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Has the time come for metronomics in low-income and middle-income countries?

Nicolas André, Shripad Banavali, Yuliya Snihur, Eddy Pasquier

In 2008, 72% of cancer deaths occurred in low-income and middle-income countries, where, although there is a lower incidence of cancer than in high-income countries, survival rates are also low. Many patients are sent home to die, and an even larger number of patients do not have access to treatment facilities. New constraint-adapted therapeutic strategies are therefore urgently needed. Metronomic chemotherapy—the chronic administration of chemotherapy at low, minimally toxic doses on a frequent schedule of administration, with no prolonged drug-free breaks—has recently emerged as a potential strategy to control advanced or refractory cancer and represents an alternative for patients with cancer living in developing countries. This low-cost, well-tolerated, and easy to access strategy is an attractive therapeutic option in resource-limited countries. Moreover, combined with drug repositioning, additional anticancer effects can be achieved, ultimately resulting in improved cancer control while maintaining minimum cost of treatment. In this Personal View, we will briefly review the rationale behind the combination of metronomic chemotherapy and drug repositioning—an approach we term metronomics. We assess the clinical experience obtained with this kind of anticancer treatment and describe potential new developments in countries with limited resources. We also highlight the need for adapted clinical study endpoints and innovative models of collaboration between for-profit and non-profit organisations, to address the growing problem of cancer in resource-limited countries.

Service d'Hématologie et Oncologie Pédiatrique, AP-HM, Marseille, France (N André MD); **Metronomics Global Health Initiative, Marseille, France** (N André, S Banavali MD, Y Snihur MRes, E Pasquier PhD); **INSERM UMR 911, Centre de Recherche en Oncologie biologique et Oncopharmacologie, Aix-Marseille University, Marseille, France** (N André); **Department of Medical and Pediatric Oncology, Tata Memorial Centre, Mumbai, India** (S Banavali); **IESE Business School, Entrepreneurship Department, Barcelona, Spain** (Y Snihur); **and Children's Cancer Institute Australia, Lowy Cancer Research Centre, University of New South Wales, Randwick, NSW, Australia** (E Pasquier)

Correspondence to:
Dr Nicolas André, Service d'Hématologie et Oncologie Pédiatrique, CHU Timone Enfants, 254, rue Saint Pierre, AP-HM, 13385 Marseille Cedex 05, France
nicolas.andre@ap-hm.fr

Introduction

Within the past decade, targeted cancer therapies have changed medical oncology in high-income countries, increasing patients' and physicians' expectations of high cure rates together with decreased toxicities. Meanwhile, the cancer burden has substantially increased in low-income and middle-income countries (LMICs) such that, according to the International Agency for Research on Cancer, most new cancer cases and deaths now occur in LMICs.[1] These discrepancies are even more pronounced among children with cancer. With 80% of all children living in LMICs and based on estimated cancer incidence and survival rates (about 200 000 new cases per year and 25% survival in LMICs versus 50 000 new cases and 75% survival in high-income countries [HICs]),[2] cancer is thought to claim the lives of ten times more children in LMICs than in HICs. In the absence of effective global strategies, by 2030 the number of cancer deaths worldwide is projected to rise to as high as 13·2 million, with 69% of deaths occurring in LMICs.[2] "The time has come to challenge and disprove the widespread assumption that cancer will remain untreated in poor countries", stated a call for action in 2010.[3] Similar calls for action have been made by the UN during the general assembly summit on non-communicable diseases,[4] the Union for International Cancer Control in their World Cancer Declaration,[5] and the American Society of Clinical Oncology, who called upon the UN to add cancer to the list of priority diseases in global health.[6]

Cancer survival tends to be lower in developing countries than in developed countries because of inferior infrastructure related to socioeconomic restrictions, leading to a lethal combination of late stage at diagnosis and limited access to timely and effective treatment.[2] Modern cancer care now relies on expensive and complex technology. State-of-the-art surgery and newly developed anticancer drugs now represent the cornerstone of cancer care in HICs but they are seldom, if at all, accessible in LMICs. As a result, LMICs can only rarely make curative treatments available. Only a limited fraction of the resources spent yearly on cancer care are estimated to be spent on patients living in LMICs.[7] Delayed diagnosis, late presentations, and limited resources are responsible for high mortality rates and the resulting cultural misunderstanding that cancer is systematically a death sentence for patients living in LMICs.[8] Similarly, findings from a recent study from India showed that poorer and less educated patients from rural areas had a greater risk of dying from cancer than did patients living in metropolitan areas.[9] Furthermore, more than 70% of deaths from cancer occurred in the so-called productive ages between 30 and 70 years, most of which could be avoided through education and prevention.[9]

In 2008, the worldwide cost of cancer due to premature deaths and disability was estimated to be US$895 billion, due to a combination of an increase in absolute numbers and increasing expenses in cancer care.[10] Moreover, this estimation did not take into account the direct medical cost of cancer treatments. The burden of cancer is increasing and the disease is becoming a major economic burden even for developed countries. By 1999, the USA was spending an average of $70 000 per cancer case.[11] This amount increased to more than $100 000 in 2010 with the advent of targeted therapies.[12] In the USA, the annual direct cost of cancer is projected to rise from $104 billion in 2006 to over $173 billion by 2020.[12] The typical new cancer drug coming on the market a decade ago cost about $4500 per month (in 2012 dollars); since 2010, the median cost has been around $10 000 per month. If this trend is not sustainable for an HIC such as the USA,[13] it is even more problematic for LMICs.

One of the most important challenges facing oncologists practising in LMICs at present is not just finding cures for their patients with advanced cancers, but finding affordable cancer care for them. Ways must be found to reduce costs of everyday care so that more patients can be treated in LMICs without jeopardising their entire families after catastrophic expenditure. A substantial proportion of the cancer burden could be prevented through the worldwide implementation of programmes for tobacco control, vaccination (for liver and cervical cancers), early detection (for oral, breast, and cervical cancers) and treatment, and public health campaigns promoting physical activity and healthy diet.[2]

In LMICs, many specific difficulties can preclude the management of cancer. Some of these obstacles have been well identified, such as cultural barriers or previous consultation with traditional practitioners, distance to oncology unit, availability of drugs and treatment facilities, compliance with treatment, and cost of anticancer treatments. Delayed diagnosis and limited follow-up, which contribute to poor prognosis, also constitute important hurdles.[6] Furthermore, besides all the political, structural, and cultural limitations in LMICs, being able to offer effective, safe, and low-cost cancer treatments remains a challenge and every oncologist's ultimate goal. One of the key aspects to reducing cost is use of inexpensive anticancer drugs, such as those on WHO's list of essential drugs for cancer therapy,[14] most of which have generic equivalents. Still, cancer care in LMICs must not be limited to copying unrealistic and sub-optimal strategies used in the past in HICs, but demands innovation. Thinking outside the box and outside of our present standards is mandatory to generate new constraint-adapted therapeutic strategies for patients with cancer living in LMICs. Many low-cost and low-technology endeavours exist that could be potentially administered by non-specialists and that have a substantial effect on cancer control in developing countries.[6,15] As we discuss here, metronomics is one such approach that represents a promising and exciting alternative strategy for the improvement of cancer care in LMICs.

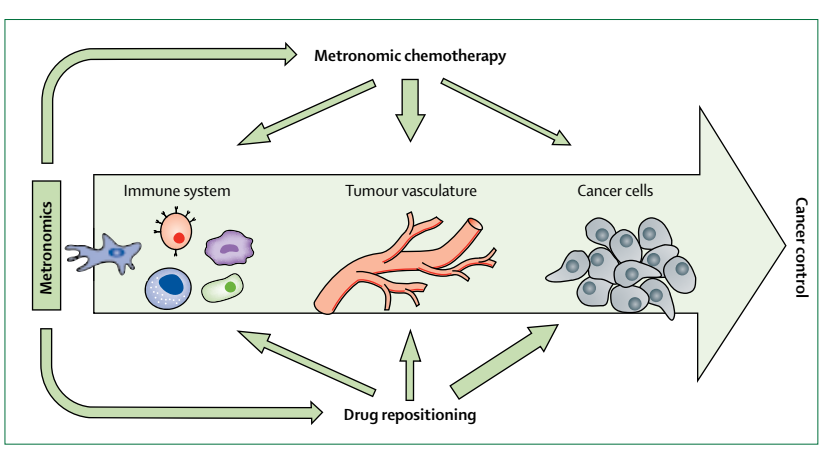

Figure: **Schematic representation of the mechanisms of action of metronomics**
By combining metronomic chemotherapy and drug repositioning, metronomics can target the three main compartments of the tumour microenvironment (ie, cancer cells, the tumour vasculature, and the immune system), ultimately leading to cancer control. Arrow sizes are proportional to the potential difference in intensity of effect on the different targets.

Metronomics: metronomic chemotherapy and drug repositioning

Although there is no clear definition of metronomics, it can be defined as the science associated with metronomic scheduling of anticancer treatment, which therefore embraces both metronomic chemotherapy and drug repositioning.[16,17] The figure summarises the notion and different targets of metronomics.

Metronomic chemotherapy

Metronomic chemotherapy is the chronic administration of chemotherapy at low, minimally toxic doses on a frequent schedule of administration, with no prolonged drug-free breaks.[18] Klement and Kamen[19] proposed an alternative definition, suggesting that metronomic chemotherapy is the minimum biologically effective dose of a chemotherapeutic drug that, when given at a regular dosing regimen with no prolonged drug-free breaks, leads to antitumour activity. Although metronomic chemotherapy was initially defined as an anti-angiogenic anticancer strategy,[20] new mechanisms have since been identified, such as the restoration of the anticancer effect of the immune system.[18] Therefore, metronomic chemotherapy can be regarded as a multi-targeted therapy.[18]

Although the rationale of metronomic chemotherapy is yet to be fully elucidated, the use of low-dose oral chemotherapy in the clinic has been mainly restricted to palliative purposes for many decades, both in adult and paediatric patients, with good response rates and sometimes lasting results.[16,18] After the publication of several phase 2 trials, especially for metastatic breast cancer or prostate cancer, physicians have given more credit to metronomic chemotherapy, leading to the initiation of several phase 3 clinical trials for the treatment of patients with triple-negative (NCT01112826) and metastatic (NCT01131195) breast cancers and advanced colorectal carcinoma (NCT00442637 and NCT01229813). In paediatric oncology, the clinical development of metronomic chemotherapy is still in its early stage[18] and only one randomised trial is underway in children with rhabdomyosarcoma (NCT00379457).

Drug repositioning

Drug repositioning consists of using old drugs for new indications.[21] Testing drugs already approved for non-malignant diseases on the basis of newly identified anticancer properties presents several advantages. These drugs have side-effects that are known, usually moderate, and well documented. Phase 1 studies are therefore not mandatory and further clinical development can often start directly with phase 2 trials

to assess the efficacy of the drug for cancer treatment. Because most of these drugs now have generic equivalents, they are inexpensive. One of the main challenges in drug repositioning in oncology is identification of the right disease to prospectively test for a given drug. Several examples of successful drug repositioning are available in medical oncology. For instance, celecoxib can be used as an antiangiogenic drug,[22,23] valproic acid as a histone deacetylase inhibitor,[24,25] statins as multi-targeted drugs,[26] metformin as an AMP kinase and mTOR inhibitor or epithelial–mesenchymal transition inhibitor,[27,28] itraconazole as a sonic hedgehog inhibitor,[29] and nifurtimox as an inhibitor of tyrosine-related kinase B.[30] More recently, propranolol has been shown to display both immunomodulatory and antiangiogenic properties.[31–33] Repositioned drugs can exhibit new mechanisms of action that can otherwise be obtained only with expensive targeted anticancer drugs, therefore providing new opportunities to develop effective and affordable alternative treatment regimens for patients with cancer.

Overall, many clinical and preclinical studies investigating the potential of drug repositioning and metronomic chemotherapy are ongoing in HICs, thus showing that these approaches are anything but cheap second-hand treatments. By combining metronomic chemotherapy and drug repositioning, metronomics enables generation of innovative treatments targeting both the tumour itself and its microenvironment while maintaining a low cost and minimal toxicity.

Metronomics for developing countries

So far, adult cancer programmes in developing countries have mainly focused on frequent and potentially curable diseases such as breast cancer or, as mentioned earlier, preventable diseases.[4] Similarly, childhood cancer programmes have mainly aimed at treating curable diseases such as lymphoma, leukaemia, Wilms' tumour, or retinoblastoma.[34] As a result, the major burden lies in the management of patients with high-risk or advanced disease without any curative option. Moreover, the treatment of patients with relapsed or progressive disease with second-line intensive or experimental treatments with new expensive drugs, as is done in Europe or in the USA, is an unrealistic option in LMICs. In this context and with its many practical advantages, metronomics seems to be an attractive approach that has the potential to improve the lives of many patients with cancer in LMICs.[19]

Potential advantages of metronomics in LMICs

First, metronomic treatments can have a low direct cost because they are mostly based on the use of old and inexpensive generic drugs. Second, these drugs are usually available in oral form, thus avoiding the need for costly hospital stays and intravenous injections. As a result, the use of central venous access is not mandatory, therefore contributing to decreasing both the cost of treatment and the risk of infection. Third, oral treatments can be taken at home and therefore patients do not need to travel to care centres, thus potentially decreasing abandonment of treatment. Fourth, because metronomic chemotherapy is given at low, minimally toxic doses, it should not expose patients to higher risk of infections or additional nutrition problems. Unlike standard regimens that use the maximum tolerated dose (MTD) of chemotherapy, which have high chances of haematological, hepatic, or renal adverse events, with metronomic chemotherapy regimens these adverse events are rare and thus minimal monitoring and supportive care is needed.[18] Execution of metronomic therapies therefore needs little blood and platelet support, limited use of broad-spectrum antibiotics, and no intensive care unit admission or total parenteral nutrition support, thus further decreasing the cost of treatment while increasing the feasibility of treatment. Lastly, for systemic intravenous administration of chemotherapy, multidisciplinary teams are needed that include physicians, pharmacists, nurses, and laboratory technicians who must be properly trained. Because metronomic chemotherapy is easy to administer and does not need complex infrastructure or highly trained human resources, basic oncology units could be readily introduced even in rural areas where specialised services are absent.

One of the main causes of treatment failure in LMICs, even in curable diseases such as some forms of childhood cancer, is abandonment of treatment.[34] The main reasons for treatment abandonment are the direct costs and the need to travel long distances to metropolitan care centres. Since metronomic therapies can be implemented at a fraction of the cost of standard MTD therapies and can be easily administered in rural cancer centres, one of the major benefits of metronomic chemotherapy could be a decreased abandonment of treatment, which would thus help increase cure rates.

Lastly, there are two settings in which metronomics seem to be well adapted for patients living in LMICs. In patients with advanced disease, for whom chances of survival are close to zero, a metronomic prolonged therapy without significant side-effects that can help to control the symptoms of the disease and that has a favourable risk:benefit ratio would be particularly valuable. In the adjuvant setting or as maintenance therapy where the tumour burden is limited, the introduction of a well-tolerated and easy to take metronomic treatment is also logical. Available experience with maintenance therapy in leukaemia[20] and several types of solid tumours[16] provides a comprehensive clinical rationale for the use of metronomics in settings of minimal residual disease. Furthermore, the intrinsic antiangiogenic and pro-immune nature of metronomic chemotherapy makes it a good candidate for re-induction of tumoral dormancy or eradication of residual cancer cells.[18] This type of approach is also being investigated

in HICs using a metronomic methotrexate–cyclophosphamide maintenance regimen for women with oestrogen-receptor-negative and progesterone-receptor-negative breast cancer (NCT00022516).

Potential disadvantages of metronomics

A crucial issue regarding metronomics is patient compliance. On the one hand, easy access, low cost, and low toxicity of metronomics will probably decrease patient abandonment of treatment. However, on the other hand, compliance decreases with treatment duration and the number of pills and number of takes per day.[35] Although Ruddy and colleagues[36] reported good compliance to oral anticancer treatment, personal (eg, emotional state and outcome expectations), treatment (eg, reasons for treatment and treatment schedule), and system interaction (eg, relationship with providers and satisfaction with care) factors that influence adherence to treatment have been identified, and metronomic protocols should take these factors into account. Patients should also be provided with information on the regimen and should be followed up regularly. Similarly, monitoring patient compliance is more difficult with oral drugs that are taken at home than with intravenous injections administered in hospital. New technologies using daily mobile phone alerts could be used to help patients to remember to take their daily treatment. Also, deciding the optimum dose for a metronomic protocol remains a problem.

Although Klement and Kamen[19] advocated for use of the minimum effective dose in metronomic protocols, no validated biomarkers are available to identify such optimum dose even in HICs. As a result, overall dosing of metronomic protocols remains largely empirical.

Although most of the drugs used in metronomic protocols are off patent, some oral drugs, such as oral gemcitabine prodrug and vinorelbine are still on patent and expensive. Thus, while developing metronomic protocols for LMICs, use of drugs from the WHO essential drug list would be highly desirable, because these drugs are off patent, cheap, and are more likely to be available in developing countries. Overall, although many challenges remain, metronomics should be further investigated in LMICs.

Experience with metronomics in HICs

Valuable information can be obtained from studies using metronomics in HICs. Table 1 provides examples of successful studies undertaken in HICs that could be readily translated into LMIC settings. Protocols using oral formulations and off-patent drugs are particularly attractive. For instance, oral methotrexate in combination with oral cyclophosphamide has proven activity in metastatic refractory breast cancer, reaching a clinical benefit of 36% at 6 months.[37] [A: table 1 states 32 %, please clarify] The same oral metronomic regimen given in combination with intra-muscular fulvestrant recently led

	Patient population	Metronomic protocol	Response (%)	Other outcomes (median)	Clinical benefit (median)
Colleoni et al (2002)[37]	Metastatic breast cancer (n=66)	Oral cyclophosphamide once daily plus oral methotrexate twice daily on days 1 and 2 of every week	CR 3%, PR 15%, SD 8%	..	32% (95% CI 21–45) at 6 months
Aurilio et al (2012)[38]	Advanced breast cancer (arm A: n=33, after progression on fulvestrant n=20; arm B (treatment upfront n=13)	Arm A: oral cyclophosphamide once daily, oral methotrexate twice daily on days 1 and 2 of every week, and fulvestrant once per month. Arm B: oral cyclophosphamide once daily, oral methotrexate twice daily on days 1 and 2 of every week, and fulvestrant once per month	Arm A: CR 0%, PR 0%, SD 55%. Arm B: CR 0%, PR 0%, SD 58%	Arm A: EFS 5 months (95% CI 4–5), OS 43 months (25–88). Arm B: TTP 9·7 months	56% (95% CI 38–74) at 24 months
Fedele et al (2012)[39]	Relapsing metastatic breast cancer (n=60)	Oral capecitabine once daily	..	EFS 7 months, OS 17 months	62% at 6 months
Yoshimoto et al (2012)[40]	HER2-negative metastatic breast cancer (n=51)	Oral capecitabine twice daily on days 1 and 2 of every week and oral cyclophosphamide twice daily on days 1–14 of every 3-week cycle	CR 4%, PR 23%, SD 13%	EFS 12 months (95% CI 9–19)*	58% at 6 months
Ang et al (2012)[41]	Advanced hepatocellular carcinoma (n=42)	Capecitabine once daily on days 1–14 of every 3-week cycle and thalidomide once daily	CR 7·5%, PR 7·5%, SD 32·5%	EFS 5 months. OS 10 months	..
Gebbia et al (2011)[42]	Castration-refractory metastatic prostate cancer docetaxel-resistant (n=58)	Oral cyclophosphamide once daily and oral methotrexate twice daily on days 1 and 2 of every week	CR 0%, PR 18% (95% CI 4–31), SD 24% (4–44); 50% decrease in PSA: 35%	EFS 5 months, OS 11 months, 36% PFS at 6 months	..
Buckstein et al (2006)[43]	Relapsing refractory lymphoma (n=35)	Oral celecoxib twice daily and oral cyclophosphamide once daily	CR 6%, PR 25%, SD 22%	EFS 5 months, OS 14 months	..
Coleman et al (2008)[44]	Relapsing refractory lymphoma (n=75)	Oral cyclophosphamide once daily, oral etoposide once daily, oral prednisone once daily, and oral procarbazine once daily	CR 36%, PR 33%	TOT 10 weeks (range 3 weeks to 48 months)	..
Mir et al (2011)[45]	Elderly patients with inoperable or metastatic soft-tissue sarcoma (n=26)	Oral cyclophosphamide twice daily plus prednisolone daily on days 1–7 of every 2-week cycle	CR 4%, PR 22%, SD 33%	PFS 6·8 months	69% at 12 weeks

CR=complete response. EFS=event-free survival. PR=partial response. PSA=prostate-specific antigen. SD=stable disease. OS=overall survival.TOT=time on treatment. TTP=time to progression. *OS not reported.

Table 1: **Examples of published metronomic studies undertaken in high-income countries**

to improved outcome in 33 patients with advanced breast cancer with a clinical benefit of 56% after 24 months.[38] Low-dose capecitabine can also provide long-lasting clinical benefit to patients with refractory metastatic breast cancer or hepatocellular carcinoma.[39–41] Similarly, cyclophosphamide-based metronomic treatments have demonstrated clinical activity in prostate cancer,[42,46] in elderly patients with soft-tissue sarcoma when combined with steroids,[45] and in relapsing lymphoma.[43,44]

Experience with metronomics in LMICs

Table 2 lists some examples of completed or ongoing metronomic trials in LMICs. Although the term metronomic chemotherapy is new, low-dose metronomic chemotherapy has been coined in different settings in LMICs even before the term was used. In relapsing diseases, the use of oral tamoxifen, etoposide, and cyclophosphamide in patients with Ewing's sarcoma or rhabdomyosarcoma yielded a response rate of 71·4%.[47] These results compare favourably with findings from a recent phase 2 trial of an MTD gemcitabine–docetaxel combination that reported a 40% overall survival after 1 year of follow-up and two responses (one complete and one partial response) out of 19 patients with relapsing sarcoma.[56] Similarly, a recent phase 2 study using a monoclonal antibody to the insulin-like growth factor 1 receptor in patients with recurrent or refractory Ewing's sarcoma family of tumours reported a 10% response rate and a median overall survival of 7·6 months.[57]

For children and young adults with acute myeloid leukaemia, Banavali and colleagues[48] developed a simple, oral, low-cost protocol with prednisolone, etoposide, and tioguanine (PrET). The investigators assessed this treatment regimen in LMICs in patients with acute myeloid leukaemia who could not receive standard therapy, either because their condition was too poor or because they could not afford the treatment. In another study, in patients with acute promyelocytic leukaemia not eligible for standard therapies, a combination of prednisolone, etoposide, and tioguanine and all-trans retinoic acid [A: tretinoin, as in table 2?] was used.[49] These pragmatic approaches led to a response rate of 89% in acute myeloid leukaemia and 91% in acute promyelocytic leukaemia.[48,49]

	Patient population	Metronomic protocol	Response (%)	Other outcomes (median)	Clinical benefit
Paediatric studies					
Banavali et al (2002)[47]	Residual or recurrent Ewing's sarcoma or rhabdomyosarcoma (n=7)	Oral tamoxifen once daily, oral etoposide once daily for 3 weeks, and cyclophosphamide once daily for 3 weeks	CR 28·5%, PR 42·8%, SD 28·5%,	EFS 5 months, OS 14 months	..
Banavali et al (2004)[48]	Children and young adults with acute myeloid leukaemia (n=26)	Oral prednisolone for 21 days, oral etoposide for 21 days, and oral tioguanine for 21 days	RR 89%, CR 62%, PR 27%	OS 13 months (range 3–30)	..
Banavali et al (2005)[49]	Children and young adults with acute promyelocytic leukaemia (n=23)	Oral prednisolone for 21 days, oral etoposide for 21 days, and oral tioguanine for 21 days with tretinoin	CR 91·3%,	Two induction deaths, OS 84% at 2 years	..
Fousseyni et al (2011)[50]	Refractory or relapsing solid tumours (n=12)	Oral cyclophosphamide once daily for 3 weeks alternating with oral methotrexate twice a week for 3 weeks and intravenous vincristine once a week every 8 weeks	RR 0%	..	Mean 58% at 20 weeks
Banavali et al (2011)[51]	Maintenance after standard acute therapy in children with acute myeloid leukaemia (n=87)	Oral etoposide once daily for 3 weeks and oral tioguanine for 21 days	Relapse rate decreased to 23·7%	EFS 67% and OS 64% at 28 months	..
Adult studies					
Pai et al (2011)[52]	Advanced operable newly diagnosed oral cancers (n=33)	Oral methotrexate once per week, oral celecoxib twice daily, and oral methotrexate once per week	RR 73% (1 CR), SD 27%,	2-year DFS 89% in the metronomic group *vs* 71% in the standard treatment group	..
Mwanda et al (2009)[53]	First-line treatment for AIDS-related non-Hodgkin lymphoma (n=49)	Oral lomustine on day 1, oral etoposide on days 1–3, and cyclophosphamide and procarbazine on days 22–26	RR 78% (95% CI 62–88)	EFS 8 months (95% CI 3–13), OS 12 months (5–32)	..
Patil et al (2012)[54]	Advanced oral cancer (n=18)	Oral celecoxib twice daily and weekly low-dose oral methotrexate	..	..	Median 67% at 2 months and 44% at 5 years
Bhattacharyya et al (2009)[55]	Second-line metastatic triple negative breast cancer (randomised study; n=126)[55]	Arm A: intravenous cisplatin once a week, oral cyclophosphamide once daily, and oral methotrexate twice a week. Arm B: oral cyclophosphamide once daily and oral methotrexate twice a week	Arm A: CR 8%, PR 55%, SD 27%. Arm B: CR 5%, PR 28%, SD 30%	Arm A: EFS 13 months, OS 16 months	..

CR=complete response. DFS=disease-free survival. PR=partial response. PFS=progression-free survival. RR=response rate. OS=overall survival.

Table 2: **Examples of published studies using metronomics in developing countries**

Mwonda and colleagues[53] used an oral low-dose chemotherapy regimen with lomustine, etoposide, cyclophosphamide, and procarbazine to treat 49 patients with AIDS-related non-Hodgkin lymphoma. This treatment led to an overall response rate of 78% at a median follow-up time of 8 months and had almost no effect on viral replication and CD4+ cells in this poor performance status group. 33% of patients were alive after 5 years of follow-up.[53]

After the discovery of the anti-angiogenic effects of metronomic chemotherapy, metronomic protocols started to be assessed in various other cancers in LMICs, including childhood cancer. The first paediatric experience with metronomic chemotherapy in LMICs was published by Fousseyni and colleagues,[50] who prospectively tested the role of a multidrug metronomic regimen and showed the tolerability and potential efficacy of such an approach. Among the 12 treated children, although no objective response was noted, seven patients experienced disease stabilisation, three of whom had stable disease for at least 6 months after completion of treatment. Another study using Fousseyni and colleagues'[50] protocol as a backbone to which valproic acid was added as a histone deacetylase inhibitor is ongoing in Mali. Banavali and colleagues[51] also showed that oral etoposide and tioguanine given as maintenance therapy for 6 months decreased the relapse rate in children with acute myeloid leukaemia compared with historical data and improved the disease-free survival to 67·1% even though no patients received bone-marrow transplantation.[51]

Although none of these studies are randomised trials comparing metronomic chemotherapy with MTD chemotherapy or best supportive care, these examples show that metronomics can be used safely and with some clinical activity in adult and paediatric populations. Nevertheless, well-designed phase 3 trials combining drug repositioning and metronomic chemotherapy are mandatory to confirm the therapeutic potential of these strategies. However, state-of-the-art phase 3 studies that compare metronomics versus palliative care, or upfront metronomics versus traditional MTD chemotherapy, will be difficult to initiate in LMICs. Specific challenges such as increasing awareness about metronomics in working groups involved in cancer care and research in LMICs, gathering funding for studies involving generic drugs, and creating a network to bring treatments to rural areas limit the immediate use of metronomics in phase 3 trials.

Integrating metronomics into a comprehensive rural cancer centre

The Tata Memorial Centre (TMC) in Mumbai commissioned a rural cancer control programme entitled TMC–Rural Outreach Program (TMCROP) in western India where approximately 3 million people live.[58] BKL Walawalkar Hospital was selected as the base hospital for implementation of the TMCROP project (panel).

Since many patients were referred to BKL Walawalkar Hospital for palliative care with advanced or recurrent disease, metronomic protocols were developed for patients with head and neck, breast, ovary, and other cancers, which proved to be affordable and effective. Later, these were also used in patients with newly diagnosed cancer with advanced disease at presentation.

The inexpensive nature of the drugs used in the metronomic protocols resulted in a low overall cost of drugs (US$100 per patient). These protocols were delivered with minimal infrastructure: only occasionally did a patient need blood or platelet support, and in most patients even laboratory investigations such as complete blood count, liver function test, and renal function test were done only once every 2–3 months. Using metronomics combined with surgery and later radiotherapy, 830 patients were treated in the TMCROP. Considering the large numbers and low socioeconomic condition of patients, an oral protocol was developed using celecoxib (200 mg twice daily) along with low-dose methotrexate (15 mg/m² per week) for patients with head and neck cancers. In view of the excellent response rate reported in the rural setting, the same regimen was used at the TMC in the neoadjuvant setting[52] as well as in the palliative setting.[53] A matched-pair analysis of this regimen with standard of care was done in advanced operable head and neck cancer and showed that the disease-free survival was 89% in the metronomic group compared with 71% in the standard therapy group.[52]

The TMCROP illustrates that metronomics is a promising strategy, especially in rural areas where cost is a major limiting factor and where infrastructures and training are not adequate to deliver the so-called standard of care therapies that are available in HICs.

Metronomics and sustainable new business models

A business model describes the system of interdependent activities undertaken by a local actor and their partners and the mechanisms that connect these activities to each other and to the final customer or patient.[59] Business model innovation involves the design of a new activity system that affects the total value created as well as the distribution of that value to the different participants in the business model.[60] Business model innovation represents an overlooked source of value creation, in addition to the more familiar product or process innovations,[60,61] especially in low-income markets.[62,63] Designing new business models in these settings allows achievement of common benefits for the actors involved through private and public sector partnerships.[62,64] Moreover, implementation of new business models can also help developing local communities; by structuring the activity system accordingly, broader social interests of various actors can be incorporated linking each actor's internal resources and developing the ecosystem's capabilities.[62,63]

In developed countries, pharmaceutical companies rely on business models that maximise profits by selling expensive products to small markets. However, the rising cost of health care has become one of the crucial problems for funders of health care (ie, society in general, funding agencies, governments, or patients), even in HICs.[65] Academics have suggested that business model innovation could provide a possible solution for ever-increasing costs and the continuing scarcity of widespread health-care affordability.[66,67] Metronomic treatments often rely on off-patent drugs in combination with a modified delivery process of these drugs,[68] which could be combined with the development of new business models to respond to the needs of patients with cancer in LMICs.[66]

Aravind Eye Hospital in India is a successful example of a new business model.[68,69] Founded with the primary objective of eliminating preventable blindness, it has now become the largest provider of eye care in the world.[69] The Aravind Eye Hospital offers free surgeries to patients who could not afford them otherwise, thus establishing a system in which patients paying for more sophisticated non-medical services cross-subsidise non-paying patients. As a result, the Aravind business model is simultaneously innovative on the medical side and financially self-sustaining. The Aravind business model includes in-house manufacturing of intraocular lenses needed for cataract surgeries, training of young girls from local villages to become mid-level ophthalmologists, high patient volume, and optimised surgical techniques.[68] Key features of the Aravind business model are cross-subsidisation of non-paying by paying patients, access to low-cost technologies, development of standardised treatment protocols, generation of large patient volume, and ability to attract and train a specialised workforce.[69]

Metronomics offer an alternative that is less expensive than conventional cancer therapies based on patented drugs. Combined with new business models, metronomics could facilitate sustainable research as well as the administration of inexpensive drugs to patients who cannot afford or do not have medical access to anticancer treatments. Before these new business models are developed and validated in oncology, the limited financial support obtained from pharmaceutical companies to undertake metronomic clinical trials remains a major concern. Financial help from government agencies, global health organisations, and the not-for-profit sector will be mandatory to initiate metronomic clinical studies.

Metronomics and new clinical models

Although metronomics can overcome many of the constraints associated with treatment of patients with cancer in LMICs, several potential caveats must be taken into consideration. First, although the utility of metronomics can be extrapolated from the data obtained in studies undertaken in HICs, results must be confirmed in LMIC settings. For instance, in children living in Malawi, a non-intensive weekly treatment with dactinomycin and vincristine[20] was too toxic in undernourished children with Wilms' tumour, leading to severe neutropenia in a third of the patients.[70] Moreover, not all drugs can be easily used in LMICs. For instance, although oral metronomic vinorelbine has been successful in the treatment of various tumour types,[71,72] vinorelbine needs to be stored at a temperature ranging from 2°C to 8°C, precluding its use in many LMICs. Standard of care treatments are not universal but context dependent.

Lastly, the study design model used in HICs at present (ie, randomisation, selected patient populations, use of RECIST, therapeutic drug monitoring, and MRI, CT

***Panel:* Development of an oncology programme in a rural area in India: Tata Memorial Centre–Rural Outreach Program**

Objectives

- To create health awareness about cancer in general and specifically for oral, breast, and cervical cancers
- To screen for early diagnosis of the most frequent cancers
- To treat cases detected through screening

Principles

- Implementation of a successful cancer control programme depends on providing comprehensive cancer care services locally to get maximum compliance to treatment
- Most rural patients are non-compliant for treatment if referred to tertiary cancer centres in cities, which are far away from their home
- All aspects of cancer care including diagnosis, surgery, chemotherapy, and later radiotherapy, were provided locally
- Oncology consultants from Tata Memorial Centre regularly visit the base hospital; the existing pathologists, physicians, and surgeons at the BKL Walawalkar Hospital were trained by Tata Memorial Centre doctors locally to enable them to undertake cancer treatment and management
- Low-cost and effective cancer screening techniques were used
- Patient care was developed taking into consideration:
  - the local infrastructure and supportive care available
  - the socioeconomic conditions of the patient, since most treatments in low-income and middle-income countries are at the patient's own expense and not covered by insurance or government funds
- Low-cost systemic therapies for treatment of diagnosed patients were developed:
  - all the chemotherapy protocols used drugs from the WHO essential drug list
  - oral anticancer drugs were given priority

Outcome

- 830 patients have been treated since 2008

scan, or PET scan for assessment) limits the achievability of such trials in developing countries and might also affect the potential for publication of such data. For example, although all-trans retinoid was first introduced for clinical use for treatment of acute promyelocytic leukaemia by Chinese investigators in 1987,[73] it was not until the data were confirmed in 1990 by investigators from France[74] that it was taken up for randomised studies in most HICs.[75] Although no compromise on scientific and ethical rigour should be made, the context must also be taken into account. For instance, the standard in developed countries to assess the metastatic response of neuroblastoma is an MIBG scan. This examination is rarely available to patients living in LMICs. Does this preclude further investigation of metronomics in patients with neuroblastoma in developing countries and publication of results? Stakeholders must work together to define what methodology, endpoints, and criteria of assessment should be used in these trials.

Conclusions

In view of present trends in cancer incidence, there is no doubt that the cancer burden will increase in the next decade and that this increase will be more substantial in LMICs than in HICs and will result in an even larger proportion of cancer deaths occurring in LMICs because of their resource limitations.[8] Although there is growing awareness of the magnitude of the increasing cancer problem in LMICs, concrete innovative proposals to help solve this issue are still rare. One of the challenges is to propose an affordable, accessible, safe, and effective treatment for patients with cancer living in LMICs. The present strategies and standards of care in developed countries mostly rely on high-dose chemotherapy or targeted therapies and, although appealing for their efficacy and innovation, are not optimal for LMICs because of their cost, toxicities, and the complex infrastructure and technology needed. Metronomics—the combination of metronomic chemotherapy and drug repositioning—might provide a way to overcome some of the major constraints associated with cancer treatment in developing countries and might represent a promising alternative strategy for patients with cancer living in LMICs.

Search strategy and selection criteria

References for this Personal View were identified through searches of PubMed with the search terms "metronomic", "low dose chemotherapy", and "low income countries" alone or in combination from 1990 until November, 2012. Articles were also identified through searches of the authors' own files. Only papers published in English were included. Abstracts from conferences were included. The final reference list was generated on the basis of originality and relevance to the broad scope of this Personal View.

Will we ever be able to treat cancer for US$1 a day?[15] The answer might be an absolute yes, provided we encourage scientific research and clinical studies on metronomic treatments and develop an evidence base that is suitable to the local existing conditions in LMICs, rather than one that is adapted to standards set in HICs. Physicians should know more about costs of treatments or medical procedures[4] and not accept exorbitant new technologies when they bring only limited benefit, and they should be more aware of the value of inexpensive drugs in our modern high-tech era.[76]

Contributors

NA, SB, YS, and EP contributed equally and participated in the literature search and writing of the manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

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