Metronomics — an alternative P4 medicine

> "...metronomic therapy with an alternative definition of P4 medicine — pragmatic, practical, proactive and (re)purposed medicine"

In May 2016, I had the pleasure of attending the Metronomics@Mumbai conference. The advantages of metronomic scheduling of anticancer or repurposed drugs include a substantially lower treatment cost, the convenience of an oral agent, and a home-based care programme that requires minimal monitoring and supportive care compared with inpatient drug administration. Additional advantages for patients are lower toxicity and, in some cases, quite striking efficacy that exceeds that of maximum-tolerated-dose therapy. Amid the stark reality of our unsustainable global health-care systems, and articles published on an almost weekly basis in the literature about the exorbitant costs of cancer treatment, the organizers of this outstanding meeting felt it was pertinent to host this conference in a low-income or middle-income country, such as India.

The meeting kicked off with an explanation of the window-of-opportunity that some metronomic therapies provide, owing in part to their immunomodulatory and anti-inflammatory mechanisms of action. Drug repurposing in the perioperative period offers a number of unique opportunities to improve the outcome of patients with cancer, with changes as simple as using the right analgaesic during surgery to decrease post-surgical relapse. Exciting developments were presented on the promise of next-generation drug repurposing using high-throughput screening technology, as well as the timely identification of drug targets that are most suitable for drug-repurposing approaches. By harnessing 'omics' technologies and the use of knockdown experiments with small interfering RNA screens, efforts are already underway to decipher the best therapy combinations for patients.

Impressive results were discussed from a retrospective trial involving women in India with stage III or IV triple-negative breast cancer who received metronomic chemotherapy following disease relapse. Following standard cyclophosphamide, doxorubicin and 5-fluorouracil chemotherapy, patients were randomly assigned to observation or 12 weeks of maintenance with celecoxib, cyclophosphamide and cisplatin chemotherapy followed by 1 year of maintenance therapy consisting of oral daily metformin and cyclophosphamide along with weekly methotrexate. The maintenance therapy was shown to prevent relapse and significantly improve outcomes of women with this extremely difficult-to-treat cancer, and was associated with fewer toxicities than conventional regimens. Perhaps the most-striking data presented were the outcomes of a phase I trial conducted in the USA in which children with high-risk neuroblastoma were treated with difluoromethylornithine (DFMO) and etoposide. The combination was shown to be safe and well tolerated, and relapse was prevented. These children experienced an improved quality of life; moreover, extended and ongoing follow-up data demonstrate that some children are in remission. Despite these promising results, the company that provided the drug and funded the trial wanted to close the trial before the primary end point was met, as they considered the data collected were sufficient for the purposes of the trial. The parents of the children on the trial, however, decided to take control and set up their own company to produce the drug; they imported the active ingredients and worked with the FDA to get their drug approved and to continue the trial.

In a News & Views article in this issue of the journal, three of the presenters at this metronomics conference discuss fulfilling unmet needs beyond level A evidence in paediatric oncology, an area that is crying out for further progress and alternative approaches beyond our ill-defined 'standards of care'. The authors highlight that 80% of children with cancer live in low-income or middle-income countries, where the survival rate of patients with childhood cancers stagnates at around 20%. Thus, we are saving fewer than four out of 10 patients with childhood cancer, globally!

More than a decade ago, Leroy Hood coined the term 'P4 medicine' — that is, predictive, personalized, preventive, and participatory (P4) medicine. I would liken metronomic therapy with an alternative definition of P4 medicine — pragmatic, practical, proactive and (re)purposed medicine. We know that the permutations of trying to decipher the 'best' combinations of the existing and upcoming cancer drugs using our traditional trial and drug-development approaches is not only impossible in practical terms, but also prohibitive regarding cost and trial end-point measures. The cancer community has recognized the importance of capturing patient-reported outcomes and the need to pay more attention to patient toxicities. Thus, metronomics and drug repurposing is an excellent starting point to tackle the issues of cost, toxicity, practicality and efficacy — without the necessity of testing the efficacy and safety of all agents from scratch. In the new era of metronomic P4 medicine, what is there not to like?

Lisa Hutchinson is the Chief Editor of *Nature Reviews Clinical Oncology*.

Competing interests
The author is a member of the DFMO Task Force that is initiating a maintenance trial for patients with high-risk neuroblastoma in India.