Biomedical & Pharmacology Journal, September 2025. Vol. **18**(3), p. 1917-1924

Metronomic Chemotherapy: An Alternative Strategy in Cancer Treatment Based on Continuous Low-Dose Administration

Giorgio Attina', Stefano Mastrangelo, Alberto Romano, Dario Talloa, Palma Maurizi and Antonio Ruggiero*

Department of Woman and Child Health and Public Health, Pediatric Oncology Unit, Fondazione Policlinico Universitario A.Gemelli IRCCS, Universita' Cattolica Sacro Cuore, Rome, Italy.
*Corresponding Author E-mail: antonio.ruggiero@unicatt.it

https://dx.doi.org/10.13005/bpj/3224

(Received: 18 April 2025; accepted: 13 May 2025)

Traditionally, cancer treatment relied on the maximum tolerated dose (MTD) approach, in which chemotherapeutic agents are given at the highest dose that patients can tolerate, with scheduled breaks to allow for recovery. However, this method has notable drawbacks, including significant toxicity, tumor regrowth during drug-free intervals, and the development of resistance. Metronomic chemotherapy offers an innovative alternative, characterized by continuous low-dose administration without treatment interruptions. This approach primarily targets the tumor microenvironment, including tumor vasculature and cancer stem cells, while also affecting the immune system. By maintaining a steady level of drug exposure, metronomic therapy prevents the recovery of tumor endothelial cells and enhances immune surveillance, leading to prolonged disease stabilization and potentially improved long-term outcomes. Due to its reduced toxicity, cost-effectiveness, and suitability for oral administration, metronomic chemotherapy is especially beneficial for long-term maintenance therapy for the elderly, or frail patients. This review explores the mechanisms, clinical advantages, and challenges of metronomic chemotherapy, as well as its potential for integration with other treatment modalities to improve patient outcomes. Additional research is needed to optimize drug dosing, identify biomarkers for treatment response, and conduct large-scale clinical trials comparing metronomic approaches with standard chemotherapy regimens.

Keywords: Cancer; Chemotherapy; Drug dosing; Metronomic; Toxicity.

The historical foundation of cancer treatment has been built upon the maximum tolerated dose (MTD) paradigm, wherein chemotherapeutic agents are administered at the highest possible dose that produces acceptable toxicity, followed by treatment-free intervals to facilitate recovery of healthy tissues.[1] This approach, which emerged during the mid-20th century, operates on log-kill kinetics principles with the objective of eliminating the maximum proportion of tumor cells during each treatment cycle.[2]

Despite its widespread adoption, conventional MTD chemotherapy faces significant limitations. The considerable collateral damage to non-malignant tissues frequently results in debilitating adverse effects, including bone marrow suppression, gastrointestinal toxicity, cardiac damage, and peripheral neuropathy.[3]

These complications often necessitate therapeutic compromises through dose adjustments or treatment suspensions, potentially undermining clinical efficacyw . Moreover, the obligatory treatment-free intervals between cycles create opportunities for tumor regeneration and the development of adaptive resistance mechanisms.[4]

For solid malignancies, the MTD strategy presents a challenge, as it preferentially eliminates drug-sensitive cell populations while creating a selective advantage for resistant subclones.[5,6] This evolutionary pressure facilitates the emergence of treatment-refractory disease phenotypes, contributing to therapeutic failure and disease progression.[5,6] The typical clinical trajectory following conventional chemotherapy often involves initial tumor regression followed by recurrence, with progressively diminishing benefits from subsequent treatment lines.[7]

In an attempt to address these shortcomings, clinical oncology has historically pursued intensified multidrug combinations, embracing the"more is better" philosophy.[8,9] While such combination strategies have yielded improvements in certain cancer types, they frequently result in compounded toxicity profiles without proportional therapeutic advantages.[9]

Contemporary advances in tumor biology have redirected attention from direct cytotoxicity toward modulation of the complex tumor microenvironment (TME).[10,11] This conceptual evolution recognizes neoplastic disease as an intricate ecosystem rather than simply an aggregation of transformed cells. Within this framework, sustained disease stabilization and improved survival outcomes have supplanted immediate tumor size reduction as primary therapeutic objectives, particularly when such reductions fail to translate into meaningful clinical benefits.[10-13]

Metronomic chemotherapy represents an innovative therapeutic paradigm that aligns with this evolving biological understanding.[14-17] This approach involves regular, often daily, administration of chemotherapeutic agents at substantially reduced doses, without the extended treatment-free periods characteristic of conventional protocols.[18,19] The persistent exposure to low-concentration cytotoxic agents targets both neoplastic cells and their supporting microenvironment, with particular effects on tumor vasculature, also helping to reduce potential side effects.[20-22] This alternative administration strategy, also described as continuous low-dose chemotherapy or anti-angiogenic chemotherapy, employs distinctive mechanistic principles compared to traditional approaches.[23-26] Unlike conventional schedules, metronomic protocols maintain continuous therapeutic pressure on the tumor ecosystem without permitting recovery intervals between treatment cycles.[24,27-30]

The metronomic strategy offers numerous pragmatic advantages, including attenuated toxicity profiles, enhanced cost-effectiveness, and accessibility of oral administration, eliminating requirements for vascular access devices or extended infusion sessions.[21,31-33] These characteristics render it particularly appropriate for long-term maintenance therapy, the treatment of elderly or medically compromised patients, and its integration within multidisciplinary treatment frameworks.[34-39]

MATERIALS AND METHODS

Study Design

This comprehensive review evaluates the mechanistic principles, clinical applications, and therapeutic advantages of metronomic chemotherapy compared to conventional maximum tolerated dose (MTD) regimens. An analysis of preclinical and clinical evidence was conducted to elucidate the multidimensional mechanisms through which metronomic scheduling exerts anti-neoplastic effects.

Literature Search Strategy

A systematic search of electronic databases including PubMed/MEDLINE, Embase, Web of Science, and the Cochrane Library was performed. Search terms included combinations of "metronomic chemotherapy," "continuous low-dose chemotherapy," "anti-angiogenic chemotherapy," "dose-dense chemotherapy," "chemotherapy scheduling," and "tumor microenvironment." Additional references were identified through citation tracking of key articles. Publications were limited to English-language studies published until October 2024.

RESULTS

Mechanistic Findings

Metronomic chemotherapy exhibits antineoplastic activity through multiple complementary mechanisms, extending beyond conventional cytotoxicity. This multidimensional approach targets various components of the tumor ecosystem, creating an inhospitable environment for cancer proliferation and dissemination.[19,20,40-43]

Direct Cytotoxic Effects on Tumor Cells

Though administered at concentrations below those of conventional regimens, metronomic chemotherapy maintains persistent cytotoxic agent exposure within the tumor microenvironment.[30] This sustained presence impedes cellular DNA repair mechanisms between treatment cycles, potentially resulting in cumulative genomic damage within susceptible neoplastic populations.[31,34] Additionally, the consistent low-level exposure may affect slowly cycling cells, including those in dormant states, which frequently evade pulsed high-dose chemotherapy effects.[44,45]

Specific subpopulations of malignant cells demonstrate enhanced vulnerability to continuous low-dose exposure compared to intermittent high-dose administration. This differential sensitivity pattern may relate to distinctive cell cycle kinetics, metabolic characteristics, or specific molecular vulnerabilities exploited by the metronomic approach.[25,28]

Targeting Cancer Stem Cells

Cancer stem cells (CSCs) constitute a pivotal subpopulation within tumors, possessing self-renewal capacity and being frequently implicated in therapeutic resistance, disease recurrence, and metastatic progression. These cells commonly demonstrate resistance to standard chemotherapy through various mechanisms, including enhanced DNA repair capacity, upregulated drug efflux transporters, and adaptive metabolic pathways.[46-48]

Notably, metronomic chemotherapy has demonstrated efficacy against CSC populations in numerous preclinical models.[20,33] The continuous exposure to low-concentration chemotherapeutics may circumvent certain resistance mechanisms by preventing the activation of adaptive responses typically occurring during treatment-free intervals. Furthermore, the anti-angiogenic properties of metronomic regimens may disrupt specialized microenvironmental niches supporting CSC maintenance and self-renewal functions.[11,25]

Anti-angiogenic Effects

The most thoroughly characterized mechanism of metronomic chemotherapy involves its potent anti-angiogenic activity.[12] Solid tumors depend critically on neovascularization to support growth beyond minimal dimensions, with tumor-associated endothelial cells (TECs) undergoing rapid proliferation during angiogenic processes.[13-15] These actively dividing endothelial populations demonstrate particular vulnerability to chemotherapeutic agents, even at concentrations substantially below those required for direct tumor cell cytotoxicity.[14]

Metronomic administration creates an imbalance between pro-angiogenic and angiostatic factors within the tumor microenvironment.[11] Specifically, these regimens enhance the expression of endogenous angiogenesis inhibitors, including thrombospondin-1 (TSP-1), while simultaneously suppressing pro-angiogenic mediators such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and hypoxia-inducible factor 1 (HIF-1).[16-18]

Remarkably, anti-angiogenic effects manifest at picomolar concentrations, with endothelial cells exhibiting 10-100,000-fold greater sensitivity compared to non-endothelial cellular populations.[11-18] This therapeutic window enables selective targeting of tumor vasculature while minimizing systemic toxicity. The dose-response relationship for tumor cells versus tumor endothelial cells reveals that TECs can effectively be targeted at drug concentrations substantially below those required for direct tumor cell elimination. This differential sensitivity enables metronomic regimens to indirectly suppress tumor growth by compromising vascular support, while avoiding the intense selection pressure that promotes resistant clone emergence.[16,17]

Conventional MTD regimens, despite inherent anti-angiogenic potential, permit endothelial recovery during treatment-free intervals.[4] This recovery frequently features a "rebound" phenomenon, characterized by augmented pro-angiogenic factor expression during treatment breaks, potentially accelerating tumor revascularization. By eliminating these

Table 1. Common drugs for metronomic therapy

Drug Class	Examples	Mechanism of Action	Common Metronomic Dosing
Alkylating agents	Cyclophosphamide	DNA cross-linking, anti-angiogenic effects	50 mg daily oral
Antimetabolites	Methotrexate, Capecitabine	Inhibition of DNA synthesis, anti-angiogenic effects	Methotrexate: 2.5-5 mg twice weekly; Capecitabine: 500-1000 mg twice daily
Taxanes	Paclitaxel	Microtubule stabilization, anti-angiogenic effects	20-30 mg/m² weekly
Vinca alkaloids	Vinorelbine, Vinblastine	Microtubule inhibition, anti-angiogenic effects	Vinorelbine: 30-50 mg three times weekly; Vinblastine: 3-5 mg/m² weekly
Platinum compounds	Carboplatin	DNA cross-linking, anti-angiogenic effects	AUC 2 weekly
Topoisomerase inhibitors	Etoposide, Irinotecan	Inhibition of DNA unwinding, anti-angiogenic effects	Etoposide: 50 mg daily for 14-21 days; Irinotecan: 50 mg/m² weekly

treatment gaps, metronomic protocols maintain consistent pressure on tumor vasculature, preventing angiogenic recovery.[13-16]

Inhibition of Endothelial Progenitor Cell Mobilization

Beyond its effects on established tumor vessels, metronomic chemotherapy disrupts the recruitment of bone marrow-derived endothelial progenitor cells (EPCs). These progenitor populations contribute significantly to tumor neovascularization by responding to angiogenic signals and incorporating themselves into developing vascular networks.[21,22] While conventional chemotherapy affects circulating EPCs, treatment-free intervals allow compensatory mobilization from bone marrow reserves, replenishing depleted populations. This "rebound" mobilization has been associated with accelerated tumor revascularization and growth during treatment interruptions.[21]

Metronomic administration eliminates these recovery periods, while maintaining persistent suppression of EPC mobilization and circulation. This sustained inhibition prevents vascular repair processes that would otherwise support tumor regrowth, contributing to the long-term efficacy of the metronomic approach.[12,19,21]

Immunomodulatory Effects

An increasingly appreciated mechanism of metronomic chemotherapy involves its substantial impact on the tumor immune microenvironment. While conventional high-dose chemotherapy typically induces generalized immunosuppression, metronomic dosing demonstrates selective immunomodulatory effects that potentially enhance antitumor immunity.[22,24]

Metronomic regimens preferentially deplete immunosuppressive cellular populations, particularly regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs).[18] These immunoregulatory cells play critical roles in tumor immune evasion by inhibiting effector T cell and natural killer (NK) cell functions. Their selective reduction shifts the immunological balance toward an antitumor state.[18,19] Concurrently, metronomic chemotherapy enhances dendritic cell (DC) maturation and functional capacity, improving antigen presentation efficiency. This effect, combined with increased expression of tumor-associated antigens and antigen-presenting molecules on malignant cells, facilitates more effective tumor recognition by immune surveillance mechanisms.[26-28] Metronomic administration promotes immunogenic cell death (ICD) through several pathways. It induces calreticulin (CRT) externalization on tumor cell surfaces, serving as a recognition signal for phagocytic cells. Additionally, it stimulates the release of endogenous danger-associated molecular patterns (DAMPs) including high-mobility group box 1 (HMGB1) and adenosine triphosphate (ATP), which activate dendritic

cells and promote adaptive immune responses.[30] The membrane expression of heat shock proteins (HSPs) represents another immunostimulatory consequence of metronomic chemotherapy. These molecular chaperones facilitate antigen presentation and enhance recognition by immune effector populations.[30,32] Finally, metronomic regimens induce the expression of natural killer cell receptor ligands on tumor cells, rendering them more susceptible to innate immune surveillance and elimination.[32,33]

The temporal dynamics of antitumor effects differ substantially between conventional and metronomic approaches.[34] MTD regimens typically produce rapid but transient tumor regression, followed by recurrence as resistant clones emerge. In contrast, metronomic chemotherapy demonstrates a delayed response pattern, with initial disease stabilization or even continued progression followed by gradual but sustained regression over time. This pattern reflects the indirect nature of its mechanisms, particularly anti-angiogenic and immunomodulatory effects, which require time to fully manifest but potentially offer superior long-term outcomes.[32-34]

In Table 1, common drugs used in metronomic chemotherapy and their respective mechanisms of action are presented.

DISCUSSION

Metronomic chemotherapy represents a paradigm shift in cancer treatment approaches, moving away from the traditional maximum tolerated dose (MTD) paradigm toward a more sustainable, continuous administration strategy. This approach has gained significant attention due to its multifaceted mechanisms of action that extend beyond direct cytotoxicity.[2-8]

The primary advantage of metronomic chemotherapy lies in its ability to target the tumor microenvironment, particularly focusing on the tumor vasculature. By maintaining constant, low-level drug exposure, this approach effectively prevents the compensatory angiogenic rebound typically observed during treatment breaks in conventional chemotherapy regimens. The continuous presence of chemotherapeutic agents, even at significantly reduced doses, creates persistent pressure on tumor-associated endothelial cells, which are particularly sensitive to these agents. This sensitivity allows for effective anti-angiogenic effects at doses that cause minimal toxicity to normal tissues.

Another crucial aspect of metronomic chemotherapy is its immunomodulatory effect. Traditional high-dose chemotherapy often causes significant immunosuppression, potentially counteracting any immunogenic tumor cell death it might induce. In contrast, metronomic dosing has been shown to selectively deplete immunosuppressive cell populations like regulatory T cells and myeloid-derived suppressor cells while preserving or even enhancing effector immune populations. This immune remodeling creates a more favorable environment for anti-tumor immune responses, potentially converting "cold" tumors into "hot" ones that are more responsive to immune surveillance.[48-50]

The reduced toxicity profile of metronomic regimens also allows for more extended treatment periods and improved quality of life for patients. This is particularly valuable in palliative settings or for elderly or frail patients who may not tolerate conventional MTD regimens. Additionally, the oral administration of many metronomic protocols reduces hospital visits and healthcare costs, making this approach more patient-friendly and economically sustainable.

Despite these advantages, several challenges remain in optimizing metronomic chemotherapy. Determining the optimal dosing and scheduling for different drugs and tumor types requires further investigation. The balance between maintaining effective anti-angiogenic pressure and avoiding the development of resistance mechanisms needs careful consideration. Moreover, identifying reliable biomarkers to predict response to metronomic therapy and monitor treatment efficacy remains an unmet need. Combination strategies incorporating metronomic chemotherapy with other treatment modalities such as targeted therapies, immunotherapies, or radiation therapy also represent promising avenues for research. These combinations might exploit synergistic effects while maintaining favorable toxicity profiles.

CONCLUSION

Metronomic chemotherapy offers a promising alternative to conventional maximum tolerated dose regimens in oncology. Its multi-target approach—affecting tumor cells directly, disrupting tumor vasculature, eliminating cancer stem cells, and modulating the immune microenvironment—provides a comprehensive strategy against cancer that may improve long-term outcomes.

The lower toxicity profile, reduced costs, and patient-friendly administration make metronomic chemotherapy particularly valuable in various clinical scenarios, including maintenance therapy, palliative care, and treatment of frail or elderly patients. Moreover, this approach aligns with the evolving understanding of cancer as a complex ecosystem rather than simply a collection of malignant cells.

Future research should focus on optimizing drug selection, dosing, and scheduling for different tumor types, developing reliable biomarkers for patient selection and response monitoring, and exploring rational combinations with other therapeutic modalities. Additionally, well-designed randomized controlled trials comparing metronomic approaches with standard treatments across various cancer types are needed to solidify the evidence base.

In summary, metronomic chemotherapy represents a paradigm shift in cancer treatment that emphasizes the quality and sustainability of response over short-term tumor shrinkage. By targeting multiple aspects of tumor biology while minimizing toxicity, this approach has the potential to transform cancer therapy from acute intervention to chronic disease management, ultimately improving both survival outcomes and quality of life for cancer patients.

ACKNOWLEDGMENT

The authors thank "Fondazione per l'Oncologia Pediatrica ONLUS" for their dedicated patient care and scientific support.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

Permission to reproduce material from other sources

Not Applicable.

Authors' contributions

Antonio Ruggiero: Conceptualization, Methodology, Writing – Original Draft; Giorgio Attinà: Data Collection, Analysis, Writing – Review & Editing; Stefano Mastrangelo: Visualization, Supervision, Review; Palma Maurizi: Visualization, Supervision, Review; Alberto Romano: Data Collection, Analysis, Writing, Review; Dario Talloa: Data Collection, Analysis, Writing, Review & Editing.

REFERENCES

1. Skipper HE, Schabel FM, Wilcox WS. Experimental evaluation of potential anticancer agents. XIII. On the criteria and kinetics associated with "curability" of experimental leukemia. *Cancer Chemother Rep*. 1964;35:1-111.
2. Frei E, Canellos GP. Dose: a critical factor in cancer chemotherapy. *Am J Med.* 1980;69(4):585-594.
3. Shapiro CL, Recht A. Side effects of adjuvant treatment of breast cancer. *N Engl J Med.* 2001;344(26):1997-2008.
4. Bonadonna G, Valagussa P. Dose-response effect of adjuvant chemotherapy in breast cancer. *N Engl J Med.* 1981;304(1):10-15.
5. Shah MA, Schwartz GK. Cell cycle-mediated drug resistance: an emerging concept in cancer therapy. *Clin Cancer Res*. 2001;7(8):2168-2181.
6. Mross K, Steinbild S. Metronomic anti-cancer

therapy – an ongoing treatment option for advanced cancer patients. *J Cancer Ther Res*. 2012;1:32-36.
7. DeVita VT, Young RC, Canellos GP. Combination versus single agent chemotherapy: a review of the basis for selection of drug treatment of cancer. *Cancer.* 1975;35(1):98-110.
8. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol.* 2003;21(8):1431-1439.
9. Ferrara P, Marrone G, Emmanuele V, et al. Homotoxicological remedies versus desmopressin versus placebo in the treatment of enuresis: a randomised, double-blind, controlled trial. *Pediatr Nephrol.* 2008;23(2):269-274.
10. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. *Nat Med.* 2013;19(11):1423-1437.
11. Balkwill FR, Capasso M, Hagemann T. The tumor microenvironment at a glance. *J Cell Sci*. 2012;125(Pt 23):5591-5596.
12. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med*. 1971;285(21):1182-1186.
13. Kerbel RS, Kamen BA. The anti-angiogenic basis of metronomic chemotherapy. *Nat Rev Cancer.* 2004;4(6):423-436.
14. Hanahan D, Bergers G, Bergsland E. Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice. *J Clin Invest.* 2000;105(8):1045-1047.
15. Browder T, Butterfield CE, Kräling BM, et al. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. *Cancer Res.* 2000;60(7):1878-1886.
16. Klement G, Baruchel S, Rak J, et al. Continuous low-dose therapy with vinblastine and VEGF receptor-2 antibody induces sustained tumor regression without overt toxicity. *J Clin Invest.* 2000;105(8):R15-R24.
17. Pasquier E, Kavallaris M, André N. Metronomic chemotherapy: new rationale for new directions. *Nat Rev Clin Oncol*. 2010;7(8):455-465.
18. Ghiringhelli F, Menard C, Puig PE, et al. Metronomic cyclophosphamide regimen selectively depletes CD4+CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients. *Cancer Immunol Immunother*. 2007;56(5):641-648.
19. Kamat AA, Kim TJ, Landen CN Jr, et al. Metronomic chemotherapy enhances the efficacy of antivascular therapy in ovarian cancer. *Cancer Res*. 2007;67(1):281-288.
20. Bertolini F, Paul S, Mancuso P, et al. Maximum tolerable dose and low-dose metronomic chemotherapy have opposite effects on the mobilization and viability of circulating endothelial progenitor cells. *Cancer Res*. 2003;63(15):4342-4346.
21. Bocci G, Nicolaou KC, Kerbel RS. Protracted low-dose effects on human endothelial cell proliferation and survival in vitro reveal a selective antiangiogenic window for various chemotherapeutic drugs. *Cancer Res.* 2002;62(23):6938-6943.
22. Klement G, Huang P, Mayer B, et al. Differences in therapeutic indexes of combination metronomic chemotherapy and an anti-VEGFR-2 antibody in multidrug-resistant human breast cancer xenografts. *Clin Cancer Res*. 2002;8(1):221-232.
23. Ruggiero A, Rizzo D, Attinà G, et al. Phase I study of temozolomide combined with oral etoposide in children with recurrent or progressive medulloblastoma. *Eur J Cancer.* 2010;46(16):2943-9.
24. Penel N, Adenis A, Bocci G. Cyclophosphamide-based metronomic chemotherapy: after 10 years of experience, where do we stand and where are we going? *Crit Rev Oncol Hematol.* 2012;82(1):40-50.
25. André N, Padovani L, Pasquier E. Metronomic scheduling of anticancer treatment: the next generation of multitarget therapy? *Future Oncol*. 2011;7(3):385-394.
26. Scharovsky OG, Mainetti LE, Rozados VR. Metronomic chemotherapy: changing the paradigm that more is better. *Curr Oncol*. 2009;16(2):7-15.
27. Hamano Y, Sugimoto H, Soubasakos MA, et al. Thrombospondin-1 associated with tumor microenvironment contributes to low-dose cyclophosphamide-mediated endothelial cell apoptosis and tumor growth suppression. *Cancer Res*. 2004;64(5):1570-1574.
28. André N, Carré M, Pasquier E. Metronomics: towards personalized chemotherapy? *Nat Rev Clin Oncol.* 2014;11(7):413-431.
29. Fetoni AR, Ruggiero A, Lucidi D, et al. Audiological Monitoring in Children Treated with Platinum Chemotherapy. *Audiol Neurootol*. 2016;21(4):203-211.
30. Shaked Y, Emmenegger U, Man S, et al. Optimal biologic dose of metronomic chemotherapy regimens is associated with maximum antiangiogenic activity. *Blood*. 2005;106(9):3058-3061.

31. Bocci G, Falcone A, Fioravanti A, et al. Antiangiogenic and anticolorectal cancer effects of metronomic irinotecan chemotherapy alone and in combination with semaxinib. *Br J Cancer.* 2008;98(10):1619-1629.
32. Cazzaniga ME, Cortesi L, Ferzi A, et al. Metronomic chemotherapy with oral vinorelbine (mVNR) and capecitabine (mCAPE) in advanced HER2-negative breast cancer patients: is it a way to optimize disease control? Final results of the VICTOR-2 study. *Breast Cancer Res Treat.* 2016;160(3):501-509.
33. Kareva I, Waxman DJ, Lakka Klement G. Metronomic chemotherapy: an attractive alternative to maximum tolerated dose therapy that can activate anti-tumor immunity and minimize therapeutic resistance. *Cancer Lett*. 2015;358(2):100-106.
34. Chan TS, Hsu CC, Pai VC, et al. Metronomic chemotherapy prevents therapy-induced stromal activation and induction of tumor-initiating cells. *J Exp Med*. 2016;213(13):2967-2988.
35. Perrone MG, Ruggiero A, Centonze A, Carrieri A, Ferorelli S, Scilimati A. Diffuse Intrinsic Pontine Glioma (DIPG): Breakthrough and Clinical Perspective. *Curr Med Chem.* 2021;28(17):3287-3317.
36. Ruggiero A, Ariano A, Triarico S, Capozza MA, Ferrara P, Attinà G. Neonatal pharmacology and clinical implications. *Drugs Context*. 2019;8:212608.
37. Simsek C, Esin E, Yalcin S. Metronomic Chemotherapy: A Systematic Review of the Literature and Clinical Experience. *J Oncol*. 2019;2019:5483791.
38. Meco D, Attinà G, Mastrangelo S, Navarra P, Ruggiero A. Emerging Perspectives on the Antiparasitic Mebendazole as a Repurposed Drug for the Treatment of Brain Cancers. *Int J Mol Sci.* 2023;24(2):1334.
39. Pruneri G, Vingiani A, Denkert C. Tumor infiltrating lymphocytes in early breast cancer. *Breast*. 2018;37:207-214.
40. Batlle E, Clevers H. Cancer stem cells revisited. *Nat Med*. 2017;23(10):1124-1134.
41. Riccardi A, Mazzarella G, Cefalo G, et al. Pharmacokinetics of Temozolomide given three times a day in pediatric and adult patients. *Cancer Chemother Pharmacol*. 2003; 52: 459-464
42. Lazzareschi I, Ruggiero A, Riccardi R, Attinà G, Colosimo C, Lasorella A. Hypersensitivity reactions to carboplatin in children. *J Neurooncol.* 2002; 58:33-37
43. Kareva I. A Combination of Immune Checkpoint Inhibition with Metronomic Chemotherapy as a Way of Targeting Therapy-Resistant Cancer Cells. *Int J Mol Sci.* 2017;18(10):2134.
44. Ruggiero A, Rizzo D, Mastrangelo S, Battaglia D, Attinà G, Riccardi R. Interactions between antiepileptic and chemotherapeutic drugs in children with brain tumors: is it time to change treatment?. *Pediatr Blood Cancer*. 2010;54(2):193-198
45. Vives M, Ginestà MM, Gracova K, et al. Metronomic chemotherapy following the maximum tolerated dose is an effective anti-tumour therapy affecting angiogenesis, tumour dissemination and cancer stem cells. *Int J Cancer.* 2013;133(10):2464-2472.
46. Cham KK, Baker JH, Takhar KS, et al. Metronomic gemcitabine suppresses tumour growth, improves perfusion, and reduces hypoxia in human pancreatic ductal adenocarcinoma. *Br J Cancer.* 2010;103(1):52-60.
47. Posteraro B, Bruno S, Boccia S, et al. Candida parapsilosis bloodstream infection in pediatric oncology patients: results of an epidemiologic investigation. *Infect Control Hosp Epidemiol.* 2004;25(8):641-5.
48. Lien K, Georgsdottir S, Sivanathan L, Chan K, Emmenegger U. Low-dose metronomic chemotherapy: a systematic literature analysis. *Eur J Cancer.* 2013;49(16):3387-3395.
49. Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nat Med*. 2007;13(9):1050-1059.
50. Zitvogel L, Kepp O, Kroemer G. Immune parameters affecting the efficacy of chemotherapeutic regimens. *Nat Rev Clin Oncol*. 2011;8(3):151-160.