Abstract

Metronomic chemotherapy – the delivery of doses in a low, regular manner so as to avoid toxic side effects – was introduced over 12 years ago in the face of substantial clinical and pre-clinical evidence supporting its tumor-suppressive capability. It constituted a marked departure from the classic maximum tolerated dose (MTD) strategy which, given its goal of rapid eradication, uses dosing sufficiently intense to require rest periods between cycles to limit toxicity. Even so, up-front tumor eradication is frequently not achieved with MTD, whereupon a de facto goal of longer-term tumor control is often pursued. As metronomic dosing has demonstrated tumor control capability, even for cancers that have become resistant to the same drug delivered under MTD, the question arises whether it may be a preferable alternative dosing approach from the outset. To date, however, our knowledge of the coupled dynamics underlying metronomic dosing is neither sufficiently well developed, nor widely enough disseminated, to establish its actual potential. Meeting organizers thus felt the time was right, armed with new quantitative approaches, to call a workshop on “Tumor Metronomics: Timing and Dose Level Dynamics” for the oncology community to gain a deeper, systems-level appreciation of the metronomics concept. The Workshop proved to be a forum where experts from the clinical, biological, mathematical and computational realms could work together to clarify the principles and underpinnings of metronomics. Among other things, the need for significant shifts in thinking regarding endpoints to be used as clinical standards of therapeutic progress was recognized.

Introduction

The second of a series of Annual Workshops organized by the Center of Cancer Systems Biology and supported by the National Cancer Institute’s Integrative Cancer Biology Program took place this last July in Boston. The goal of these annual workshops is to bring together oncologists, cancer biologists, mathematicians and computational scientists to re-examine a critical cancer issue from a multi-scale, systems perspective. This year, the goal was to examine the biological and quantitative ramifications of metronomic chemotherapeutic dosing on tumor dynamics. The concept of metronomic chemotherapy – the administration of low, uniform doses of an agent over time with no rest periods between dosing cycles – was first introduced more than 12 years ago (1-4). It represents a possible alternative address of the troubling fact that, unlike the successes achieved with maximum tolerated doses of chemotherapy for leukemias (5), over 50 years of applying the same regimens for solid tumors has not provided similar successes, despite sometimes impressive initial tumor regressions. One explanation for this conundrum may lie in the fact that solid tumors, unlike
hematologic malignancies, have a long occult prodrome during which many host survival reactions can be hijacked to promote tumor growth, and that growth of these cancers therefore relies in large part on protracted tumor-host dynamics. Conceptually, a suitable therapeutic response might therefore be to apply a similarly protracted treatment to enable and perhaps encourage a reversal of these same dynamics, i.e., metronomic chemotherapy. To explore this notion, plenary lectures reviewing the issues from clinical and quantitative perspectives were supplemented by small-group breakout sessions intended to reconcile disparate points of view about the metronomic concept. The overall goal was to unify thinking, identify inconsistencies, and start on the road of building predictive frameworks leading to more productive directions for clinical implementation.

Proceedings

Setting the stage, and providing context for the Workshop lectures, Dr. Dan Gallahan, Deputy Director of the Cancer Biology Division of the National Cancer Institute and head of NCI’s Integrative Cancer Biology Program, presented an insightful overview of the promise and potential of cancer systems biology to offer quantitative approaches to deal with many of the complexities of cancer development and cancer treatment.

In the opening lecture by Dr. Barton Kamen (The Cancer Institute of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ), the histories of traditional and metronomic chemotherapies were summarized. In his lecture, we were reminded of the shortcomings of the concept of log-kill first introduced by Skipper and Schabel in 1970’s in the context of leukemia (6). He reviewed reasons why this model is not easily transferable to the more highly heterogeneous solid tumors subpopulations, including its development \textit{in vitro} and its subject population being a homogeneous population of non-mutagenic/non-adaptable cells in exponential phase. He reviewed the involvement of immune cells in cancer (7,8) and put forward several reasons for the implausibility of eradicating the reactive inflammatory response with high doses of chemotherapy (9,10). He recounted how even in childhood leukemias, the most commonly noted oncological successes, it was not the early dose intensification that had delivered improvements in outcomes (POG Study 9006) (11). Quite possibly, it was the introduction of 18 months of low-dose, continuous “maintenance” chemotherapy to the protocols that improved the survival rates of these patients. Reinforcing this notion, shortening the low-dose maintenance period led to increased recurrence rates. Thus, from a pharmacological perspective, metronomic dosing arguably makes extension of time of drug delivery the more critical factor in treatment success than \textit{intensification of drug delivery over a fixed time}.

Philip Hahnfeldt (Center of Cancer Systems Biology, Steward St. Elizabeth’s Medical Center, Tufts University School of Medicine, Boston, MA) and Urszula Ledzewicz (Dept. of Mathematics and Statistics, Southern Illinois University, Edwardsville, IL) next discussed quantitative models of tumor dynamics under high- and low-dose chemotherapy. Dr. Hahnfeldt described how target heterogeneity favors a metronomic approach, demonstrating formally how the presence of heterogeneity argues for a diametrically different dosing scheme than that embodied in the maximum tolerated dose (MTD) standard (12). He showed how this follows from recognizing: 1) that the target of drug therapy is a multi-compartment population of intercommunicating cells, heterogeneous in both proliferation rate and drug sensitivity, and 2) that the optimum way to suppress the combined population is by uniformly suppressing its various sub-
compartments together to minimize cross-compartment negative feedback resistance to drug action. Through metronomic dose delivery, the overall population ‘resensitization’ that takes place between increments of dose is optimized. As a corollary, it was shown that, since endothelium should be more efficient at ‘resensitization’ than tumor cells, it stands to reason the adoption of metronomic dosing will lead to greater antiangiogenic efficacy. Looking forward, Dr. Hahnfeldt argued that the more realistic goal of best long-term suppression of cancer will require correspondingly longer-term standards, beyond standard short-term ‘partial’ and ‘complete’ response criteria, for identifying superior drug performance.

Dr. Ledzewicz addressed the question of how much, how often and in what sequence anti-cancer drugs should be administered. She formulated this mathematically as an optimal control problem that considered chemotherapy, both with cytotoxic and cytosstatic agents, angiogenic inhibitors, and immunotherapy, alone or in combination (13). Her conclusion was that the way a given dose is administered over time makes a significant difference as far as the shrinkage of the tumor and cumulative side effects are concerned (14). It was seen that “more is not better” is not always true, that is to say, MTD is not necessarily the best way to achieve the goal of tumor suppression, but that a properly designed, constant or even variable lower dose rate may provide a better outcome. This in turn would suggest that metronomic drug delivery, which shows much promise judging from the available clinical data, may well be a more efficient means of drug administration. So while the general principle appears validated, it is proposed that the tools of optimal control theory can further refine the issue to provide insight into how, in terms of the dose level, duration, presence or absence of rest-periods, a metronomic protocol should be designed.

Eddy Pasquier (Children’s Cancer Institute Australia for Medical Research, Sydney, Australia, and a co-founder of the Metronomics Global Health Initiative) opened the second day by discussing how the type of endothelial cell response depends on dose, focusing on the unique involvement of cytoskeletal dynamics. Dr. Pasquier showed that high concentrations of microtubule-targeting drugs (e.g. taxanes and vinca alkaloids) suppress microtubule dynamics, but low concentrations can do the reverse (15,16), impairing the motility and angiogenic potential of endothelial cells without cell killing (17). To illustrate, he compared vinblastine, an anti-microtubule drug, to VP16 and mafosfamide. While differential effects could be achieved with low dose (1nM) vs high dose (20nM) vinblastine, 0.5 vs 50μM topoisomerase/VP16, or 2.5 vs 50μM mafosfamide, only vinblastine showed differential effects at nM concentrations. He went on to show that repeated exposure to high-dose chemotherapy led to increased proliferation rates and drug resistance in endothelial cells, while repeated exposure to low-dose metronomic chemotherapy impaired the angiogenic capacity of endothelial cells and increased chemosensitivity through downregulation of MRP2, βII and βIII tubulin expression. An intriguing incidental finding was preliminary evidence that the expression of VEGFR2 increases with MTD, but decreases with low-dose metronomic chemotherapy (18). Considering that the remaining VEGFR2 receptors following low-dose chemotherapy should have an improved efficiency per receptor on account of the now relatively greater abundance of ligand, additional direct inhibition of the receptor should enhance overall tumor suppression. If so, this would offer one explanation for the previously observed synergistic activity of the combination of low dose continuous chemotherapy and VEGFR2 inhibition (2,19). A stimulating discussion about the differential effect of low protracted doses of chemotherapy vs high doses with prolonged periods of interruptions ensued.
Citing both pre-clinical data and evidence from clinical trials, Carl Panetta (Dept. of Pharmaceutical Sciences at St. Jude Children’s Research Hospital, Memphis, TN) proposed that “protracted” doses possess a very different mechanism of action than high doses coupled with prolonged dose interruptions. Data supported the differential effect of varying the frequency based on interruptions to allow for bone marrow recovery (usually every 3-4 weeks), vs protracted dosing regimens without interruption. He summarized the clinically applicable mathematical modeling methods currently used to describe the complex effects of chemotherapy, concluding that quantitative models provide an efficient means to anticipate the implications of tumor heterogeneity in the consideration of alternative treatment schedules. He included three examples of agents that have been modeled in clinical setting: methotrexate and asparaginase, which are used in childhood acute lymphoblastic leukemia (ALL) (20,21), and topotecan (22), used in pediatric neuroblastoma. In each case, mathematical models were developed to describe the disposition and mechanism of action of the agent, which were then employed to help define effective doses and treatment schedules. These model-predicted treatments were validated using current and historical clinical data, and in particular, suggested a superiority of topotecan in protracted regimens. Dr. Panetta concluded by advocating that drug pharmacokinetics/pharmacodynamics be considered in the planning of specific metronomic regimens.

Sebastian Benzekry (Center of Cancer Systems Biology, Steward St. Elizabeth’s Medical Center, Tufts University School of Medicine, Boston, MA) presented a novel mathematical model for combination cytotoxic and anti-angiogenic therapies in the treatment of metastatic cancers. Using tumor size and vascular carrying capacity as critical variables in a transport equation construct, he focused on the effect of varying drug scheduling on the response of the tumor-metastasis system. He demonstrated that the therapeutic response of metastases is likely different than that of the primary. He went on to present a novel simulation of the dynamical differences of MTD vs metronomic dose and frequency regimens, and a model for time to development of metastases, their distribution, size, and carrying capacity (23). He further showed how this construct can be used to theoretically study the effects of scheduling of anti-cancer drugs (both cytotoxic and anti-angiogenic) on the treatment of disseminated cancer (18). He emphasized the differences between the treatment of an isolated lesion and a population of metastases, and derived the theoretical “optimal schedule” that showed a superior effect on the total metastatic mass by a continuous metronomic regimen vs a classical MTD scheme where the dose is given as one concentrated administration.

Starting out the third day, Nicolas André (Aix-Marseille University Medical School, Marseille, France, and a co-founder of the Metronomics Global Health Initiative) pointed out that metronomic chemotherapy was initially thought to be ‘anti-angiogenic’ by definition, likely a carryover from earlier studies that emphasized this aspect (e.g. (1,3)), but noted we now appreciate a broader involvement of the microenvironment beyond the endothelial component (15,16). He reminded us that employing metronomic chemotherapy/biologic response modifier combinations might be less toxic and more effective than MTD implementations that have historically failed due to toxicity limitations. He recalled several successful experiences with low-dose chemotherapy, including: 1) pediatric cases dating back to the 60’s; 2) maintenance purinethol-methotrexate regimens used in ALL, and 3) the use of low-dose oral etoposide in palliative management of incurable brain tumors (24), sarcomas (25-27), and pediatric refractory tumors (25,28,29). He recounted how, despite the renewed focus on
metronomic dosing and reports of its antiangiogenic effect (2,19,30,31), it has been
difficult to evaluate clinical trials. He attributed part of this to the fact that, in traditional
therapeutic regimens, efficacy is measured by immediate tumor shrinkage,
whereas in metronomic chemotherapy, effect is only evident after 6-8 months. Other
problems include the paucity of response biomarkers and models for multi-drug
regimens. Dr. Andre, who leads several metronomic trials in France, summarized key
considerations for proper metronomic protocol design. These include: endpoints to use
in lieu of classic ‘partial’ or ‘complete’ response, the value of single vs combination
therapies, evaluation of synergism/antagonism between two agents, the utility of
avoiding dosing breaks, the use of MTD efficacy standards in the metronomic context,
the existence of a universal metronomic scheduling standard, and the extrapolation
of single-agent drug information to a multi-drug dosing setting.

Heinz Schaettler (Dept. of Electrical and Systems Engineering, Washington University,
St. Louis, MO) discussed mathematical models for various combinations of
chemotherapeutic strategies using multiple agents, or chemotherapy/radiation given with
and anti-angiogenic treatment. He presented how these models can be used to
determine optimal tumor burden control and minimize the cancer volume. Addressed
was the challenge that arises in the search for optimal protocols of combination
therapies. Since more than one agent is involved, in addition to the natural question of
timing and dosage, there is also the important question of proper sequencing. Thus, the
question “in what order” can significantly influence the outcome. Discussed were
detailed mathematical models for various combination therapies such as multi-drug
chemotherapy and antiangiogenic treatment combined with cytotoxic agents or
radiotherapy. These models were reviewed as optimal tumor control problems.
Depending on the model construct and treatment specifics, different optimal scenarios
were seen to arise that include mixtures of singular controls corresponding to varying
lower dose regimens, and so-called ‘bang-bang’ controls corresponding to maximum
dose treatments with rest periods in between. The combination of an initial
cytoreductive MTD (bang-bang) regimen followed by metronomic chemotherapy, which
Dr. Schaettler called a chemo-switch strategy and suggested may be the optimal
strategy, has already been used both in pre-clinical studies in vivo (2) and in humans (in
current ALL protocols).

David Waxman (Division of Cell and Molecular Biology, Boston University, Boston, MA)
presented on the topic of innate immunity-induced tumor regression by metronomic
chemotherapy. He stressed that metronomic chemotherapy regimens are often anti-
angiogenic, reflecting the high chemosensitivity of tumor endothelial cells to metronomic
schedules of cytotoxic drugs (32). He also presented data using preclinical brain tumor
xenograft models where cyclophosphamide given in a 6-day repeating metronomic
schedule activated potent anti-tumor innate immunity (33), leading to tumor ablation.
Unexpectedly, VEGFR-selective inhibitors blocked these responses, suggesting that the
use of VEGFR inhibitors in clinic may inhibit tumor immunosurveillance. Using wild-type
and immunocompromised mouse models, he showed how immunosurveillance
suppression can be avoided by instead using anti-angiogenic agents that act by means
other than by VEGFR inhibition. In contrast, traditional high-dose chemotherapy induced
an innate immune response that was transient and weak, suggesting that sustained
drug-induced stress and its associated cytokine response are required for immune-
facilitated tumor regression (33,34). In his closing remarks, Dr. Waxman emphasized
that the timing and frequency of metronomic drug treatment was critical. The innate
immune response leading to tumor regression was lost when the frequency of
metronomic administration of a given total amount of drug was increased from once every 6 days to every 3 days, or daily. A very lively discussion ensued after Dr. Waxman’s suggestion that “metronomic chemotherapy may also benefit from breaks and that daily, or every 3 days, may be too frequent”. The ensuing discussion into this and other potential intricacies relating to implementation of the metronomics concept reflected the difficulty faced testing various regimens in the clinic without harming patients, and the increasing difficulty justifying pre-clinical experiments with dose- or frequency-finding goals. As an alternative, the group agreed on the need to develop additional quantitative modeling tools to evaluate the consequences of different frequencies of metronomic chemotherapies on innate immunity, angiogenesis and various populations within the tumor.

In her presentation delving into hindrances to translation of metronomic chemotherapy to the clinic, Giannoula Lakka Klement argued that the main obstacle may be our reluctance to change. Even though the advent of anti-cancer chemotherapy some 75 years ago brought about a striking increase in survival rates, it was done at a very high cost to patients. Moreover, although the survival rates for childhood ALL rose from 25% in 1960 to 95% in 2012, a number of leukemia subtypes and stages, e.g. the MLL-AF4 fusion variant of ALL and post-blast crisis CML, carry dismal prognoses. Similarly, for many solid tumors of the CNS or disseminated sarcomas, the survival rates, while rising from 8% to >60% in the 70’s, have not further improved. Unfortunately, many of the newer biologic response modifiers that were developed over the last 40 years have not performed well in the setting of standard dose chemotherapy. Such agents interfere with host physiological responses recruited by the cancer, thereby stripping the cells (both normal and cancerous) of many of their survival mechanisms and thus enhancing the toxic effects of chemotherapy. Thus, it is often the case that when standard MTD doses are used, the outcome of adding a biologic response modifier is increased toxicity. This contributes to why many clinical trials, which employ standard endpoint measurements e.g. overall survival or event-free survival, eventually fail despite meaningful initial tumor regressions. Biologic response modifiers (e.g. antiangiogenic agents, cox-2, tyrosine kinase inhibitors, and antibodies against pro-tumor factors) are particularly suited to combinations with metronomic chemotherapy, as their ability to inhibit stromal reaction can give rise to a synergistic habitualization of the microenvironment. Dr. Klement reminded us that when dealing with resistant cancers, even myeloablative doses requiring peripheral stem cell rescue rarely succeed at eradication, and increasing the dose leads to unnecessary toxicity. Further, while the cancer cells develop drug resistance, normal host cells keep responding, and their damage manifests as bone marrow suppression, hair loss, etc. throughout the chemotherapeutic course. This persistent sensitivity of normal cells, this “resistance to resistance”, can be exploited with a combination of low-dose metronomic chemotherapy and a biologic response modifier. In particular, the ‘resistance’ of normal endothelial cells to developing resistance makes them an excellent target for therapy (35). If endothelial cells are less prone to developing resistance and if they are sensitive to very low doses of chemotherapy, then the addition of an anti-angiogenic agent to extremely low doses of chemotherapy could result in a superior, non-toxic strategy unlikely to develop drug tolerance. Clinical trials support the use of maintenance chemotherapy in solid tumors, particularly those at high risk for relapse. A recent Canadian experience in children with Ewing sarcoma suggests that the combination of vinblastine/celecoxib metronomic therapy following standard treatment results in statistically significant event-free survival (36). Dr. Klement suggested that the availability of a plethora of new targeted agents is likely to change the culture of oncology, with treatments moving from treating advanced disseminated
cancers with highly toxic combinations, to intervening early in carcinogenesis with minimally toxic, albeit slower acting, drug combinations.

The Keynote lecture was given by Dr. Larry Norton (Memorial Sloan-Kettering Cancer Center, New York, NY), and addressed the difficulty with our search for the ultimate single drug sought by pharmaceutical companies, physicians and patients alike. As one of the first investigators to point out limitations with the traditional MTD implementation of the log-kill theory of Skipper, Schabel and Wilcox, he reminded us that fast-growing tumors are killed fast, and slow tumors are killed slowly (37,38), and how this translates to the same speed of recurrence. He shared experimental evidence that adjusting dose densities and sequence can lead to improved responses compared to myeloablative doses requiring time for bone marrow recovery (39-42). The 20 years that passed since this simple observation, he said, were committed to finding the “right drug” because the idea of having ever more potent single agents against cancers was more conceptually accessible than the formidable dynamical understanding that would be needed to match dose schedules to tumor dynamics. As a strong advocate for including tumor dynamical considerations in treatment planning, Dr. Norton gave further examples of the importance of early leucocyte migration into tumors, of tumor ‘self-seeding’ (43), and the ability to infer tumor progression from genomic heterogeneity (44,45). He suggested that ductal carcinoma in situ (DCIS) amounts to a breast cancer that has not developed pathways to self-seed, and that DCIS may therefore be a good setting for using anti-migration agents, e.g. anti-CXCR2, rather than methods like cryoablation, which may be counterproductive because it leads to macromolecular debris. He pointed out that cancer cells overexpressing CXCL1 and 2 attract CD11b+ myeloid cells into the tumor, where they produce cytokines that promote cancer cell survival. He closed with the thought-provoking suggestion that chemotherapy should be given in a dose- and frequency-specific manner so as to target the tumor-promoting myeloid CD11b+ cells, and that the optimal time to apply chemotherapy is when the tumor is undergoing the most change.

Conclusions

The Workshop confirmed the urgent need for collaboration between the biomathematical and biomedical arenas in the effort to optimize therapeutic dosing strategies. On the last day, breakout groups, each consisting of biologists, MDs and mathematicians, presented their consensus views on the vital questions surrounding optimum frequency and dose administration for chemotherapeutic agents, and what might be an appropriate surrogate endpoint for the evaluation of treatment efficacy. Melds of the viewpoints of group members were presented, ranging from testable quantitative models, to general roadmaps connecting clinical and pre-clinical data on dose-relevant parameters, to potential optimal clinical implementation. Novel points of view emerged from the group discussions as well as the discussion in the large plenary forums.

With respect to impact on perspective and clinical applications, it was noted that progress in less toxic approaches to cancer therapy may have been hindered by the unfortunate expectation, of patients and physicians alike, that any approach should lead to immediate tumor eradication. It appears inevitable, however, with the ever-increasing evidence attesting to the efficacy of low, uniform dosing – metronomic therapy – a shift away from the common expectation of “immediate regression” that accompanies high-dose therapy will eventually occur. Indeed, a search for the word ‘metronomic’ in the U.S. National Institutes of Health ‘ClinicalTrials.gov’ online database...
Metronomic chemotherapy (http://clinicaltrials.gov/ct2/results?term=metronic&Search=Search) presently yields 104 trials, 56 of which are open, and over 90% of which are in combination with a targeted biological agent. Hopefully, with further development of molecularly-based cancer therapies, this change may gain additional momentum. Looking forward, it is anticipated that as we work to overcome the frustrating fact that combining targeted therapies with already maximally-toxic standard therapies often leads to unacceptable toxicities without the offsetting benefit of prevention of relapse, the embrace of metronomic chemotherapy will grow. A combination of targeted treatments and metronomic chemotherapy may represent a marriage of two goals – the ability to optimize selection for the cancer cells of interest, while at the same time anticipating and minimizing untoward physiological reactions of the host.

Acknowledgments:

This Workshop Proceedings Report is dedicated to Dr. Barton Kamen, whose relentless work, enthusiasm, and collegial spirit has been the source of inspiration for colleagues and junior scientists alike. Several of us were driven to appreciate the importance of lower-dose scheduling only after many stimulating discussions with Barton. He was the force that, almost single-handedly, kept the field of metronomics alive through a time of great resistance to clinical acceptance. His participation in the Workshop was a testimonial to his selfless commitment to the cause; timed as it was after Barton had already become ill. Although he was not able to review our recollections in this report, the authors felt his presence in every thought and discussion we have here related. The essence of a most supportive and encouraging mentor, Barton passed to us his legacy of “the good fight”, inspiring us to move forward with the challenges the paradigm-shifting field of metronomics has placed upon us. Support for this Workshop came from National Cancer Institute grant #U54-CA149233 (to L.H.).

References:


Center of Cancer Systems Biology Second Annual Workshop -
Tumor Metronomics: Timing and Dose Level Dynamics

 Philip Hahnfeldt, Lynn Hlatky and Giannoula Lakka Klement

Cancer Res  Published OnlineFirst March 14, 2013.

Updated version  Access the most recent version of this article at:  
doi:10.1158/0008-5472.CAN-12-3807

Supplementary Material  Access the most recent supplemental material at:  
http://cancerres.aacrjournals.org/content/suppl/2013/03/14/0008-5472.CAN-12-3807.DC1

Author Manuscript  Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, use this link  
http://cancerres.aacrjournals.org/content/early/2013/03/14/0008-5472.CAN-12-3807.  
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.