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Metronomic chemotherapy from rationale to clinical studies: A dream or reality?

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Abstract

Metronomic chemotherapy (MC) refers to the close administration of a chemotherapeutic drug for a long time with no extended drug-free breaks. It was developed to overcome drug resistance, partly by shifting the therapeutic target from tumor cells to the tumor vasculature, with less toxicity. Because of this peculiar way of administration, MC can be viewed as a form of long-term 'maintenance' treatment, and can be integrated with standard and conventional chemotherapy in a "chemo-switching" strategy. Additional mechanisms are involved in its antitumor activity, such as activation of immunity, induction of tumor dormancy, chemotherapy-driven dependency of cancer cells, and the '4D effect'. In this paper we report the most important studies that have analyzed these processes. In fact, a number of preclinical and clinical studies in solid tumors as well as in multiple myeloma, have been reported regarding several chemotherapy drugs which have been proposed with a metronomic schedule: vinorelbine, cyclophosphamide, capecitabine, methotrexate, bevacizumab, etoposide, gemcitabine, sorafenib, everolimus and temozolomide. The results of these studies have been sometimes conflicting, highlighting the need to develop reliable tools for patient selection and stratification. However, a more precise evaluation of MC strategies with the ongoing randomized phase II/III clinical is fundamental, because of the strict correlation of this approach with translational research and target therapy. Moreover, because of the low toxicity of MC, these studies will also help to better evaluate the clinical benefit of this treatment, with a special focus on elderly and low performance status patients.

Keywords: Angiogenesis; Bevacizumab; Chemo-switching; Cyclophosphamide; Immunity; Maintenance; Metronomic chemotherapy; Toxicity

1. General: Definition of metronomic chemotherapy and antiangiogenic power

Chemotherapy represents the mainstay of cancer medicine for both locally and advanced neoplasms, the maximum tolerated dose being the regular model for the past 50 years [1]. However, clinicians must fight against collateral and side effects linked to high-dose and cyclic schedules, which limit dosing and hamper anti-tumor efficacy. What is more, despite impressive tumor regression or even remission, regrowth and recurrence are common events in metastatic and high-risk tumors [2]. Accordingly, dosing and scheduling of chemotherapy to redirect it toward antiangiogenic efficacy is entailed by low-dose metronomic chemotherapy [2,3].

"Metronomic chemotherapy" was first coined by Hanahan, and refers to the close, regular administration of a chemotherapeutic drug for a long time with no extended drug-free breaks [4]. It was originally developed to overcome drug resistance by shifting the therapeutic target from tumor cells to the tumor vasculature [5,6]. The rationale stems from the low-rate of endothelial cell division compared to tumor cells: by using the standard chemotherapy cycles this causes only weak endothelial cell damage [2,7]. Endothelial cells therefore became able to repair themselves and recover during the rest period. Since endothelial cells support tumor growth, their regrowth produces tumor resistance. This concept led to the hypothesis that more compressed or accelerated schedules of drug administration using much smaller individual doses would be more effective and less toxic [8,9].

Several preliminary experiments showed that metronomic continuous administration of chemotherapy drugs in cultures induced endothelial cell death in conjunction with tumor cell death [10]. Metronomic chemotherapy also induces the antiangiogenic glycoprotein *Thrombospondin-1* (TSP1), which is endowed with further anti-tumor effects [11–13]. In fact, it also inhibits proliferation and/or induces apoptosis of activated endothelial cells, it inhibits endothelial cell migration, and decreases levels and viability of bone marrow-derived endothelial progenitor cells [14–17].

Since these mechanisms are typical of other antiangiogenic drugs which determine only mild antitumor effects when used alone, it is plausible that other mechanisms underlie the higher antitumor effect of metronomic chemotherapy. The initial intuition of Folkman, father of angiogenic theory [18], was developed by Browder and Kerbel, who first highlighted the anti-angiogenic metronomic schedule of cyclophosphamide which was more effective than the conventional schedule in overcoming drug resistance in cultured breast cancer cells [2,19].

In addition, cancer in the elderly or in patients with several co-morbidities and suboptimal performance status must be managed carefully. These patients may be the ideal candidate for a first-line or second-line oral metronomic therapy due to the low toxicity profile of this approach [20].

Possible different activities of metronomic chemotherapy are resumed in Fig. 1.

2. Dose-dense chemotherapy and new concepts: "Maintenance" and "chemo-switching"

Metronomic use of anti-cancer drugs can be considered a type of "dose-dense" chemotherapy, although differing from *classical* dose-dense administration. First, it is neither "dose-intense" since it doesn't deliver more total drug per unit time, nor is it a cyclic maximum tolerated dose regimen with three week break periods between cycles [1]. Hence, the metronomic regimens are less toxic, and have reduced bone marrow toxicity and gastrointestinal disorders, including vomiting, nausea, and mucositis. This good toxicity profile is evident also in heavily pre-treated cancer patients [21,22]. In fact, the schedule, usually, does not

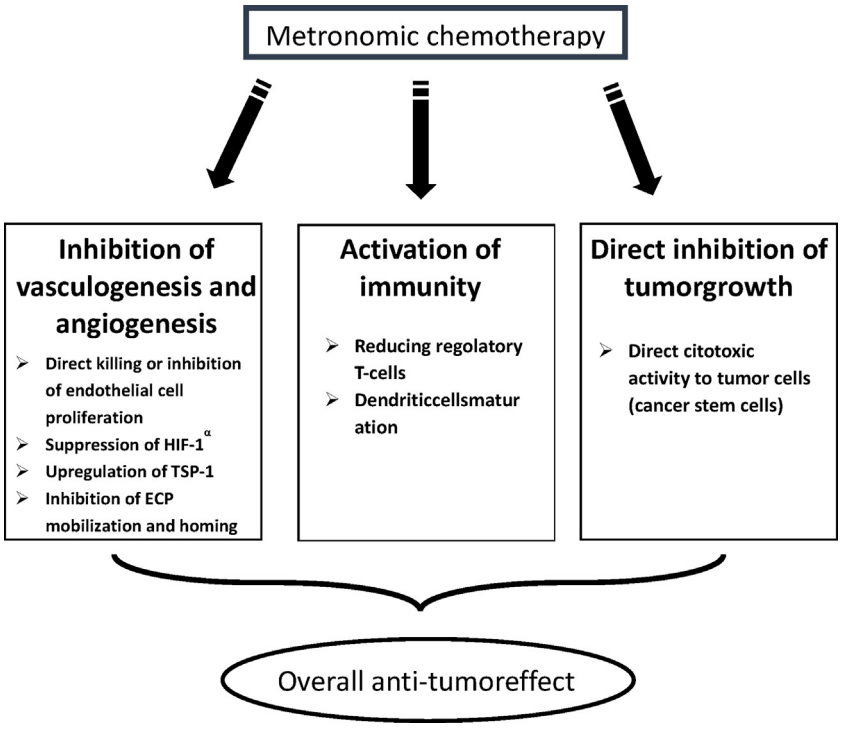

Fig. 1. Metronomic chemotherapy activity.

require supportive care procedures, including prophylactic growth factors and intense antiemetic schedules. Furthermore, because of the above described mechanism of action, metronomic chemotherapy can exercise a stronger activity against drug resistant tumors. Lastly, the metronomic schedule often implies oral drug administration (i.e. capecitabine, vinorelbine, cyclophosphamide, methotrexate), thus increasing convenience because of the possibility of home therapy [23,24], also reducing costs because of the low drug dosage.

Metronomic chemotherapy can be also viewed as a form of long-term 'maintenance' chemotherapy that can be used on its own, or combined with long-term biologic targeted therapies, especially anti-angiogenic drugs such as anti-VEGFR-2 antibodies or small molecule multi-targeted VEGFR-2 antagonist receptor tyrosine kinase inhibitors [25].

Moreover, it was recently suggested, that metronomic drugs may be integrated with standard chemotherapy in a regimen called "chemo switching", where brief courses of conventional chemotherapy are followed by long-term maintenance metronomic chemotherapy, eventually combined with targeted therapies [26,27].

Since the predominant mechanism of metronomic chemotherapy is thought to be anti-angiogenesis, involving the tumor's growing vasculature and the endothelial progenitor cells (CEPs), several authors investigated whether the latter cells and/or Circulating Endothelial Cells (CECs) could be used as a surrogate marker of activity [28–32]. The results of these studies suggest that high baseline CECs (likely reflecting an active vascular turnover) may predict a prolonged clinical benefit, and that VEGF-A and basic fibroblast growth factor levels after 2 months of therapy may be also useful to identify patients whose disease is likely to progress [30].

More recently, other potential mechanisms of action were suggested for metronomic chemotherapy involving the anticancer immune response and other "actors" belonging to the tumor microenvironment (see Fig. 2).

3. Additional mechanisms of action of metronomic chemotherapy

The interactions between tumor cells and the microenvironment have led researchers to hypothesize new mechanisms that may be involved in antitumor activity: (i) activation of immunity, (ii) induction of tumor dormancy, (iii) chemotherapy-driven dependency of cancer cells, also known as the '4D effect'.

3.1. Activation of immunity

Several authors have proposed that tumor escape from immuno-surveillance could be the most important hallmark of cancer development [33–35], and that the immunosuppression caused by chemotherapy, may contribute to the tumor cell growth, because of the reduction of the white blood cell count [36–38]. In contrast, more recently, other authors have suggested that some cytotoxic drugs, such as anthracyclines, taxanes and cyclophosphamide, could display substantial immuno-stimulatory properties. Specifically, these drugs

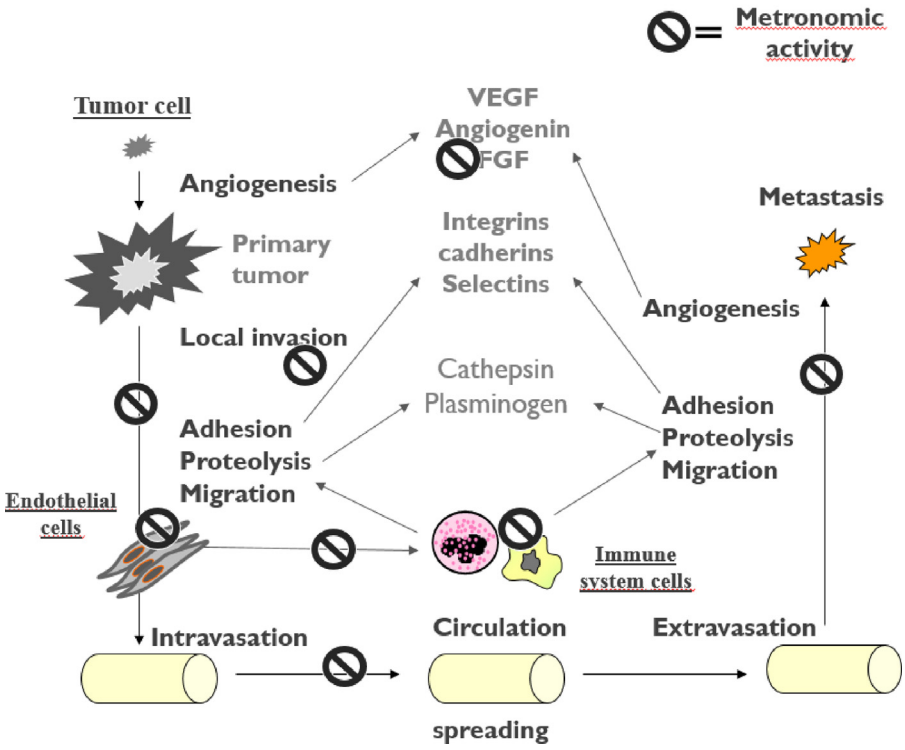

Fig. 2. Angiogenic process: the correlation between tumor, microenvironment and immune system and possible targets of metronomic therapy.

may have an effect on *Regulatory T* (T-reg) cells that seem to be relevant in the context of metronomic schedules [38,39]. T-reg cells are CD4+CD25+ lymphocytes, enriched in TNF receptor and cytotoxic *T-lymphocyte-associated antigen-4* (TLA4). T-reg cells inhibit antigen-specific immune response via cytokine-dependent and cell contact-dependent processes [40]. In particular, T-reg cells suppress tumor-specific effector cells, such as CD8+ cytotoxic T lymphocytes, CD4+ T helper cells and natural killer T cells. Kono et al. showed that T-reg cells increase in step with tumor stage in patients with gastric and oesophageal cancers, and that these cells are particularly numerous in patients with ovarian, colorectal and lung cancer in whom they increase in step with tumor progression and lack of treatment response [39].

Other studies have showed that T-reg cells are markedly reduced in patients undergoing metronomic schedules, including low-dose cyclophosphamide in breast cancer, and temozolomide in glioblastoma, and that T-reg cell reduction was deeper than in patients treated with conventional schedules [41–44]. Tanaka et al. analyzed the activity of 54 different chemotherapeutic drugs, belonging to four different classes (microtubule-targeting agents, topoisomerase inhibitors, alkylating agents and anti-metabolites), to induce dendritic cell maturation and inhibit T-reg cells. These authors concluded that some chemotherapeutic drugs, such as vinblastine, paclitaxel and etoposide, when used in metronomic chemotherapy regimens, are able to promote T-reg cell reduction, contrasting tumor escape and progression [45].

3.2. Induction of tumor dormancy

Berger et al., focusing on the angiogenic switch, demonstrated that during the early phase of tumor progression, before the vascular phase, tumor cells are not active. They called this phase ‘tumor dormancy’ [27]. Other authors confirmed that this phase usually appears after completion of anticancer treatments, when the remission phase is induced [46,47]. The metronomic activity of some anticancer drugs attempts to induce a tumor dormancy [48], which implies angiogenic dormancy, as shown by Folkman et al. [49], which seems to be the predominant mechanism involved in the maintenance of the avascular phase [50]. A possible link between angiogenic dormancy and the immune system has been hypothesized: tumor-specific cytotoxic CD8+ T lymphocytes involved in tumor apoptosis may represent this link. When tumor cells escape from immune surveillance, they can unleash the angiogenic development of the tumor [51,52]. Therefore, a reinforcement of anticancer immunity by metronomic chemotherapy can constitute an alternative mechanism promoting tumor dormancy, inhibiting tumor development for a long-term control of the disease [52].

3.3. The '4D effect'

Many authors have demonstrated that the tumor response to metronomic schedules is due not only to antiangiogenic and immuno-stimulatory effects, but also to a direct anticancer activity. A theoretical model of this anticancer effect is based on chemotherapy-driven cell dependency, followed by a subsequent drug deprivation: this phenomenon is known as the '4D effect' [53]. Seruga et al. first evaluated, in prostate cancer patients, the role of the intermittent androgen blockade [54]. Previously, several clinical and pre-clinical studies had demonstrated the positive effect of a break in long-term anticancer therapies. *In vitro* data showed cell death upon withdrawal of microtubule-targeting agents (taxanes, epothilones) compared to long-term exposure, suggesting a potential high efficacy of this administration modality [55–58]. However, these data need to be confirmed by larger and prospective studies, even if this new theoretical model induces a new possible value in the metronomic paradigm: a direct and indirect effect on tumor cells, as a multitargeted therapy, able to strike both tumor cells and their microenvironment.

4. Preclinical data

Cyclophosphamide was the most frequently used drug in preclinical evaluations [59]. Its effects on tumor cell viability, proliferation, chemotaxis, chemochine production and the angiogenic switch were evaluated. Very interesting long-term survival effects were observed with the combination of this drug with methotrexate, UFT and vinorelbine. Browder et al. studied traditional and metronomic therapy in EMT-6 breast cancer cells, resistant to previous treatments. Data showed that metronomic administration of methotrexate and vinorelbine could revert tumor resistance with a continuous activity in time, while the tumor volume rapidly increased (after 15–20 days) during the classic schedule administration [19]. Bertolini et al. showed that different administration of metronomic chemotherapy could influence the growth of endothelial and microenvironment cells [60]. In fact, methotrexate exerts its inhibition of cell proliferation through the reduction of human endothelial cell levels at the concentration of 5×10^{-9} M. Paclitaxel at a dose of 10 pM down-regulates chemotoxins and subsequently endothelial cell chemotaxis and proliferation. Lower doses of docetaxel exert a strong inhibition of cell migration and capillary sprouting with an activity 10 times more effective than paclitaxel. Vinblastine has been investigated for its important role in inhibiting human endothelial cell proliferation, migration and metalloproteinase secretion at ultra-low concentrations (0.1–1 pM) [61]. Vacca et al. demonstrated in an experimental model that after low dose vinblastine removal, the anti-angiogenic effects were rapidly abolished [62,63]. Other Authors investigated on a preclinical model evaluating the potential impact of metronomic low-dose chemotherapy combined with anti-angiogenic drugs such as pazopanib for the treatment of ovarian cancer cells [64,65]. Topotecan showed an antitumor effect in preclinical studies in prostate cancer, using alternate dosing schedules. A concentration-dependent increase in cytotoxicity was observed in cultured prostate cancer cells after topotecan treatment using metronomic protocols rather than a conventional one, especially as regards decreased tumor volume, cell cycle arrest and angiogenic inhibition [66].

5. Clinical studies

Although there is a wealth of preclinical and theoretical data on metronomic therapy, translation from the laboratory to the bedside has met with mixed results. Vinorelbine, cyclophosphamide, capecitabine, methotrexate and bevacizumab have been tested with initial promising benefit in patients with breast cancer. Vinorelbine, cyclophosphamide, etoposide and methotrexate have been proposed as alternative treatments in patients with Castration Resistant Prostate Cancer or Non Small Cell Lung Cancer (NSCLC). Capecitabine plus/minus bevacizumab showed interesting results in gastric, colorectal and hepatocellular carcinoma. Cyclophosphamide and bevacizumab were proposed in ovarian cancer. Gemcitabine, capecitabine, sorafenib and everolimus were administered in renal cell cancer, and temozolomide and bevacizumab in glioblastoma.

6. Breast cancer

Breast cancer represents the tumor with the majority of data with metronomic chemotherapy, although all clinical trials have been conducted in phase II studies, and no phase III studies are available.

In a phase II study, Addeo et al. evaluated the safety and activity of vinorelbine administered orally at 70 mg/m^2, fractionated on days 1, 3, and 5 for 3 weeks, every 4 weeks, for a maximum of 12 cycles, in 34 elderly patients with metastatic breast cancer. Safety was confirmed by the application of the entire treatment to all patients without grade 4 toxicities. The overall response rate (ORR), primary endpoint of this study, was 38%, with 6% and 32% of complete (CR) and partial response (PR), respectively. Disease control was 68%, with 7.7 months of median progression free *survival* (PFS) and 15.9 months of median *overall survival* (OS) [67]. Recently, a group of Italian clinicians reported the results of a phase I–II study evaluating the use of vinorelbine with a metronomic schedule combined with capecitabine in patients with metastatic breast cancer previously treated with anthracyclines and taxanes. Vinorelbine was administered in three different dosages to 3 patient cohorts (20–30–40 mg/m^2 trice weekly) and capecitabine orally at a dose of 500 mg three times/day continuously. Of the 31 patients evaluable

for efficacy 58,1% obtained a clinical benefit. With regard to the safety, two cases of grade 4 leukopenia one case of grade 3 thrombocytopenia, and one case of grade II diarrhea were observed [68]. Vinorelbine was also evaluated together with cyclophosphamide in a small phase II study conducted by Pluma Jimenez et al. In this study 20 patients previously treated with anthracyclines and taxanes were evaluated. Vinorelbine was administered orally at a dose of 60 mg/m^2 once a week for 3 weeks in a 4 week cycle, and cyclophosphamide orally at a dose of 50 mg once a day, continuously. These data also confirmed a positive clinical benefit (60%), with comforting safety (only 1 case of grade 4 neutropenia) for this combination [69].

The efficacy of capecitabine administered with metronomic schedule was confirmed by another Italian phase II study which enrolled 58 heavily pretreated patients with metastatic breast cancer. The drug was administered at 1500 mg once a day. The clinical benefit rate, primary study endpoint, was 62%, with a median duration of response of 7 months. Median *time to progression* (TTP) and OS were 7 and 17 months, respectively, and a clinical benefit was recorded in 13 patients who had previously received capecitabine intermittently (2000 mg/m^2/day on days 1–14 every 21 days). The schedule was safe and hematologic toxicity was uncommon (5%) [70].

Recently Schwartzberg et al. evaluated capecitabine together with Fulvestrant in HER-2 negative, estrogen positive post-menopausal breast cancer women. This phase II study showed a PFS of 15 months and a median TTP of 27 months in 41 patients, with a median OS of 29 months and a good toxicity profile (only 9% of grade 3 palmar–plantar erythrodysesthesia). [71].

Also *pegylated liposomal-doxorubicin* (PLD) has been recently tested in metastatic breast cancer with metronomic dosage. In a phase II study, 52 patients (mixed population of anthracycline-naive and pre-treated) underwent a metronomic schedule of PLD at 20 mg/m^2 intravenously every two weeks. Clinical benefit was 45%, with an 18% PR. Neither grade 3 nor grade 4 hematological or cardiac side effects were recorded, only 2 patients developed grade 3 palmar-plantar erythrodysesthesia. The authors suggested a potential activity of this drug as an alternative to classic anthracyclines, with a good quality of life [72].

Methotrexate was evaluated at a metronomic dose of 2.5 mg/day twice weekly together with oral cyclophosphamide at 50 mg once a day, continuously, by Gebbia et al. who enrolled 61 pre-treated metastatic breast cancer patients. Despite a good clinical benefit rate (52%), this combination induced hepatic toxicity, with 33% of patients presenting high levels of AST/ALT [73].

Dellapasqua et al. first evaluated the combination of metronomic chemotherapy plus targeted therapy. Forty-six patients with advanced breast cancer received oral capecitabine (500 mg three times/day), cyclophosphamide (50 mg/day) and bevacizumab at 10 mg/kg every 2 weeks. The results showed CR in 2%, PR in 46%, stable disease in 41% of patients, respectively, with an ORR of 48% and clinical benefit (for 24 weeks or more) of 68%. At univariate analysis, clinical benefit was significantly related to hormone receptor status (86% in ER+ vs 33% in ER− patients, respectively: $p = 0.04$). This schedule was generally well tolerated. Moreover, higher baseline CECs was correlated with overall response, clinical benefit, and improved PFS [74].

Metronomic low dose chemotherapy with cyclophosphamide and methotrexate in combination with Trastuzumab has been tested in HER2/neu overexpressed metastatic breast cancer. An Italian study enrolled 22 patients with metastatic breast cancer with overexpression or amplification of HER2-/neu, all pre-treated with trastuzumab and other cytotoxic drugs. Trastuzumab at 6 mg/kg every three weeks was combined with metronomic chemotherapy: methotrexate at 2.5 mg bid on Day 1 and Day 4 every week, and cyclophosphamide at 50 mg/day continuously. The study showed PR in 18%, stable disease in 46%, progressive disease in 36%, and a general clinical benefit in 46% of cases. Median TTP was 6 months, with mild toxicity. In a subgroup analysis, evaluating the trastuzumab-resistant breast cancer patients, 22% clinical benefit was observed, confirming a potential role of this combination to delay acquired trastuzumab-resistance [75].

Conflicting data emerge from other studies. Colleoni et al. evaluated the benefit of adding thalidomide to a cyclophosphamide and methotrexate combination. In 171 patients, the ORR was 16.4% and clinical benefit rate was 41.5%. There was a statistically significant reduction in the serum VEGF levels with both the combinations however the addition of thalidomide did not add any benefit to oral chemotherapy [76] (Table 1).

Summarizing these data, the metronomic approach in breast cancer patients is associated with a good toxicity profile for either primary systemic or palliative treatment, with a median overall clinical benefit of 57% (range 12–88%). Better results were observed when metronomic cyclophosphamide and methotrexate were combined with trastuzumab.

7. Prostate cancer

Several studies have been conducted in patients with prostate cancer to explore the metronomic approach, especially in hormone refractory patients (Table 2). Prostate cancer was previously believed to be a chemo-resistant disease, however taxane-based chemotherapy has shown to prolong survival in patients with castration-resistant prostate cancer (CRPC) [77]. Phase II trials investigating chemotherapy administered with metronomic schedules in patients with CRPC have shown beneficial therapeutic effects. Ketoconazole in combination with doxorubicin alternating with vinblastine in combination with estramustine (KA/VE regimen) was analyzed in a phase II trial, enrolling 45 patients with CRPC. In this study it was observed a PSA reduction >50% in 69% and >80% in 58% of patients, with a median OS of 18.1 months [78]. The palliative and survival

Table 1
Clinical trials with metronomic chemotherapy in breast cancer.

Author	Tumor type	Patient population	No. (pts)	Protocol	Response rates	Response duration
Addeo et al.	Breast	Elderly MBC	34	Vinorelbine	ORR: 38%	OS: 15.9 mth
Cazzaniga et al.	Breast	Previously treated MBC	31	Vinorelbine, capecitabine	ORR: 55%	–
Pluma Jmenez et al.	Breast	Previously treated MBC	20	Cyclophosfamide, vinorelbine	ORR: 60%	–
Fedele et al.	Breast	Both pretreated and not treated MBC	58	Capecitabine	ORR: 62%	OS: 17 mth TTP: 7 mth
Schwartzberg et al.	Breast	Not treated ER + HER2 − MBC	41	Capecitabine, fulvestrant	–	OS: 28.6 mth PFS: 26.9 mth
Munzone et al.	Breast	Both pretreated and not treated MBC	52	Pegylated liposomal-doxorubicin	ORR: 57%	–
Gebbia et al.	Breast	Previously treated MBC	61	Cyclophosfamide, methotrexate	ORR: 52%	–
Dellapasqua et al.	Breast	Previously treated MBC	46	Bevacizumab, cyclophosfamide, capecitabine	ORR: 48% CBR: 68%	TTP: 9.4 mth
Orlando et al.	Breast	Previously treated HER2 + MBC	22	Trastuzumab, cyclophosfamide, methotrexate	PR: 18% CBR: 46%	TTP: 6.0 mth
Colleoni et al.	Breast	Both pretreated and not treated MBC	171	Cyclophosfamide, methotrexate, Thalidomide	ORR: 20.9 CBR: 41.5	TTP: 4.7 mth

effects compared favorably with several docetaxel-based studies, with a better toxicity profile. Seventeen patients with chemo-naive CRPC were enrolled in a pilot study evaluating an orally administered chemo-hormonal regimen using a weekly sequential combination, including ketoconazole in combination with cyclophosphamide or etoposide in combination with estramustine (KEES combination), administered on alternate weeks. Prednisone was administered throughout the treatment period. Eighty-seven percent of patients demonstrated a median reduction in PSA. Thrombocytopenia and anemia were the most common side effects. The authors concluded that KEES might be a promising option for patients with CRPC, resulting in a clear reduction in PSA with limited toxicity [79]. In a phase II study, Gebbia et al. investigated the activity and toxicity of metronomic chemotherapy with low-dose oral cyclophosphamide (50 mg/day) and methotrexate (2.5 mg twice/week), without rest periods, in 58 patients with metastatic CRPC that progressed after docetaxel. The results showed a 50% decrease in PSA in 25% of patients, an objective PR of 18%, a stable disease of 24%, and a pain decrease in 30% of patients. Toxicity was very low (7% leukopenia, 7% anemia) [80].

On the other hand, another study evaluating the same drugs together with celecoxib did not show results in terms of ORR and PSA 50% reduction, while median TTP was 57 days. [81].

8. Ovarian cancer

Vascular endothelial growth factor (VEGF) plays an important role in the biology of ovarian cancer, and the recent approval of bevacizumab combined with conventional platinum-based doublet therapy confirms this strong correlation [82]. Garcia et al. analyzed a possible concomitant use of bevacizumab with oral metronomic cyclophosphamide

Table 2
Clinical trials with metronomic chemotherapy in prostate cancer.

Author	Tumor type	Patient population	No. (pts)	Protocol	Response rates	Response duration
Millikan et al.	Prostate	CRPC	45	KA/VE regimen (ketoconazole, doxorubicin/vinblastine, estramustine)	PSA 50% reduction: 58%	OS: 18.1 mth
Jellvert et al.	Prostate	CRPC	17	KEES regimen (ketoconazole, cyclophosphamide, etoposide, estramustine)	PSA 50% reduction: 87%	–
Gebbia et al.	Prostate	CRPC after taxane	58	Cyclophosphamide, methotrexate	PSA 50% reduc: 30% ORR: 42%	–
Khan et al.	Prostate	CRPC after taxane	67	Cyclophosphamide, methotrexate, celecoxib	ORR: 5%	TTP: 1.8 mth

Table 3
Clinical trials with metronomic chemotherapy in ovarian cancer, renal cancer and glioblastoma.

Author	Tumor type	Patient population	No. (pts)	Protocol	Response rates	Response duration
Garcia et al.	Ovarian	Recurrent ovarian cancer	70	Cyclophosphamide, bevacizumab	–	OS: 16.9 mth TTP: 7.2 mth
Bellmunt et al.	Renal	Intermediate risk metastatic renal cancer	40	Sorafenib, gemcitabine, capecitabine	PR: 50% ORR: 82.5%	OS: 11.1 mth
Stockhammer et al.	GBM	Relapsed GBM	28	Celecoxib, temozolomide	–	6-mts OS: 43%
Zustovich et al.	GBM	Relapsed GBM	43	Sorafenib, temozolomide	–	OS: 7.4 mth 6-mts PFS: 26% TTP: 3.2 mth

in women with recurrent ovarian cancer. This trial was conducted in 70 ovarian cancer patients with a disease progressing after prior platinum-containing regimens. The treatment consisted of bevacizumab 10 mg/kg intravenously every 2 weeks and oral cyclophosphamide 50 mg/daily. The results showed a probability of being alive and progression free at 6 months of 56%, with 24% PR, a median TTP of 7.2 months and a median OS of 16.9 months. With regard to toxicity, hypertension, fatigue, and pain were recorded. Bevacizumab-related toxicity included four episodes of gastrointestinal perforation or fistula, one episode of central nervous system ischemia and one of pulmonary hypertension. Plasma levels of VEGF, E-selectin, and TSP-1 were evaluated and no correlation with the clinical outcome was observed [83] (Table 3). Cyclophosphamide (50 mg/day) in combination with pazopanib is also being investigated in the ongoing phase I/II PACOOVAR trial in recurrent, platinum-resistant epithelial ovarian cancer. Primary endpoints are the definition of the optimal dose of pazopanib (phase I) and the overall response rate tin combination with cyclophosphamide (phase II). TTP, OS, safety and tolerability are secondary endpoints [84].

9. Renal cancer

Renal cancer is a tumor well correlated to the mechanisms of cell growth, cell proliferation, angiogenesis, and survival through the angiogenic process [85]. Bellmunt et al. evaluated this concept in a Spanish multicentre phase II study, investigating gemcitabine (intravenous infusion at 1000 mg/m^2 on day 1 and 8) combined with metronomic capecitabine (at 500 mg/m^2 twice a day, days 1–14) and the multikinase inhibitor sorafenib (oral dose of 400 mg twice a day), every 21 days, in 40 patients with mRCC. After six cycles, chemotherapy was stopped and sorafenib was administered as a maintenance therapy. Forty-four patients were enrolled in this study, and median PFS for these patients was 11.1 months. The toxicity included rare grade 3 adverse events as fatigue, hand-foot skin reaction, mucositis and infections [86] (Table 3).

The inhibition of the mTOR pathway plays an important role in renal cancer cell immunoregulation, with a better control of homeostasis and balance between effector T cells and regulatory T cells. In several studies the mTOR-inhibitor *everolimus* has been shown to prolong PFS. The Netherlands phase I/II multi-center Study Trial NTR3085, currently ongoing, evaluates the combination of everolimus (5 mg daily) with the metronomic schedule of cyclophosphamide in patients with mRCC not amenable to, or progressive after a VEGF-receptor tyrosine kinase inhibitor containing regimen [87].

10. Glioblastoma

Gliobastoma (GBM) is a neoplasm that even after gross tumor resection and combined radio-chemotherapy with temozolomide recurs within a few months. Salvage therapy often consists of re-challenging with temozolomide in a dose-intensified schedule. However, some preclinical data have highlighted a possible efficacy of low-dose metronomic temozolomide in combination with cyclo-oxigenase 2 inhibitors. Stockhammer et al. reported results in 28 patients with recurrent glioblastoma after standard treatment, who received continuous low-dose temozolomide at 10 mg/m^2 twice daily and 200 mg celecoxib. Patients presented a median TTP of 4.2 months, and PFS at 6 months of 43%. Treatment was well tolerated considering that it was a second-line therapy, with no grade 3 or 4 toxicity. MGMT promoter methylation status and microvessel density, provided in this study, did not correlate with PFS [88] (Table 3).

In recent years bevacizumab has obtained great consensus in the treatment of this neoplasm, with many studies ongoing in all lines of therapy [89,90]. Based on these data, Reardon et al. evaluated in a phase II study the efficacy of metronomic etoposide (50 mg/m^2 daily for 21 consecutive days each month) or daily temozolomide (50 mg/m^2), administered with bevacizumab (10 mg/kg every 2 weeks) among 23 recurrent glioblastoma patients who progressed after prior bevacizumab-based therapies. This study was closed at the first interim evaluation due to lack of anti-tumor activity [91].

Table 4
Clinical trials with metronomic chemotherapy in lung cancer.

Author	Tumor type	Patient population	No. (pts)	Protocol	Response rates	Response duration
Del Conte et al.	Lung	Pre-treated lung cancer	21	Vinorelbina	ORR: 29%	OS: 4.5 mth
Correale et al.	Lung	IIIB-IV stage lung cancer	45	mPEBev regimen (cisplatin, etoposide, beva-cizumab → bevacizumab, erlotinib)	ORR: 65%	PFS: 9.5 mth

Recently an Italian phase II study was designed to investigate an oral regimen of sorafenib and metronomic temozolomide for relapsed glioblastoma. Forty-three patients naive for antiangiogenic agents received 400 mg sorafenib twice daily plus temozolomide 40 mg/m^2/day until disease progression. The median TTP was 3.2 months, the 6-month PFS was 26%, and median OS was 7.4 months. Toxicity was mostly grade 1–2. The authors concluded that this combination is feasible and safe, [92].

11. Lung cancer

Little evidence is available regarding metronomic schedules used in clinical trials of patients with lung adenocarcinoma (Table 4). Del Conte et al. carried out a phase II trial evaluating oral vinorelbine at 40 mg/m^2, fractionated on days 1, 3, and 5, every week, continuously in previously treated non small cell lung cancer (NSCLC) patients. In case of good tolerability, a dose escalation to 50 mg was permitted. Out of 21 patients evaluated, disease control was 29% with a median PFS of 4.5 months and an OS of 11.1 months. Hematologic toxicity observed was 9.5% neutropenia [93]. The interest in vinorelbine as a possible metronomic treatment in lung cancer has been confirmed by another recent study which concluded that 50 mg given orally three times a week is the optimal dose [94]. Correale et al. designed a phase II trial in advanced NSCLC patients to evaluate the antitumor activity and the safety of a regimen including cisplatin (30 mg/m^2, days 1–3), oral etoposide (50 mg, days 1–15) and bevacizumab (5 mg/kg, day 3) every three weeks (mPEBev regimen). Forty-five patients with stage IIIB/IV NSCLC were enrolled. Patients who achieved an ORR received maintenance treatment with bevacizumab in combination with erlotinib until progression. Grade I-II hematological, mucosal toxicity and alopecia were the most common adverse events. The occurrence of infections (17%), thromboembolic events (4.4%) and severe mood depression (6.7%) was also recorded. A PR was achieved in 31 patients (69%), with a PFS of 9.53 months [95].

12. Gastric cancer

He et al. evaluated the efficacy and safety of metronomic capecitabine in 45 pretreated elderly patients with advanced gastric cancer after fluoropyrimidine-based chemotherapy. Forty-three eligible patients were treated with capecitabine at a fixed dose of 1000 mg daily (days 1–28 continuously, every 5 weeks) until disease progression or significant toxicity. A median of 3 cycles (range 1–12) was administered. Results showed a disease control rate at 8 weeks of 51.1% and an objective response rate of 20.9%, with a median TTP and OS of 3.6 and 7.6 months, respectively. Grade II neutropenia and thrombocytopenia were observed in 13.3% and 2.2% of patients. Grade II/III non-hematological toxicity included diarrhea (4.4%), stomatitis (13.4%), and hand-foot syndrome (15.5%). No grade IV toxicity occurred. This single data suggest that metronomic capecitabine can sustain a response, as palliative treatment in elderly patients even pretreated with fluoropyrimidine-based chemotherapy [96] (Table 5).

13. Colorectal cancer

Carreca et al. proposed a metronomic schedule for the treatment of elderly people with colorectal cancer (CRC), to reduce severe toxicity (primary endpoint) and to improve patient compliance. This treatment schedule was a combination of three drugs, including oxaliplatin, capecitabine and bevacizumab in a metronomic mode, named M-COB (oxaliplatin 65 mg/m^2 plus bevacizumab 7.5 mg/kg on day 1, and capecitabine at a fixed dose of 1000 mg bid, delivered from day 2 to day 15 every 3 weeks for 12 cycles). In this study which accrued 75 elderly patients with advanced CRC, were observed 50.1% tumor response rate, 86.7% clinical benefit, a median PFS of 12.3 months and a median OS of 23.5 months. No patients experienced grade 4 toxicity [97].

The rationale to combine biological drugs and metronomic chemotherapy was confirmed also in another phase I study which aimed to determine the safety, maximum-tolerated dose (MTD), and pharmacokinetics of imatinib, bevacizumab, and metronomic cyclophosphamide in patients with advanced CRC. Thirty-five patients were enrolled, and the MTD observed for cyclophosphamide, imatinib and bevacizumab were 50 mg q.d., 400 mg q.d., and 5 mg kg i.v. every 2 weeks, respectively. Dose-limiting toxicities included nausea/vomiting, neutropaenia, hyponatraemia, fistula, and hematuria. Twenty percent of patients experienced stable disease for >6 months. In this study circulating tumour,

Table 5
Clinical trials with metronomic chemotherapy in gastric and colon cancer.

Author	Tumor type	Patient population	No. (pts)	Protocol	Response rates	Response duration
He et al.	Gastric	Elderly pre-treated metastatic gastric cancer	45	capecitabine	ORR: 20.9% CBR: 51.1%	OS: 7.6 mth TTP: 3.6 mth
Carreca et al.	Colon	Elderly metastatic colorectal cancer	75	Oxaliplatin, capecitabine, bevacizumab	ORR: 50.1% CBR: 86.7%	OS: 23.5 mth
Kelley et al.	Colon	Metastatic CRC	35	cyclophosphamide, imatinib, bevacizumab	ORR: 20%	–
Lin et al.	Colon	Recurrent metastatic CRC	28	Tegafur, Leucovorin, 5-Fluorouracil regimen	ORR: 45.5%	OS: 13.4 mth TTP: 5.2 mth

endothelial, or immune cells were evaluated, but no association with PFS was showed [98].

Taking advantage of the potential effectiveness of metronomic therapy, tegafur/uracil (UFT) was incorporated into an oxaliplation/infusional fluouracil (5-FU)/leucovorin (LV) protocol in a Japanese phase II study. Twenty-eight patients with metastatic CRC resistant or refractory to 5-FU/LV were enrolled. Chemotherapy was administrated every 2 weeks sequentially with a 2-h infusion of oxaliplatin (85 mg/m^2) and LV (200 mg/m^2), intravenous bolus 5-FU (400 mg/m^2), a 22-h infusion of 5-FU (600 mg/m^2) on day 1 followed by 10-day daily oral UFT (200 mg/m^2)/LV (30 mg/m^2). Partial response was seen in 35.7% of patients, with median TTP and OS of 5.2 and 13.4 months, respectively. No grade 3–4 toxicity above 5% occurred except for some cases of sensory neuropathy (10.7%). No cases of hand-foot syndrome were found. [99].

At the ASCO 2014 Koopman et al. reported the preliminary results of the CAIRO-3 Study on maintenance treatment with capecitabine and bevacizumab, versus observation, in metastatic CRC patients not progressing during induction treatment with capecitabine, oxaliplatin and bevacizumab (CAPOX-B schedule). Previously untreated patients with stable disease or better after 6 cycles of CAPOX-B were randomized between observation (arm A) or maintenance treatment (arm B). Upon first progression (PFS1), 558 patients in both arms were to be treated with CAPOX-B until 2nd progression (PFS2), the primary endpoint of the study. CAPOX-B was reintroduced in 61% of patients in arm A and 47% in arm B, with evidence of significant benefit (PFS2 of 8.5 months vs 11.7 months, respectively; HR 0.67, $p < 0001$). Secondary endpoints (OS and QoL) were also reached (median OS 18.0 m (A) versus 25.0 m (B) ($p < 0.0001$), with QoL maintained during maintenance treatment and clinically not inferior compared to QoL in the observation arm [100].

The authors of the AIO KRK 0207 Study also investigated whether after a 24-week standard induction with Fluorouracil/Oxaliplatin/Bevacizumab schedule, no continuation of therapy (N) or continuation with bevacizumab alone (B) were non-inferior to Fluorouracil plus bevacizumab (FB). After 24 weeks of induction treatment, the investigators used as a primary endpoint the 'time to failure of strategy' (TFS), comprising maintenance plus re-induction after first progression. Secondary endpoints included time to first progression (PFS1) and overall survival (OS). After induction, the median PFS1 in arms N, B, and FB were 3.6, 4.6 and 6.2 months, respectively ($p < 0.0001$). The TFS favored arm FB over arm N (HR 1.31), but no difference between arms FB and B (HR 1.04) was observed. These data confirm the similar activity of bevacizumab alone versus FB as maintenance therapy [101].

14. HCC

Sorafenib, a mall molecule with anti angiogenetic properties represents the only approved treatment for Hepatocellular Carcinoma (HCC) [102,103]. In fact, no chemotherapy standard regimens are currently available in this neoplasm due to the predictable high toxicity because of the underlying cirrhosis. Moreover, for patients with cirrhosis-associated HCC with Child-Pugh class B and C, no systemic treatment of documented efficacy and safety exist [102]. Brandi et al. have treated metastatic HCC patients, associated with Child-Pugh class B cirrhosis, with low metronomi doses of capecitabine (1000 mg/day continuously). The authors reported a good compliance to treatment, with response maintained for 15–18

Table 6
Clinical trials with metronomic chemotherapy in HCC.

Author	Tumor type	Patient population	No. (pts)	Protocol	Response rates	Response duration
Brandi et al.	HCC	Child-Pugh B HCC	10	Capecitabine	–	TTP: 9 mth
Brandi et al.	HCC	Pretreated and naïve HCC	90	Capecitabine	–	OS: 15.6 mth

Table 7
Clinical trials with metronomic chemotherapy in melanoma and NETs.

Author	Tumor type	Patient population	No. (pts)	Protocol	Response rates	Response duration
Bhatt et al.	Melanoma	Refractory metastatic melanoma	20	Celecoxib, paclitaxel	ORR: 20%	OS: 7.1 mth TTP: 1.9 mth
Borne et al	Melanoma	Elderly metastatic melanoma	13	Cyclophosfamide	ORR: 47%	OS: 8 mth
Koumarianou et al.	NETs	Advanced NETs	15	temozolomide, bevacizumab, long-acting octreotide	ORR: 86%	TTP: 8 mth

months. The therapy was well tolerated, with hand-foot syndrome as the main toxicity [104] (Table 6).

Based on these preliminary data, same Italian authors reported the results of the ITALICA Group evaluating metronomic capecitabine at the same dosage as in their above-mentioned study in 59 previously untreated patients with advanced HCC and 31 patients resistant or intolerant to sorafenib. The first cohort achieved a median PFS of 6.03 months and an OS of 14.47 months, with 2 cases of complete response. The second cohort achieved a median PFS of 3.27 months and a median OS of 9.77 months. No grade 4 toxicity was evidenced and grade 3 cutaneous toxicity was less than 7% [105].

15. Melanoma, neuroendocrine tumors, multiple myeloma

Also in the pathogenesis of other neoplasms, such as melanoma, neuroendocrine tumors, and multiple myeloma, the microenvironment plays an important role in the evolution of tumor burden and the acquisition of a metastatic phenotype [106–108]. Several studies have demonstrated that angiogenesis is associated with poor prognosis in patients with metastatic melanoma [109,110], and microtubule stabilizers and cyclooxygenase (COX)-2 inhibitors, alone or in combination, have shown inhibitory effects on endothelial cells and tumor angiogenesis [111]. Bhatt et al. combined COX-2 inhibitors (celecoxib at 400 mg bid orally) with paclitaxel at metronomic doses (10 mg/m^2 for 96 h weekly) to determine its effect on patients with refractory metastatic melanoma. Out of 20 previously heavily pre-treated patients 4 (20%) achieved an objective response. Median TTP was 57 days and median OS was 212 days [112] (Table 7). Borne et al. retrospectively evaluated 13 elderly patients with advanced melanoma treated with 50 to 100 mg of cyclophosphamide daily for 3 weeks out of 4. The Overall Disease Control rate was 46%, with one partial response and five stable diseases. Toxicity was negligible [113]. Based on preclinical data and the strong association between cromogranin A, the tumor microenvironment and angiogenesis activity [107], Koumarianou et al. tested a combination metronomic schedule of temozolomide, bevacizumab and long-acting octreotide in 15 patients with advanced neuroendocrine tumors (NETs) who progressed after at least one regimen of chemotherapy. Responses included one CR (7%), eight PR (57%), three stable diseases (21%) and two PD (14%). The median TTP was 36 weeks [114] (Table 7). Zhou et al. evaluated in their retrospective study the efficacy and tolerability of continuous low-dose cyclophosphamide and prednisone as a salvage therapy for pre-treated multiple myeloma patients [115] (Table 8). Twenty-seven patients with multiple myeloma received a regimen of oral cyclophosphamide 50 mg daily and prednisone 15 mg daily. Patients had previously received 1 to 4 chemotherapeutic regimens. The ORR (including complete remission, very good PR, and PR) was 66.7%, with a median time to response of 2 months and absence of grade 3–4 toxicity. [115]. Similar results

Table 8
Clinical trials with metronomic chemotherapy in multiple myeloma.

Author	Tumor type	Patient population	No. (pts)	Protocol	Response rates	Response duration
Zhou et al.	MM	Pretreated MM	27	Cyclophosphamide, prednisone	ORR: 66.7%	–
Suvannasankha et al.	MM	Relapsed MM	37	Cyclophosphamide, prednisone, thalidomide	ORR: 63%	PFS: 13 mth
Papanicolaou et al.	MM	Relapsed MM	186	Bortezomib, thalidomide, dexamethasone, doxorubicin, cisplatin (rapamycin)	ORR 63%	OS: 11.2 mth PFS: 3.6 mth

were observed when cyclophosphamide was administered prospectively together with thalidomide and prednisone in patients with relapsed multiple myeloma, as demonstrated by the study of Suvannasankha et al. The 37 patients enrolled in this study, achieved an ORR of 63% and a median PFS of 13 months, with a good safety profile [116]. Recently, Papanicolaou et al. evaluated a complex metronomic schedule therapy as salvage treatment for 186 heavily pre-treated relapsed/refractory MM patients. The regimen included at metronomic doses: bortezomib, thalidomide, dexamethasone, doxorubicin, cisplatin with or without the addition of the m-TOR inhibitor rapamycin, depending on renal function. These authors evidenced a relatively high ORR (63%), with a favourable toxicity profile, although grade 4 leukopenia, anemia, and/or thrombocytopenia, occurred in 58%, 6%, and 79% of patients, respectively. The median OS and PFS were 11.2 and 3.6 months, respectively [117].

16. Metronomic drugs and toxicity

All these clinical trials have demonstrated that metronomic chemotherapy, alone or in combination, is generally well tolerated. However, the metronomic strategy is not devoid of side effects. In fact, in all studies previously reported, drug-related adverse events and treatment interruption were reported. In addition, some potential risks and concerns must be taken into consideration when using metronomic chemotherapy for an extended period of time [23].

The most common toxic effects of this treatment are: grade 1 nausea and/or vomiting, grade 1 and 2 anemia, neutropenia, leucopenia and lymphopenia as well as low-grade fatigue. Vinorelbine, cyclophosphamide, capecitabine, and methotrexate are the drugs mostly involved in these toxicities. These adverse events are more frequent when a combination schedule is proposed. With this regard, it is important to note that metronomic chemotherapy can easily become toxic through the addition of modern targeted drugs, such as bevacizumab. In fact, hypertension, proteinuria and renal failure are described in some studies, even if in a few cases. Moreover, fatigue and gastrointestinal symptoms e.g. nausea, vomiting and diarrhea are more common when targeted drugs are added to metronomic chemotherapy, and high accumulation over time of etoposide, temozolomide and cyclophosphamide can lead to secondary leukemia, or myelodysplastic syndrome (MDS) [118].

17. Conclusions and future developments

Pre-clinical and clinical evidence support metronomic chemotherapy as an alternative treatment in cancer therapy. The main characteristics of this therapy are: the low toxicity and high anti-angiogenetic activity, which translates in long duration of clinical benefit. However, also in the metronomic area it seems very unlikely that a single metronomic regimen will have universal efficacy, and the optimal combination regimen for each disease remain to be determined. Future preclinical and clinical studies are needed to define the best agent to use according to tumor type, the number of agents, the doses of each agent to be used alone or in combination, and the timing of drug administration. One way to overcome these drawbacks can be the development of reliable surrogate markers [119–122]. As suggested in several studies, the viability of circulating endothelial cells and progenitor endothelial cells can became a potent predictive tool for patient stratification and treatment monitoring, but currently few data are available and methods of identification need to be determined [119]. In his model, Kerbel demonstrated that endothelial cells are genetically more stable and less likely to acquire drug resistance than cancer cells [3]. Since more recent data highlighted that tumor endothelial cells are significantly different from normal endothelial cells and that they can harbor numerous genetic abnormalities, the identification of targets on these cells can represent a future research direction [123,124].

A cancer model based on several different actors (cancer cells, microenvironment, immune system, endothelial cells, circulating cells) provides an emerging anti-cancer strategy, based on metronomic chemotherapy combined with conventional chemotherapy and/or targeted therapy. Moreover, the cancer population is extremely heterogeneous and patients seem to respond quite differently according to the primary tumor type, highlighting the need to develop reliable tools for patient selection and stratification. A precise evaluation of metronomic chemotherapy strategies is fundamental and requires future prospective, randomized, phase II/III clinical studies, with a special focus on elderly and low performance status patients.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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