic regimen can be administered with very low toxicity and can lead to long-term control of the disease in some cases.

Interestingly, one patient with a metastatic osteosarcoma had a stable disease for more than a year while receiving the experimental regimen and one patient with a metastatic neuroblastoma has been treated for more than a year leading to clearance of metastatic disease and a reduction in size of the primary tumor.

Valproic acid may have a role in these anti-tumor effect since it has been showed to have activity in neuroblastoma,[11,12] osteosarcoma[13] and retinoblastoma,[14] where it can sensitize cancer cells to chemotherapy or radiotherapy.

In two patients residual disease remained stable even after treatment cessation confirming the potential of metronomic chemotherapy to re-induce tumor dormancy[9] as previously reported.[15-17]

Compliance is a major concern when considering cancer treatments and more specifically long-term oral

Table 1: Patients characteristics and treatment outcomes

Pt nb	Sex	Tumour type	Indication	Age (year)	Weight (Kg)	Previous lines of treatment	Time on treament (weeks)	Best response	Follow-up (weeks)	Status
1	M	Unilateral metastatic retinoblastoma	VAT	5	13	0	21	PR	5	PR
2	M	Unilateral > Reese grade V retinoblastoma	VAT	6	12	0	7	?	?	?
3	F	Bilateral retinoblastoma	VAT	3	7,8	0	2	PD	4	D
4	F	Unilateral metastatic retinoblastoma	VAT	3	11	0	20	PD	3	D
5	M	Metastatic neuroblastoma	PD	5	22	1	96	PR	31	PR
6	M	Unilateral > Reese grade V retinoblastoma	VAT	4	10,2	1	12	PD	2	D
7	M	Metastatic osteosarcoma	VAT	12	25	0	60	SD	9	D

PD=Progressive disease; SD=Stable disease; VAT=Very advanced tumor; D=Died of disease

treatments. In children, giving several medications every day for a long period of time is a difficult task so that parent's understanding of the importance of strict treatment compliance must be actively sought after. Regular cellular phone checking of compliance to the treatment plan could be an interesting way to increase adherence to treatment as already demonstrated for antiretroviral therapy in India.[18]

Conclusion

The preliminary evaluation of the metronomics protocol reported here demonstrates the potential of this approach for children with cancer living in LMICs, notably as it allows the introduction of target therapies[4,19] in LMICs. Cheaper, less toxic treatment could be developed by using more often drugs that are already approved for other medical applications but have recently shown potent anti-tumor activity, such as β-blockers.[20,21] Additional state of the art studies in larger and more homogeneous patient populations are critical to further demonstrate the benefits of metronomics in developing countries. Incentive to try to reach implication of pharmaceutical companies to help funding search studies together with academics and philanthropy are mandatory.[22]

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