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De-escalating cancer treatments during COVID 19 pandemic: Is metronomic chemotherapy a reasonable option?

Palma Fedele [a,*], Valeria Sanna [b], Alessandro Fancellu [c], Antonella Marino [d], Nicola Calvani [d], Saverio Cinieri [d]

[a] Medical Oncology, Dario Camberlingo Hospital, Francavilla Fontana (Br), Italy
[b] Medical Oncology, Hospital of Sassari, Sassari, Italy
[c] Department of Medical, Surgical and Experimental Sciences, Unit of General Surgery, University of Sassari, Sassari, Italy
[d] Medical Oncology & Breast Unit, Antonio Perrino Hospital, Brindisi, Italy

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ABSTRACT

COVID 19 pandemic represents an emergency for public health services and containment measures to reduce the risk of infection have been promptly activated worldwide.

The healthcare systems reorganization has had a major impact on the management of cancer patients who are considered at high risk of infection.

Recommendations and guidelines on how to manage cancer patients during COVID 19 pandemic have been published. Oral administration of chemotherapy is recommended to limit the access of cancer patients to hospital facilities and in some cases to guarantee the continuum of care.

Low-dose metronomic administration of chemotherapy with different drugs and schedules has emerged in the last years as a possible alternative to conventional chemotherapy, due to its promising tumor control rates and excellent safety profiles. Moreover, given that many metronomic schedules use the oral route administration, it could represent a therapeutic strategy to ensure continuum of cancer care during COVID 19 pandemic.

In this review we have selected all the clinical studies that have used the metronomic strategy, especially with oral drugs, in order to identify the subgroups of cancer patients who can benefit most from a metronomic approach even during COVID 19 pandemic.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has forced healthcare systems to reorganize all the activities with the purpose of containing the virus infection. Medical resources have been concentrated on emergency departments and intensive care units while scheduled and non-urgent medical services have been suspended.

The reorganization of the healthcare system has had an important impact on the management of cancer patients.

Cancer patients are considered at high risk of developing coronavirus infection and its severe complications, because of their illness and immunosuppressed status (Liang et al., 2020).

In those countries where the spread of the pandemic is massive, specific measures have been taken to reduce access of cancer patients to hospitals. Elective surgeries, follow-up appointments and some types of cancer treatments have been canceled or postponed to prioritize hospital beds and care for those who are seriously ill with COVID-19 (Wang et al., 2020).

Consequently, medical oncologists must perform individual risk-benefit assessments in cancer patients before making any decision. For those patients who do not have an urgent need to start anticancer therapy, the treatment will be postponed. When the benefits for patients to undergo anti-cancer treatment outweigh the risks of being potentially exposed to the virus while traveling from home to the hospital and back, a new therapy will be initiated and in some cases the continuum of cancer care will be guaranteed.

In this regard, recommendations and practical suggestions on how to implement cancer care have been published to guide medical oncologists in the difficult decision of prioritizing patients for cancer treatments (Ontario Health and Cancer Care Ontario, 2020; NICE, 2020; Lambertini et al., 2020; You et al., 2020).

Since a priority of oncologists at this time is to minimize infection

* Corresponding author.
E-mail addresses: minafedele@hotmail.com, palma.fedele@asl.brindisi.it (P. Fedele).

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risks for cancer patients and encourage oral treatments to limit patients access to hospital facilities, we suggest to consider metronomic administration of chemotherapy as a reasonable therapeutic option to de-escalate cancer treatments and to ensure the continuum of care of some cancer patients subgroups.

Metronomic chemotherapy could allow the possibility of prolonged treatment with less side effects. It can allow the management of cancer patients at home and limit patients' dependence on hospitals and the possibility of infection in the hospital environment.

Herein we analyze results from clinical trials that have evaluated the safety and efficacy of oral metronomic therapy in cancer patients, in order to identify the subgroups of cancer patients who are ideal candidates for metronomic chemotherapy.

2. Metronomic chemotherapy: classical and new mechanisms of action

Metronomic chemotherapy (MC) is characterized by chronic administration of chemotherapy at low doses, with a frequent schedule of administration, at close and regular intervals and with no extended interruption. MC exerts both direct and indirect effects on tumor cells and on their microenvironment and causes less severe side effects than standard chemotherapy (Hanahan et al., 2000; Romiti et al., 2017; Shitara and Nishikawa, 2018; Tanaka et al., 2009; Vincent et al., 2010).

3. Metronomic chemotherapy in breast cancer

3.1. Metastatic breast cancer

The earlier studies on MC were conducted in metastatic breast cancer (MBC) patients. Given that goals of care in MBC are to optimize both length and quality of life, MC strategies are attractive for their safe toxicity profile and good tumor control. Moreover, MC is delivered by the oral route that limits patients access to hospitals and represents the favourite route of chemotherapy administration for cancer patients (Eek et al., 2016).

The first clinical reports on MC examined the all oral combination of daily low dose of CM (cyclophosphamide 50 mg daily and methotrexate 2 days a week for a total dose of 10 mg a week) in pretreated or untreated MBC patients (Colleoni et al., 2002; Colleoni et al., 2006; Salem et al., 2008).

Subsequent studies have explored the efficacy and safety of the combination of CM with different other therapies (endocrine, anti Her2, targeted agents). The study by Aurilio et al. evaluated the combination of CM plus fulvestrant 250 mg via i.m. injection q28 days. CBR was 56% (95% CI 38–74%) and the treatment did not determine relevant toxicities (Aurilio et al., 2012).

In a small study, low-dose, oral CM combined with trastuzumab have shown substantial efficacy in metastatic HER-2 positive breast cancer and provided disease control in a significant proportion of patients (Orlando et al., 2006).

The antiangiogenic agents bevacizumab and vandetanib were combined to CM in pretreated MBC patients. The CBR was 64% in the first study that explored the efficacy of CM plus vandetanib combination in patients with anthracycline- and taxane-refractory breast cancer and reported mild side effects (Garcia-Saenz et al., 2008). The phase I study by Mayer et al. that evaluated the combination of vandetanib and CM in MBC reported mild toxicities included nausea, vomiting, fatigue and rash. Out of 20 response-evaluable patients, 10% experienced partial response and 15% stable disease $\geq$24 weeks (Mayer et al., 2012).

The most widely studied metronomic therapy in MBC is capecitabine-based chemotherapy.

Metronomic capecitabine (MeC) (1500 mg once daily) has shown a CBR of 62% in pretreated MBC patients and excellent safety profile, being severe toxicity rare and in all cases non-hematological (Fedele et al., 2012).

In the phase II randomized study by Stockler et al., 323 patients with MBC received one of three regimens: standard capecitabine (1000 mg/m^2 twice daily for 14 of every 21 days), continuous MeC (650 mg/m^2 twice daily without breaks) and classical Bonadonna CMF regimen.

Capecitabine improved overall survival and was similarly active, less toxic and more tolerable than CMF. No significant differences were observed between standard and MeC in terms of survival, tumor response and toxicity (Stockler et al., 2011).

The combination of MeC with different chemotherapeutic agents, endocrine and biological therapies have been extensively investigated in phase II and III clinical trials.

The all oral combination of MeC and cyclophosphamide was safe and effective as first or second line treatment in HER2-negative MBC patients (Yoshimoto et al., 2012; Wang et al., 2012)

The VICTOR-1 and 2 studies have investigated the all-oral metronomic combination of vinorelbine 40 mg three times a week and capecitabine 500 mg three times a day in first or subsequent lines of treatment. The metronomic schedule reported a CBR of 45.7% (95% CI 28.8–63.4) and 51.1% (95% CI 35.8–66.3) in first- and $\geq$ second-line therapy, respectively. The median duration of response was 11.3 and 6.4 months and PFS rates at 1 year were 24.3 and 22.2%, respectively. In triple-negative breast cancer patients ($N = 28$, 35%) a lower, but clinically relevant CBR (35.7; 95% CI 18.6–55.9) was observed. Side effects were: non-febrile neutropenia in 1.1%, hand-foot syndrome in 1.0%, nausea and vomiting in 1.0%, leucopenia in 0.8%, fatigue in 0.7%, and diarrhea in 0.4% (Cazzaniga et al., 2014; Cazzaniga et al., 2016).

MeC was also tested in triple-drug chemotherapy combinations.

In the phase II VEX trial the triple combination of metronomic oral vinorelbine 40 mg orally 3 times a week plus cyclophosphamide 50 mg daily and capecitabine 500 mg 3 times a day were explored in untreated metastatic triple-negative breast cancer patients. Median TTP was 6.4 months in 22/25 evaluable patients.

The combination was well tolerated: most common grade 1–2 toxicities were nausea, diarrhea, leuko-/neutropenia and reversible liver enzyme alteration. Grade $\geq$ 3 adverse events were uncommon (Montagna et al., 2018).

The multi-center, randomized phase II trial METEORA II is now investigating the metronomic regimen of cyclophosphamide 50 mg orally once daily continuously, capecitabine 500 mg, orally 3 times a day (1500 mg/day) continuously, vinorelbine 40 mg orally days 1, 3, 5 each week continuously, versus the conventional paclitaxel monotherapy 90 mg/m^2 days 1, 8, 15 q4w as first-line or second-line treatment in patients with ER-positive/HER2-negative advanced or metastatic breast cancer (METEORA-II, 2020).

The phase II trial by Schwartzberg et al. has investigated efficacy and toxicity of MeC (1500 mg or 2000 mg daily, depending on the patient's weight) plus fulvestrant (loading dose 500 mg on day 1, 250 mg on days 15 and 29 followed by 250 mg every 28 days) in estrogen and/or progesterone receptor-positive, HER2-negative MBC, previously untreated or with $\leq$1 previous hormonal treatment. Median PFS was 14.98 months and median TTP was 26.94 months. Treatment was well tolerated and the most frequent adverse events were palmar-plantar erythrodysesthesia, fatigue, and nausea (Schwartzberg et al., 2014).

In the phase II trial by Dellapasqua et al. the triple combination of MeC 500 mg thrice daily plus cyclophosphamide 50 mg daily plus bevacizumab 10 mg/kg every 2 weeks has shown a high CBR in 46 untreated breast cancer patients (68% (95% CI, 51–81%). The combination resulted minimally toxic being grade 3 or 4 non hematologic adverse effects: hypertension ($n = 8$), transaminitis ($n = 2$), and nausea/vomiting ($n = 2$) (Dellapasqua et al., 2008).

The phase II trial that investigated the combination of MeC 500 mg thrice daily plus cyclophosphamide 50 mg daily plus bevacizumab 15 mg/kg every 3 weeks and erlotinib 100 mg daily as first line treatment in HER2-negative, hormone receptor poor MBC reported a CBR of 75% (95% confidence interval [CI], 53–90%). Median time to progression was 43 weeks (95% CI, 21–69). Toxicity was generally mild and

grade 3 toxicity was rare: diarrhea ($n = 1$), thrombosis ($n = 1$), and hypertension ($n = 2$) (Montagna et al., 2012).

The multicenter, randomized phase III trial SAKK 24/09 compared bevacizumab with either paclitaxel or daily oral capecitabine 500 mg thrice daily plus and cyclophosphamide 50 mg daily as first-line treatment in patients with HER2-negative advanced breast cancer. No significant differences between treatment arms were reported in PFS that was 10.3 months (95% CI 8.7–11.3) in the paclitaxel arm and 8.5 months in the metronomic arm (95% CI 6.5–11.9). Less hair loss and numbness in metronomic arm were the only clinically and statistically significant differences (Rochlitz et al., 2016).

More recently a phase II trial has explored a new metronomic regimen with cyclophosphamide 50 mg daily plus capecitabine 500 mg three times a day continuously in combination with trastuzumab in 60 HER-2 positive untreated MBC. The objective response rate that was the primary endpoint of the study was 56.7% (95% CI, 44.1–68.4%) and CBR was 78.2%. Grade 3 and 4 toxicities were rare and the most commonly reported toxicities were G1 events (Orlando et al., 2017).

Metronomic therapy with oral vinorelbine has been explored in some MBC patient subgroups.

Two phase II trials have demonstrated safety and activity of oral vinorelbine metronomic (MeV) monotherapy in elderly patients with MBC (Addeo et al., 2010; De Iuliis et al., 2015).

To validate the role of MeV in the treatment of MBC patients the Name trial, a prospective randomized phase II, multicentre study, is now comparing classical treatment of i.v Vinorelbine (60 mg/m^2 day 1, day 8 and day 15, every three weeks for the first cycle, hereafter 80 mg/m^2 day 1 and day 8, every three weeks for the following cycles) versus MeV at daily doses of 20 or 30 mg, depending on patients' age and body surface (Langkjer et al., 2019).

Similarly, the ongoing TEMPO- Breast 01 trial is enrolling HR positive, HER2 negative MBC patients to first-line chemotherapy with MeV 60 mg/mq per week or MeV 50 mg total dose three times per week (De la Haba et al., 2015).

3.2. Early breast cancer

In early breast cancer (EBC) the evidences currently reported show that the metronomic approach should be reserved for selected patients subgroups, such as triple negative, and as maintenance treatment.

The first study that has explored efficacy and safety of oral MC is a randomized phase III trial that compared adjuvant tegafur/uracil (UFT) to classical CMF in node negative, high risk EBC patients. Survival results were similar in both arms, but the two different schedules differed in toxicity profiles. The quality of life scores were better for patients given UFT than those given CMF (Watanabe et al., 2009).

The open-label phase III trial, IBCSG 22–00 randomized 1081 patients with ER and PGR negative EBC and any nodal status who have completed adjuvant chemotherapy to CM maintenance (cyclophosphamide 50 mg/day continuously and methotrexate 2.5 mg twice/day on days 1 and 2 of every week for 1 year) or to no CM.

The metronomic CM maintenance therapy did not produce a significant reduction in DFS that was the primary endpoint of the study (DFS at 5 years was 78.1% in the CM group vs 74.7% in the no CM group (hazard ratio [HR] = 0.84, $p = 0.14$). There was a non-statistically significant reduced HR ($n = 340$; HR, 0.72; 95% CI, 0.49–1.05) in the triple-negative, node-positive subgroup. Moreover, the CM maintenance chemotherapy was associated to grade 3 or 4 treatment-related adverse events that occurred in 14%. The most common side effect was elevated serum transaminases (7%) and leukopenia (2%). Two patients in the cyclophosphamide/methotrexate group developed acute myeloid leukemia (Colleoni et al., 2016).

Metronomic CM (cyclophosphamide 50 mg daily: methotrexate 2.5 mg BID on days 1, 2 of each week) was administered for 1 year after adjuvant therapy completion to patients with TNBC to improve their DFS and OS in a randomized phase III study by Nasr et al. The authors reported significantly better OS for those TNBC patients who received CM maintenance chemotherapy after adjuvant carboplatin versus patients who did not (Nasr et al., 2015).

MeC was administered to EBC patients as maintenance after adjuvant chemotherapy in two phase II trials that confirmed efficacy and good tolerability of the extended metronomic approach (Shawky and Galal, 2014; Alagizy et al., 2015).

Results from ongoing randomized adjuvant trials (ABCDE trial and MACRO trial) will better address the role of metronomic chemotherapy with CM or capecitabine in the maintenance treatment of EBC (Mayer et al., 2016; MACRO, 2020)

4. Metronomic chemotherapy in colorectal cancer

In preclinical studies MeC for colon cancer xenografts and colon cancer cells has proved to inhibit angiogenesis, decrease VEGF and microvessel density and increase antiangiogenic protein thrombospondin-1 (TSP-1) (Shi et al., 2014).

The best clinical experience in colorectal cancer (CRC) derives from advanced disease where lowered but prolonged doses of standard chemotherapy have been used especially with the aim of targeting angiogenesis. The chemotherapeutic agents mostly studied for a metronomic approach in CRC are the fluoropyrimidines, predominantly capecitabine. Other agents evaluated in very few phase II studies are: tegafur/uracil (UFT), irinotecan, cyclophosphamide.

The role of MeC has been particularly evaluated in phase II studies in the palliative setting of advanced pretreated patients and in one phase III trial in the maintenance therapy setting.

In 2000 a randomized phase II trial compared 3 capecitabine schedules; arm A: 1331 mg/m^2/day continuous dosing, arm B: 2510 mg/m^2/day [2 weeks on, 1 week off] and arm C: an additional leucovorin-containing arm [capecitabine 1657 mg/m^2/day plus leucovorin 60 mg/day, 2 weeks on and 1 week off]. Time to progression was longer in the group that received the intermittent capecitabine dose of 2510 mg/m^2/day (arm A 127 days, arm B 230 days, and arm C 165 days) and the response rates were similar in the 3 arms (arm A 21%, arm B 24%, and arm C 23%) (Van Cutsem et al., 2000).

In one retrospective study the patients who received a continuous fixed dose of capecitabine 1500 or 2000 mg daily had low toxicity profiles and no patients who were treated with capecitabine as a single agent had side effects of any grade (Lokich, 2004).

Continuous administration of a fixed daily dose of capecitabine was effective and well tolerated with a low toxicity profile (Lokich, 2004; Budman et al., 1998).

One phase 3 randomized controlled trial (CAIRO 3 study) was planned to ascertain the efficacy of maintenance chemotherapy with MeC plus bevacizumab after an induction treatment with six 3-week cycles of capecitabine, oxaliplatin and bevacizumab (CAPOX-B). 558 mCRC patients were randomized into either the maintenance or the observation group on a 1:1 basis. Capecitabine 625 mg/m^2 orally twice a day for 3 weeks and bevacizumab 7.5 mg/m^2 intravenously every 3 weeks was the maintenance treatment. With a median follow-up of 48 months PFS was significantly longer in the maintenance group (8.5 months vs 11.7 months). Furthermore, the incidence of chemotherapy-related leukopenia, peripheral neurotoxicity and other serious toxic reactions was only increased by 5–10% in the maintenance group compared with the observation group which was completely tolerated by patients and thus MeC chemotherapy combined with bevacizumab proved to be an effective and low-toxic maintenance therapy (Simkens et al., 2015).

On the contrary, a different study, the Italian phase II, no-profit, multicenter MOMA trial did not show the same positive results. 232 patients with unresectable mCRC were randomized to receive up to 8 cycles of FOLFOXIRI plus bevacizumab followed by bevacizumab (arm A) or the same induction regimen followed by bevacizumab plus MeC (capecitabine 500 mg three times per day and cyclophosphamide 50 mg

orally daily arm B) until disease progression. The primary endpoint was PFS. At a median follow-up of 47.8 months, 210 and 164 progression and death events were registered. Median PFS was 10.3 and 9.4 months in arm B and A, respectively (HR: 0.94 [70% confidence interval {CI}: 0.82 and 1.09], *p*: 0.680). No significant differences were reported in terms of overall survival (OS) (median OS arm B/A: 22.5/28 months; HR: 1.16 [95% CI: 0.99 and 1.37], *p*: 0.336). The authors concluded that the addition of MeC to maintenance with bevacizumab did not improve significantly PFS of mCRC patients (Cremolini et al., 2019). Recently Shi et al. published a project intended to study the efficacy and safety of MeC in the maintenance treatment of advanced CRC. The study is a prospective, randomized, open label, phase II clinical trial in which patients with mCRC, who had responded well after 16–18 weeks of standard doublet chemotherapy as induction therapy, were randomly assigned to the MeC group (capecitabine 500 mg twice a day orally) and capecitabine conventional chemotherapy (capecitabine 1000 mg/m^2 twice a day orally, d1–14, 3 times weekly (q3w). The aim of the study is to demonstrate that MeC is non-inferior to capecitabine conventional chemotherapy as maintenance treatment in patients who have responded to 16–18 weeks first-line chemotherapy in mCRC. The duration of disease control after randomization and progression-free survival after enrollment are the primary endpoints. Overall survival, safety, and quality of life are the secondary endpoints. The sample size required to achieve the research objectives of this project is 79 patients in each group. The study enrollment started on 29 January 2018 and will last for 36 months. After the start of the study, the first 30 months have consisted of inclusion and follow up of patients. The last 6 months consisted of follow up and analysis of results. The study will end on 29 January 2021. This project is intended to explore the strategy of low toxicity, high efficiency, economy and individualization of MeC in the maintenance treatment of advanced colorectal cancer which is suitable for China's national conditions and pharmacoeconomics. It has great prospects for clinical application and a clear socioeconomic value (Shi et al., 2020).

Metronomic regimens could be an inviting option also for frail mCRC patients. With continuous, low-dose administration of capecitabine (500 mg twice or three times a day) elderly or heavily pretreated patients with mCRC showed good disease control and minimal toxicity without impairment to quality of life. A study by Romiti et al. retrospectively evaluated the activity and safety of MeC at the dose of 1500 mg daily in 86 frail patients. Overall disease control rate was 26% with a 2% partial response and 23% stable disease. Nineteen percent of patients were progression-free for 6 months and the median OS was 8 months. No grade 4 toxicity was observed (Romiti et al., 2015).

A different trial in pretreated frail elderly patients with mCRC evaluated the efficacy and toxicity profile of MeC (1000 mg twice daily), oxaliplatin (65 mg/m^2) and bevacizumab (7.5 mg/m^2). Median progression-free survival was 12.3 months with 86.7% reaching six months. No grade 4 toxicity was observed (Carreca et al., 2011).

A different study retrospectively evaluating MeC (1500 mg daily) in mCRC patients reported a median TTP of 6.3 months and a tolerable toxicity profile (Borgonovo et al., 2016).

Based on these data metronomic chemotherapy, especially capecitabine, should probably be taken into major consideration as a reasonable and feasible option in a further line of therapy in pretreated mCRC pts and/or frail/elderly pts during the COVID-19 pandemic.

5. Metronomic chemotherapy in prostate cancer

In castration-resistant prostate cancer (CRPC), despite the availability of new anti-testosterone drugs, a debate still exists on the optimal treatment, especially because most patients are elderly and frail.

Recent reports highlight the role of MC for those patients who progressed on standard therapy, as well as docetaxel-resistant patients. In fact, many patients in this setting could be unfit for conventional treatment (Van Dodewaard-de Jong et al., 2015).

The main part of the studies investigating MC in CRPC was on the effects of cyclophosphamide alone (Caffo et al., 2019) or combined in pretreated patients.

Metronomic cyclophosphamide was well tolerated and showed efficacy also in hormone naïve patients (Calcagno et al., 2016).

Combinations of cyclophosphamide plus steroids were effective and safe in pretreated patients with no febrile neutropenia and beneficial effects in 50–79% of patients were reported, including reduction of PSA levels (Glode et al., 2003; Ladoire et al., 2010; Calvan iN et al., 2019).

Fea et al. analyzed the pharmacologic toxicity of metronomic oral cyclophosphamide in a group of heavily pretreated patients and did not find any grade 3 or 4 toxicity. Thus, in their cohort none of the patients discontinued therapy because of toxicity. The most common adverse events were asthenia G1, anemia G1-2 and leukopenia G1 (Fea et al., 2016).

Metronomic cyclophosphamide was well tolerated also in those studies that evaluated the combination with iv chemotherapy. In a study including 41 patients, where cyclophosphamide was combined with docetaxel and prednisone, no grade 4 toxicities were reported, while grade 3 neutropenia was 5%; thrombocitopenia, stomatitis and diarrhea were 2.5%. These side effects were related to docetaxel treatment. Neither major cardiovascular events nor toxicity-related deaths were observed (Derosa et al., 2014).

Only in one study, a moderate rate of myelotoxicity (about 12%) was reported in a cohort of patients with extensive bone metastasis (Jeong and Lee, 2017).

Other effective combination regimens (for example with corticosteroids, diethylstilbestrol or colecoxib and methotrexate) were studied in pretreated patients with similar results (lowering PSA; good tolerance) (Hellerstedt et al., 2003; Muraki et al., 2012; Khan et al., 2011).

In a phase II trial, in which cyclophosphamide 50 mg daily was combined with methotrexate in pretreated patients, PSA lowering was observed in 25% of patients (Gebbia et al., 2011).

In a different study of docetaxel naive patients, a 50% of reduction of PSA was observed with use of cyclophosphamide and estramustine. The safety profile was considered good, without G3/4 toxicity (Bracarda et al., 2000).

As shown in Table 1 all the studies that evaluated MC alone or in combinations in pretreated or naïve prostate cancer patients have demonstrated a manageable toxicity profile.

6. Metronomic chemotherapy in kidney cancer

Kidney cancer is usually thought to be resistant to standard chemotherapy and even targeted drugs seem to be only temporarily effective because of resistance.

As target therapy and immunotherapy have improved the prognosis of metastatic renal cancer, the issues of quality of life and of pharmacologic tolerance are of paramount importance in this scenario.

In particular, the resistance to these drugs still remains a problem. Further treatment strategy and MC could be an opportunity for renal cancer cure.

Few studies have addressed the role of MC in patients with metastatic renal cancer. In 2010 Bellmunt reported a clinical benefit in 87% of cases and no G3/4 hematological toxicity in a group of 44 patients taking MeC (Bellmunt et al., 2010)

In a pretreated population, a combination of capecitabine and antinflammatory politherapy (pioglitazone, IFN, etorocoxib) was shown to have a response rate of 35%. No febrile neutropenia and skin toxicity was seen (Walter et al., 2012).

A phase II trial confirmed a low grade of toxicity with cyclophosphamide and a long clinical benefit (24 weeks] in 40% of patients (Tupikowski et al., 2015).

There is evidence of a synergistic activity of target therapy associated with metronomic chemotherapy. There is direct effect of pazopanib on renal cancer cells, resulting in increased intracellular concentration of

Table 1
Main toxicities reported with metronomic chemotherapy in patients with prostate cancer.

Author	Year	No. of patients	Drug	FN *N*	SAE *N* (worst event)
Maulard Durdux (Maulard-Durdux et al., 1996)	1996	20	CP-E	0	0
Bracarda (Bracarda et al., 2000)	2000	32	CP-Estra	0	0
Nishimura (Nishimura et al., 2001)	2001	21	CP-Estra-U-T	0	d.n.r (mild toxicity/well tolerated)
Glode (Glode et al., 2003)	2003	34	CP-DEX	0	d.n.r (mild toxicity/well tolerated)
Robles (Robles et al., 2003)	2003	14	V-PD	0	d.n.r (mild toxicity/well tolerated)
Hellerstedt (Hellerstedt et al., 2003)	2003	36	CP-PD-DE	0	d.n.r (mild toxicity/well tolerated)
Lord (Lord et al., 2007)	2007	58	CP	0	0
Fontana (Fontana et al., 2009)	2009	28	CP-Cel-DEX	0	0
Nelius (Nelius et al., 2010)	2010	17	CP	0	0
Ladoire (Ladoire et al., 2010)	2010	23	CP-PL	0	d.n.r (mild toxicity/well tolerated)
Gebbia (Gebbia et al., 2011)	2011	58	CP-MTX	0	0
Jellvert (Jellvert et al., 2011)	2011	17	CP-Estra-E-K	0	0
Hatano (Hatano et al., 2011)	2011	57	CP-U-T-DEX	0	1 (neutropenia)
Meng (Meng et al., 2012)	2012	28	CP-Tha-Cap	0	0
Yashi (Yashi et al., 2014)	2014	14	CP	0	0
Derosa (Derosa et al., 2014)	2014	41	CP-Doc	0	0
Barroso-Sousa (Barroso-Sousa et al., 2015)	2015	40	CP-PD	0	0
Fea (Fea et al., 2016)	2016	12	CP	0	0
Di Desidero (Di Desidero et al., 2016)	2016	41	V-DEX	0	0
Tralongo (Tralongo et al., 2016)	2016	26	V	0	0
Calcagno (Calcagno et al., 2016)	2016	38	CP	0	0
Jeong (Jeong and Lee, 2017)	2017	60	CP-DEX-Cel	0	6 (myelophthisic anemia)
Dabkara (Dabkara et al., 2018)	2018	18	CP-PL	0	0
Caffo (Caffo et al., 2019)	2019	74	CP	0	1 (non neutropenic infection)
Calvani (Calvan iN et al., 2019)	2019	37	CP	0	0

(CP: cyclophosphamide; Estra: estramustina; L: lenalinomide; V: vinorelbine; E: etoposide; U: uracil; T: tegafur; DEX: dexamethasone; PD: prednisone; PL: prednosolone; DE: diethylstilbestrol; MTX: methotrexate; cel: celecoxib; Tha: thalidomide; Cap: capecitabine; Doc: docetaxel; K: ketoconazole; d.n.r: details not reported; FN: febrile neutropenia; SAE: severe adverse event, defined as any >3 grade toxicity or treatment interrupted.

topotecan (Jedeszko et al., 2015). Although these data are encouraging, further studies are needed to make this strategy applicable on a large scale.

Certainly, the manageability and low toxicity profile make MC particularly attractive also in kidney cancer.

Table 2 reports safety details of the more significant phase II trials in kidney cancer.

7. Metronomic chemotherapy in ovarian cancer

In ovarian cancer high level of response rate can be reached with debulking surgery and/or platinum based chemotherapy. However, relapse still occurs.

In ovarian cancer, angiogenesis plays an important role, thus MC could be an interesting opportunity (Kamat et al., 2007).

In most studies on ovarian cancer, MC has been used in relapsed/refractory ovarian carcinoma or in combination with standard chemotherapy to improve outcomes due to antiangiogenic effect with minimal toxicity.

This frail population, generally heavily pretreated or unfit for iv chemotherapy because of complication of surgery, could have beneficial effects by continuous administration of low doses of chemotherapy.

In animal models metronomic dosage of oral cyclophosphamide was proven to be safe in combination with irinotecan or pazopanib, with modest lowering of white blood cells and weight loss (Hashimoto et al., 2010).

Numerous experiences of metronomic cyclophosphamide in ovarian cancer have shown an optimal safety profile with an overall survival benefit from 12 to 20 months in pretreated advanced disease (Samaritani et al., 2007; Ferrandina et al., 2014).

Combinations of metronomic cyclophosphamide with 5-fluorouracile and temozolamide have given similar results (Kerbel, 2007; Bhattacharyya et al., 2017).

MC with some antiangiogenetic agents is an interesting area for research for first-line, maintenance and salvage therapy (Sanchez-Munoz et al., 2010; Alvarez et al., 1999; Jurado et al., 2008; Chura et al., 2007).

Cyclophosphamide metronomic regimen was evaluated as maintenance therapy in a retrospective study of ovarian cancer patients after surgery or complete response to standard neoadjuvant therapy (platinum salt based). In this population MC of cyclophosphamide and methotrexate was compared to observation alone with a benefit of 3 months without any grade 3 or 4 toxicity (Pandey et al., 2016a).

Oral etoposide is used as metronomic therapy in metastastic and pretreated ovarian cancer. A low level of toxicity and an overall survival of about 16 months indicate a good potential for this therapy, especially in the setting of platinum refractory patients (Markman et al., 1992;

Table 2
Main toxicities reported with metronomic chemotherapy in patients with kidney cancer.

Author	Year	No. of patient	Drug	FN *N*	SAE *N* (worst event)
Bellmunt (Tupikowski et al., 2015)	2010	44	Cape-Gem-Sor	0	1 (PE)
Walter (Jedeszko et al., 2015)	2012	45	Cape-IFN–Pi_Eto	0	16 (Hand and foot Syndrome)
Tupikowsky (Kamat et al., 2007)	2015	30	IFN-CP	0	d.n.r (mild toxicity/well tolerated)

T: tegafur; Cape: capecitabina; Gem: gemcitabine; Sor: sorafenib; IFN: interferon; Pi: pioglitazone; Eto: etoricoxib CP: cyclophosphamide; T: topotecan; Pa: pazopanib; d.n.r: details not reported; FN: febrile neutropenia; SAE: severe adverse event, defined as any >3 grade toxicity or treatment interrupted; PE: pulmonary embolism.

Kucukoner et al., 2012).

Table 3 shows main toxicity reported with metronomic chemotherapy in ovarian cancer

8. Metronomic chemotherapy in lung cancer

Although the introduction of immunotherapy has changed the prognosis of lung cancer, it remains a big killer. Most research efforts in the management of non-small cell lung cancer (NCSLC) patients are focused on discovering agents and combinations of agents, doses and dose schedules that maximally kill tumor cells while minimizing the toxicity to the host, especially beyond the second line.

MC has been used for patients who are ineligible for standard treatment options. MC is a manageable therapy in frail patients with lung cancer with low percentage of severe toxicity, also beyond second line treatments (Kontopodis et al., 2013).

For NSCLC metronomic regimens were tested in first line treatment and for maintenance or salvage therapy. Recently, a well conducted metanalysis has been published about the use of MeV with demonstration of a good benefit-risk ratio. The safety profile of oral vinorelbine appears to be better than iv regimen (Pujol et al., 2019).

The overall survival with front line vinorelbine was 7–12 months. The best results were in young patients and in patients with a good PS (Bilir et al., 2017; Camerini et al., 2015; Katsaounis et al., 2015).

The combination vinorelbine with sorafenib resulted in overall survival of about 8 months (Tan et al., 2015).

In SCLC patients oral etoposide is the most experienced drug for salvage therapies but gives a low overall survival (about 4 months) compared with iv therapy (Pfeiffer et al., 1997).

Etoposide was used also in NSCLC with an OS of 9 months and a good safety profile (Kakolyris et al., 1998; Surmont et al., 2009).

In combination with bevacizumab and cisplatin, oral etoposide showed an overall response rate of 45.2%, without G4 hematological toxicity (Correale et al., 2006).

The same combination administered as maintenance therapy reached an overall survival of 13.2 months (Petrioli et al., 2015).

Because of the high incidence of brain metastases in patients with lung cancer, many studies have evaluated the role of MC in combination with radiotherapy (RT) to improve tolerability. Temozolamide was studied as MC in advanced stage NSCLC with brain metastases. The low dose temozolamide schedule reported a response rate of about 50% in association with RT (Addeo et al., 2008).

The combination of metronomic etoposide to cisplatin and bevacizumab was safe and effective during RT (Pastina et al., 2017).

Metronomic cyclophospamide plus RT shows a significantly higher PFS clinical benefit as radiosensitizer in NCSLC frail patients (Revannasiddaiah et al., 2015). Further histological sub-group analysis demonstrated that there was an enhanced outcome with the addition of metronomic cyclophosphamide to RT for patients with adenocarcinoma histology (3.5 vs. 2.4 months; $p = 0.0053$), but there was no benefit for patients with squamous cell histology (2.6 vs. 2.6 months; $p = 1$).

Table 4 shows main toxicities reported with metronomic chemotherapy in lung cancer.

9. Metronomic chemotherapy in head and neck cancer

In patients with head and neck cancer (HNC) there are only limited management options due to the very frailty of this group of patients. MC may have a role for its good safety profile, as shown in Table 5. Low-dose, continuous metronomic drugs were particularly studied in the contest of platinum-refractory patients and the commonest adverse event was fatigue (G2–G3), while no febrile neutropenia was reported (Patil et al., 2019).

MC in recurrent HNC has shown good disease-control rates with effective palliation, minimal toxicity and preserved quality of life (Noronha et al., 2016; Patil et al., 2015).

In oral cancer methotrexate per os was evaluated with celecoxib with a significant beneficial of 15%; disease free survival was 13 months (Pai et al., 2013; Pandey et al., 2016b).

10. Metronomic chemotherapy in melanoma

Although recent advances with target therapy, immunotherapy and

Table 3
Main toxicities reported with metronomic chemotherapy in patients with ovarian cancer.

Author	Year	No. of patient	Drug	FN *N*	SAE *N* (worst event)
Beck (Beck and Boyes, 1968)	1968	126	CP	0	d.n.r (mild toxicity/well tolerated)
Markman (Markman et al., 1992)	1992	18	E	0	2 (neutropenia)
Chura (Chura et al., 2007)	2007	15	CP-Beva	0	0
Garcia (Garcia et al., 2008)	2008	70	CP-Beva	0	2 (linfopenia)
Jurado (Jurado et al., 2008)	2008	9	CP-Beva	0	0
Ferrandina (Ferrandina et al., 2014)	2014	54	CP	0	0
Handolias (Handolias et al., 2016)	2016	23	CP	0	2 (non-hematological)
Wong (Wong and Liu, 2017)	2017	20	CP	0	0
Sharma (Sharma et al., 2019)	2019	36	Pa-CP	0	d.n.r (mild toxicity/well tolerated), 5 G3/4 mucositiis

CP: cyclophosphamide; E: etoposide; Pa: pazopanib; beva: Bevacizumab; d.n.r: details not reported; FN: febrile neutropenia; SAE: severe adverse event, defined as any >3 grade toxicity or treatment interrupted.

Table 4
Main toxicities reported with metronomic chemotherapy in lung cancer.

Author	Year	No. of patient	Drug	FN *N*	SAE *N* (worst event)
Kakolyris (Kakolyris et al., 1998)	1998	61	E	0	d.n.r (mild toxicity/ well tolerated)
Kouroussis (Kouroussis et al., 2009)	2009	31	TMZ	0	2 (lymphopenia)
Correale (Correale et al., 2006)	2011	45	E-Beva_cis	0	0
Kontopodis (Kontopodis et al., 2013)	2013	46	V	4	8
Camerini (Camerini et al., 2015)	2015	43	V	0	0
Pastina (Pastina et al., 2017)	2017	69	E-Beva-Cis-RT	0	0
Mencoboni (Mencoboni et al., 2017)	2017	76	V	1	1 (diarrhea)
Banna (Banna et al., 2017)	2018	41	V	0	0
Pasini (Pasini et al., 2018)	2018	92	V	1	4 (neutropenia)
D'Ascanio (D'Ascanio et al., 2018)	2018	44	V	0	0

E: ethoposide; V: vinorelbine; SO: sorafenib; Beva: bevacizumab; TMZ: temozolamide; Cis: Cisplatunum. d.n.r: details not reported; FN: febrile neutropenia; RT: radiotherapy; SAE: severe adverse event, defined as any >3 grade toxicity or treatment interrupted.

Table 5
Main toxicities reported with metronomic chemotherapy in patients with head and neck cancer.

Author	Year	No. of patient	Drug	FN *N*	SAE *N* (worst event)
Pai (Pai et al., 2013)	2013	32	Col-MTX	0	0
Pandey (Pandey et al., 2016b)	2016	335	Col-MTX	0	0
Patil (Patil et al., 2015)	2020	76	Erlo-Col-MTX	0	d.n.r (mild toxicity/well tolerated); G3/5 iponatremia and neutropenia

MTX: methotrexate, Col: colecoxib; Erlo: erlotinib; d.n.r: details not reported; FN: febrile neutropenia; SAE: severe adverse event, defined as any >3 grade toxicity or treatment interrupted.

combinations in the treatment of metastatic melanoma (MM), there is still the need for new well-tolerated therapies for patients who have resistance or have a bad tolerance to those treatments.

Besides, as the progression-free survival duration is prolonged, the risk of treatment resistance increases.

It was shown that angiogenesis has an impact in melanoma, so it can be postulated that also MC has a role in this setting (Ugurel et al., 2001).

In MM the main experience with MC is in the use of alkylating agents.

The first study of MC in MM explored the combinations of metronomic paclitaxel and celecoxib, but the toxicity was higher compared with oral regimen in other cancers and may be correlated to iv paclitaxel (Bhatt et al., 2010).

In a group of unfit elderly patients, treatment with cyclophosphamide reached an overall survival of 8 months, ranging from 4 to 37 (Borne et al., 2010)

Similar results were reported also with cyclophosphamide combined with dendritic cell vaccine and a COX-2 inhibitor (Ellebaek et al., 2012).

A different trial showed a good tolerance using temozolamide in association with cisplatin; the combination resulted in an overall survival of 50 weeks (Simeone et al., 2009). Table 6 shows main toxicities reported with metronomic chemotherapy in patients with melanoma.

11. Metronomic chemotherapy in brain tumors

Glioblastoma is the most common malignant brain tumor. Standard therapy for glioblastoma includes surgery, radiotherapy and temozolamide. Few therapies are approved for recurrent disease and the prognosis is very poor.

A metronomic approach for glioblastoma can be useful, because low dose chemotherapy could be well tolerated in a very frail population.

Several clinical trials have studied the use of temozolamide, etoposide and cyclophosphamide which have the advantage of being manageable also in the outpatient setting, although no benefits in survival rate have been demonstrated (Kesari et al., 2007).

Temozolamide was safe with radiotherapy and the overall survival was about 7 months (Clarke et al., 2009); moreover, metronomic temozolamide was active for those patients who are refractory to standard cyclic treatment (Kong et al., 2010; Perry et al., 2010).

The addition of bevacizumab has conflicting results. Bevacizumab used with a low dose temozolamide schedule seems to get a worse response (Omuro et al., 2013)

There are suggestions that MeC and bevacizumab could be used with success (Peereboom et al., 2019)

In 2013 Chen conducted a metanalysis comparing metronomic and standard temozolamide regimens; no statistically significant difference was found between metronomic and standard schedules for response rate and no difference for overall survival at six and 12 months were reported (Chen et al., 2013).

In association with antinflammatory colecoxib, temozolamide had a very good safety profile without any G3/4 toxicity (Stockhammer et al., 2010).

In a different study with temozolamide and bevacizumab and etoposide, only 1 episode of G4 neutropenia was seen (Reardon et al., 2009; Reardon et al., 2011).

Zustovich et al. studied another tyrosine kinase inhibitor, sorafenib, twice daily with metronomic temozolamide; 6-month PFS was 26% and median OS was 7.4 months (Zustovich et al., 2013).

Table 7 shows main toxicities reported with metronomic chemotherapy in patients with brain tumors.

Table 6
Main toxicities reported with metronomic chemotherapy in patients with melanoma.

Author	Year	No. of patient	Drug	FN *N*	SAE *N* (worstevent)
Bhatt (Bhatt et al., 2010)	2010	20	Pacli-cel	0	d.n.r (mildtoxicity/ welltolerated); 4 evtherapyrelatedtoxicity G3/ 4)
Borne(Borne et al., 2010)	2010	13	CP	0	1 linfopenia
Ellebaek (Ellebaek et al., 2012)	2012	28	CP-IL2	0	0
Simeone (Simeone et al., 2009)	2016	33	TMZ-Cis	0	0

d.n.r: detailsnotreported; FN: febrile neutropenia; SAE: severe adverse event, defined as any grade 4 toxicity or treatment interrupted.

Table 7
Main toxicities reported with metronomic chemotherapy in patients with brain tumors.

Author	Year	No. of patient	Drug	FN *N*	SAE *N* (worst event)
Kesari (Kesari et al., 2007)	2007	48	CP-E	0	2 (costipation)
Clarke (Clarke et al., 2009)	2009	43	TMZ	0	0
Reardon (Reardon et al., 2009)	2009	59	E-Beva	0	0
Kong (Kong et al., 2010)	2010	38	TMZ	0	0
Stockhammer	2010	28	TMZ-Col	0	0
Reardon (Reardon et al., 2011)	2011	23	TMZ/ E-Bev	0	1 (neutropenia)
Omuro (Omuro et al., 2013)	2013	47	TMZ	0	1 (linfopenia, thrombocitopenia)
Zustovich (Zustovich et al., 2013)	2013	43	TMZ -SO	0	d.n.r (mild toxicity/well tolerated), 5 G3/4 Hand foot syndrome)
Welzel (Welzel et al., 2015)	2015	146	TMZ EBRT Col	0	0
Peereboom (Peereboom et al., 2019)	2019	11	Bev-cape	0	d.n.r (mild toxicity/well tolerated

GB: glioblastoma; CP: cyclophosphamide, TMZ: temozolamide; E: etoposide; Beva: bebavizumab; SO: sorafenib; Col: colecoxib; d.n.r: details not reported; FN: febrile neutropenia; SAE: severe adverse event, defined as any grade 4 toxicity or treatment interrupted.

12. Conclusions

Data reported so far have shown that oral metronomic regimens could be a reasonable treatment option in cancer patients. The low toxicity profile supports the chronic administration of the treatment especially in metastatic and pretreated patients and it could ensure the continuum of cancer care, preserving the prognosis of cancer patients also during COVID 19 pandemic. Low dose metronomic chemotherapy has a favorable safety profile and this reduces the need for hospitalization of cancer patients. This is particularly useful for prioritize hospital beds and care for those who are seriously ill with COVID-19.

Moreover, it represents a treatment option for the frail elderly. The frail elderly are often excluded from clinical trials, but they represent the majority of patients at risk of both cancer development and serious complications occurrence by Covid infection, if treated with a standard dose chemotherapy. Several studies demonstrate that metronomic therapy with different drugs and schedules is safe also in elderly patients. Safety is of the outmost importance in palliative situations. In general there was no life-threatening adverse event or major risk of infection with metronomic regimens.

For combination therapy it seems that adverse events were linked to other factors not related to metronomic therapy. To date the studies on this topic present some limits, the main ones being the small sample size and the retrospective design. In addition, inclusions criteria were based on clinical evaluation: dependence level, comorbidities and number of drugs taken. Thus, at present solid evidences on the role of MC in the different neoplasms are lacking.

Nonetheless, the results are encouraging for the use of metronomic drugs in a population presenting various poor prognosis factors, such as age, comorbidities, pre-treatment lymphopenia and unfitness for usual chemotherapy. The metronomic schema seems to be a good alternative treatment, because of its safety and easy oral taking, enabling patients to stay at home longer. Further prospective randomized studies are needed to confirm more accurately the efficacy of specific metronomic regimens.

Authors' contribution

Palma Fedele, Valeria Sanna: conceptualization, methodology, software. Palma Fedele, Valeria Sanna, Antonella Marino, Alessandro Fancellu: writing – original draft preparation. Saverio Cinieri, Nicola Calvani: visualization, supervision. Palma Fedele, Valeria Sanna: writing – reviewing and editing.

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Conflict of interest

The authors declare no conflict of interest related to this study. All authors declare no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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