

Nontoxic, Fiscally Responsible, Future of Oncology: Could it be Beginning in the Third World?

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In this issue of the journal, a prospective pediatric study by Fousseiny et al¹ evaluating a multidrug metronomic regimen^{2,3} in children with difficult-to-treat malignancies in Mali, is presented. It examines, for the first time in a prospective manner, the applicability of using established, off-patent agents in an alternative “metronomic”⁴ regimen. The authors, indirectly, make the case, that attainment of stable disease may be a valid alternative in places in which tertiary care necessary for the use of more toxic therapies may be difficult to provide, or in places where cost of novel biological response modifiers is prohibitive. The work suggests that even when there are no limitations or constraints on resources, a complete remission does not always translate to an increased overall survival, and the paradigm of disease control with less toxicity is worth pursuing. The concept of “cancer without disease” seems to be growing in acceptance.⁵

Unless a significant change in international health care policies occurs, experimental therapeutics are unlikely to make a significant impact in Third World countries and alternatives are badly needed. The authors suggest that the use of inexpensive, widely available agents in a minimally toxic metronomic chemotherapy setting should be explored, and provide the first example of such an effort. We agree that a well-designed metronomic chemotherapy regimen combining drugs with nonoverlapping toxicities may provide a viable option for the care of children with malignancies in countries where access to medical care and resources is limited. For one, it may change the still prevalent perception in these countries that cancer is always an incurable disease and causes rapid demise. Metronomic therapy may also create an option of keeping children alive longer with nontoxic therapies and good quality of life. As discussed below, even when resources are less limited and the “more is better” mentality is the prevailing public perception, a more rational use of information may lead to less expensive and better anticancer therapy.

The concept of metronomic chemotherapy was introduced in 2000,^{2,3} but the general acceptance of the model has been hindered by inconsistencies in its definition. Since the initial introduction, the meaning of metronomic chemotherapy is continuously being redefined. Although almost everyone understands it to mean combination therapy using continuous, frequent, low doses of chemotherapeutic agents with an angiogenic,^{3,6,7} stromal,⁸ or more recently, immunologic⁹ target, most clinicians interpret this to simply mean frequent administration of established chemotherapeutic drugs at doses below the maximal tolerated dose (MTD). Thus, what constitutes “low” dose, how “frequent”, or what agent, is continuously being renegotiated, redefined, and revised. The historical understanding of chemotherapeutic goals, that is - a remission induction through the use of MTDs, often leads investigators to simply divide the MTD of the usual agent used to treat a particular tumor into weekly doses. It is unclear why weekly, but the most likely explanation is that weekly may be the highest frequency that a patient can be reasonably expected to attend the clinic for intravenous therapy. Rarely, frequency is based on the half-life of the agent used or on the inhibition of the target (generally an enzyme or another protein). This leads to a random and very erratic manner in which doses and frequencies are chosen.

Unfortunately, until more information is available and until new oral agents are developed, the manner in which metronomic chemotherapy is applied is unlikely to change. Until this happens two main guiding principles should be observed. The intensity of a therapy should be based on the number of days rather than the total amount per dose. We should strive for the “minimally effective concentration” that will give the desired outcome, rather than a standard cumulative dose. Comparing and contrasting the field of oncology with other fields of medicine, the treatment of patients with infectious diseases, hypertension, and seizures

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may serve as examples of situations in which the variations in frequency and time, in addition to, or even more importantly than, dose, are critical to success.

There is a similar uncertainty as to the choice of agents. Most often the agents “with known efficacy in a particular tumor type” are chosen. Although it often simplifies the speed of approval of the proposed individualized protocol, choosing the agent with established efficacy may be a harmful compromise in the long term, because it is misleading as to the therapeutic target. It is misleading as to the therapeutic target. By using only the agent with established efficacy for the tumor type, few people are reminded of the fact that the target(s) of metronomic chemotherapy are host tissues, such as tumor-associated endothelium and stromal elements, rather than the cancer cell. Not inconsequentially, Dr Kathy Miller asks in her 2001 *Journal of Clinical Oncology* review¹⁰: “If all chemotherapeutics are really anti-angiogenics in disguise, why have they failed to cure most solid tumors?” The question would not have been asked if there was more clarity about the targets and their sensitivities.

Although all chemotherapeutic agents have some anti-angiogenic effect, some agents have antiangiogenic activity at doses well below those necessary for cell death and a too high dose may have untoward/undesired side effects (hormesis).¹¹ Low, nontoxic doses of tubulin inhibitors, such as vincristine, vinblastine, and taxanes are particularly efficacious in the metronomic setting, because endothelial cells are (and remain) sensitive to picomolar doses of these agents.^{12–15} This is not surprising in polarized endothelial cells whose orientation, that is the maintenance of the luminal and abluminal surfaces, is maintained by a constant and precarious cytoskeletal tension.^{16,17} The concentrations of the vincas alkaloids, which inhibit endothelial cell growth in model systems noted above are well below the plasma concentration usually achieved with standard doses. Those are often in the low micromolar range, a 4 to 5 order-of-magnitude difference, from those needed for endothelial cell inhibition. A more frequent, smaller amount of drug may not only have greater efficacy, but it is likely to be more patient friendly. Thus, it should be feasible to use agents less proven in treatment of a particular tumor type in the metronomic setting, but which have a better metronomic profile, that is, can be used at lower dose with higher efficacy.

Not every chemotherapeutic agent is a suitable metronomic agent; some may have more enhanced antitumor effect than others in this setting.^{14,18–20} Unfortunately, limited data are available to rationalize the choices, and the necessary studies that would provide information about this new use of old agents are unlikely to be funded in the present climate of continuous supply of new agents with potentially lucrative patents. A limited comparison of the IC₅₀ of select established chemotherapeutic agents on endothelial cells favored tubulin inhibitors over alkylating agents.^{18,21} Unfortunately, no antimetabolites were included in this study, even though antimetabolites are what is presently available in oral agents. Not surprisingly, methotrexate is a well-established antimetabolite that forms the backbone in the Mali study as well. In addition to being orally available, there is a lot more information about methotrexate in the metronomic setting than about any other drug. The continuous use of methotrexate at low doses has become a standard for the treatment of rheumatoid arthritis²² and forms the backbone of maintenance therapy in the treatment of acute lymphocytic leukemia in children. A significant body of evidence testifies to its antiangiogenic effect,^{23–27} and the rheumatologists may

be leading the field ahead of the oncologists in designing rational antiangiogenic metronomic combinations.^{28–31}

It is not only the drug, but also the dose and frequency that matter in metronomic therapy. It may be that to decrease the toxicities of therapeutic regimens we, in the West, may one day look for guidance to the trials conducted in developing countries. For now, we may need to revise the definition of metronomic therapy. Rather than “frequent administration of chemotherapy at doses below the maximal tolerated dose and with no prolonged drug-free breaks,” we should agree that the doses should not just be lower than MTD; they should represent the minimal therapeutically effective doses that achieve anticancer effect. The choice of the agent should be based on available preclinical efficacy rather than on the activity of the agent in the particular tumor, and the frequency of administration on the half-life of the drug for continuous anticancer effect. Perhaps a more applicable definition may be: “Metronomic Chemotherapy is the minimum biologically effective dose of a chemotherapeutic agent, which, when given at a continuous dosing regimen with no prolonged drug-free breaks leads to anti-tumor activity.” In pediatrics, we have a synonym for metronomics: it is called “continuation therapy” (or “maintenance therapy”), and the usefulness of these protocols is now expanding into adult oncology in the form of new protocols for carcinoma of the breast,^{23,26} lung,^{32,33} colon, and prostate.

The study by Fousseiny et al¹ opens the door wider, and begins the groundwork that will hopefully lead to a more general application of metronomic regimens. Even though, at least at present, the most effective agents in a metronomic setting, such as taxanes,²⁰ may not be available as oral agents, the substitutions should be guided by the most feasible alternatives. The doses of 1.5 mg/m² vincristine in the Mali study,² may fit only marginally the suggested definition of “metronomic,” but the choice was most likely influenced by the extensive pediatric clinical experience with vincristine, and by its low toxicity in the pediatric population. Cyclophosphamide and methotrexate are both accepted agents for this application, and their oral availability, low cost, and the published evidence of their efficacy in the metronomic setting direct their use.

It is our belief that as more and more targeted therapies enter clinical practice in the West, the search for less toxic and equally efficacious chemotherapeutic backbones is likely to soar, and the developing countries will be ready for the trade. To put this in perspective, metronomic therapies have the potential to be more “doable,” less expensive, and more efficacious for a variety of patients worldwide. There are an estimated 15 million new cancer patients in the world annually and the cost has been estimated to be close to \$1 trillion. Certainly, in both the developed and the developing world, we can do better on many fronts simply by rethinking and applying new knowledge to the bedside by better utilization of the tools we have, while continuously searching for the magic bullets, such as represented by imatinib and other biological response modifiers. We find it both intuitively obvious and satisfying that the newer agents, such as histone deacetylase inhibitor, proteasome inhibitors, poly ADP ribose polymerase inhibitors, and immune modulators, such as thalidomide, actually fit more of a metronomic rather than MTD paradigm. As we have earlier reviewed in this journal,³⁴ the MTD, dose limiting toxicities model was a convenient way to study how drugs work against cells, but was not necessarily the best way to use them clinically.

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