Article published online: 2021-06-28

Metronomics in Pediatric Oncology: Lessons Learned and the Way Forward

Metronomic chemotherapy appeared as a new "genre" of chemotherapy from the bench to bedside in the early 2000s and since then has secured a niche for itself in oncology practice in general and pediatric oncology in particular. Metronomic chemotherapy has been defined variously. One popular definition mentions it as the minimum biologically effective dose of a chemotherapeutic agent given continuously without prolonged drug-free breaks leading to anticancer activity.[1] Another contemporary definition is "regular administration of low, less toxic doses of chemotherapeutic drugs for prolonged periods of time, with no extended drug-free breaks."[2] Thus, the key features of metronomic chemotherapy are as follows: frequent dosing, no long breaks, doses lower than maximum tolerated dose (MTD), lower side effects, and preference for oral drugs. However, it is a common practice to repurpose noncancer drugs (e.g., thalidomide, metformin, propranolol, valproate, and statins) and add them to metronomic chemotherapy. The term "metronomics" has been coined to cover low-dose chemotherapy, drug repositioning, and drug repurposing.[3]

The mechanism of action of metronomic chemotherapy is thought to be multitargeted.[4] It has been often promoted as an innovative option for low- and middle-income countries. In reality, whenever a metastatic malignant tumor progresses after 1 or 2 lines of systemic therapy, performance status declines and further innovative clinical trials are not available to participate in; metronomics appear a feasible option.

A critical look at the chronology of the clinical research studies done in pediatric clinical metronomics suggests that the earliest trials were often in pilot mode in palliative settings using a mixed bag of different relapsed/refractory solid tumors; additionally, there were dose-finding Phase 1 studies as well. As we move ahead in time, the studies get bigger and we get to Phase II single-arm studies.[5] Finally, after 2010, we begin to get some comparison with historical cohorts and then randomized trials. We also find a conspicuous change in the composition of the metronomic combinations; for example, vinblastine, fenofibrate, and Vitamin D are being explored. Targeted agents and immunotherapy drugs are being added in future trials. Tumor-driven trials, concentrating on a particular type of tumor, for example, rhabdomyosarcoma rather than a "potpourri of histologies" and exploration for biomarkers, has been a feature of the later trials. Finally, metronomics are also being studied in the maintenance setting after curative treatment of diseases such as rhabdomyosarcoma and osteosarcoma. This is heartening to see such an evolution for this "genre" of chemotherapy from the palliative to curative settings.

On critically examining the current metronomic literature in pediatric oncology, one finds that there are very limited Phase 1 and 2 data. Most studies have recorded a clinical benefit in terms of disease stabilization only. We did not have a direct randomized comparison of metronomics with placebo, until very recently, to confidently say that really this stabilization is attributable to metronomics and not just a manifestation of the natural history of that anecdotal case. As most clinicians have been learning and practicing dose intensity and dose effect, it is challenging for them to accept low-dose chemotherapy.[2,6,7] The empiricism of metronomic protocol dosages and dosing schedules, variable terminologies and vague definitions, absence of reliable biomarkers, and lack of large randomized Phase III trial and the lack of support by the pharmaceutical industry have added to the clinician's reluctance.[5] In our randomized controlled trial published in 2017 comparing a four-drug metronomic cocktail (thalidomide, cyclophosphamide, etoposide, and celecoxib) versus placebo in 108 patients of progressive pediatric solid tumors post 2 lines of chemotherapy, the metronomic regimen did not improve the 6-month progression-free survival (the primary endpoint) or overall survival.[8] However, in an unplanned subgroup analysis, the subgroup of nonbone sarcomas had a significant benefit, hinting that histology should be a major factor in choosing metronomics wisely. Thus, this study generated a hypothesis that metronomic chemotherapy may not be a correct blanket palliative therapy for all progressive pediatric tumors. Instead, it benefits particular histological types of cancer only. This needs to be further tested in a randomized fashion in homogeneous disease-specific subgroups.

It is obvious that most studies have been done in a palliative setting only in relapsed or refractory disease. Neoadjuvant use has not been documented. However, maintenance use after curative therapy has been studied of late. It is rational to think that antiangiogenic therapy will be effective in this setting as the disease load is low, but even in this setting, biology remains the key determinant of response. A recent Phase 3 randomized study of metronomic maintenance in high-risk rhabdomyosarcoma showed a nonsignificant improvement in disease-free survival, and the authors concluded it to be the standard of care in future European studies.[9,10] Evidently, the efficacy of metronomics clearly depends on the biology of that particular cancer. Studies clearly show that low-grade gliomas and rhabdomyosarcoma benefit from

metronomic chemotherapy, while osteosarcoma doesnot benefit at all. As metronomics is not a single drug or combination, failure of a one-drug regimen does not mean the failure of metronomic chemotherapy as a whole. Rational combinations using modern targeted drugs with novel mechanisms should be used in further studies. Another key finding from the translational arm of our study, that analyzed vascular endothelial growth factor and thrombospondin-1 as biomarkers of metronomics, showed that these cytokines are probably not the way to go ahead as biomarkers for solid tumors.[11] Newer biomarkers such as cell-free DNA, Hypoxia Inducible Factor-1alpha, and circulating tumor cells should be evaluated in upcoming studies. Scientific dosing, newer biomarkers, and robust study designs are the needs of the hour to boost this "genre" of chemotherapy.

In the coming future, we should expect interesting results from metronomic therapy in combination with immunotherapy, radiotherapy, and MTD chemotherapy which is likely to change the way we think about and use metronomic chemotherapy. Metronomics must imbibe the concept of personalized medicine. Targeted agents appropriate to the activated pathway must be part of the metronomic regimen. For the future success of metronomic chemotherapy,[12] we have to do away with the empiricism and accept mathematical modeling based on the "top–down" or "bottom–up" approach.[13] In a nutshell, clinical experience in pediatric metronomics is growing. Its widespread usage remains limited by empiricism and skepticism. Integrating pharmacokinetics, pharmacogenomics, and mathematical modeling for dosing and designing trials focused on specific tumor types in palliative as well as curative settings will go a long way to harness the true potential of metronomic therapy in pediatric oncology.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Raja Pramanik, Sameer Bakhshi

Department of Medical Oncology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence: *Dr. Sameer Bakhshi, Department of Medical Oncology, Dr. B. R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi - 110 029, India.*
E-mail: sambakh@hotmail.com

Submitted: 21-Jan-2020
Revised: 14-Apr-2020
Accepted: 16-Apr-2020
Published: 27-Jun-2020

References

1. Bocci G, Kerbel RS. Pharmacokinetics of metronomic chemotherapy: A neglected but crucial aspect. Nat Rev Clin Oncol 2016;13:659-73.
2. André N, Carré M, Pasquier E. Metronomics: Towards personalized chemotherapy? Nat Rev Clin Oncol 2014;11:413-31.
3. Maiti R. Metronomic chemotherapy. J Pharmacol Pharmacother 2014;5:186-92.
4. Bahl A, Bakhshi S. Metronomic chemotherapy in progressive pediatric malignancies: Old drugs in new package. Indian J Pediatr 2012;79:1617-22.
5. Pramanik R, Bakhshi S. Metronomic therapy in pediatric oncology: A snapshot. Pediatr Blood Cancer 2019;66:e27811.
6. Kerbel RS. Improving conventional or low dose metronomic chemotherapy with targeted antiangiogenic drugs. Cancer Res Treat 2007;39:150-9.
7. Pasquier E, Kavallaris M, André N. Metronomic chemotherapy: New rationale for new directions. Nat Rev Clin Oncol 2010;7:455-65.
8. Pramanik R, Agarwala S, Gupta YK, Thulkar S, Vishnubhatla S, Batra A, *et al*. Metronomic chemotherapy vs. best supportive care in progressive pediatric solid malignant tumors: A randomized clinical trial. JAMA Oncol 2017;3:1222-7.
9. Bisogno G, De Salvo GL, Bergeron C, Jenney M, Merks JH, Minard-Colin V, *et al*. Maintenance low-dose chemotherapy in patients with high-risk (HR) rhabdomyosarcoma (RMS): A report from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). J Clin Oncol 2018;36 18 Suppl: LBA2.
10. Koscielniak E, Klingebiel T. A new standard of care for patients with high-risk rhabdomyosarcoma?. Lancet Oncol. 2020;21:e1. doi:10.1016/S1470-2045(19)30731-4.
11. Pramanik R, Tyagi A, Agarwala S, Vishnubhatla S, Dhawan D, Bakhshi S. Evaluation of Vascular Endothelial Growth Factor (VEGF) and Thrombospondin-1 as Biomarkers of Metronomic Chemotherapy in Progressive Pediatric Solid Malignancies [published online ahead of print, 2020 Mar 12]. Indian Pediatr. 2020;S097475591600146.
12. Bocci G, Kerbel RS. Pharmacokinetics of metronomic chemotherapy: A neglected but crucial aspect. Nat Rev Clin Oncol 2016;13:659-73.
13. Barbolosi D, Ciccolini J, Meille C, Elharrar X, Faivre C, Lacarelle B, *et al*. Metronomics chemotherapy: Time for computational decision support. Cancer Chemother Pharmacol 2014;74:647-52.

Access this article online

Quick Response Code:

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_22_20

How to cite this article: Pramanik R, Bakhshi S. Metronomics in pediatric oncology: Lessons learned and the way forward. Indian J Med Paediatr Oncol 2020;41:317-8.