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

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ARTICLE INFO

Keywords:
Metronomic chemotherapy
Cancer treatment
COVID 19
De-escalation
Safety

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
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 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 has 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 ≥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/m² twice daily for 14 of every 21 days), continuous MeC (650 mg/m² 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 overall 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 ≥ 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 ≥ 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/m² 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 ≤ 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 palmoplantar erythrodysaesthesia, 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 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 (Rocklitz 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 (Addo et al., 2010; Deiuliis 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 1 v Vinorelbine (60 mg/m² day 1, day 8 and day 15, every three weeks for the first cycle, hereafter 80 mg/m² day 1 and day 8, every four weeks for the following cycles) versus MeV at daily doses of 20 or 30 mg, depending on patient’s age and body surface (Langjker 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/m² 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 (ABCD study 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 thrombospordin-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/m²/day continuous dosing, arm B: 2510 mg/m²/day [2 weeks on, 1 week off] and arm C: an additional leucovorin-containing arm [capecitabine 1657 mg/m²/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/m²/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/m² orally twice a day for 3 weeks and bevacizumab 7.5 mg/m² 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, non-profit, multicenter MAMA 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
with a 2% partial response and 23% stable disease. Nineteen percent of
PFS. At a median follow-up of 47.8 months, 210 and 164 progression
oxaliplatin (65 mg/m² months. No grade 4 toxicity was observed (Romiti et al., 2015).
sistance 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 mainte-
nance 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 pa-
tients with mCRC showed good disease control and minimal toxicity
without impairment to quality of life. A study by Romiti et al. retro-
spectively 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/m²) and bevacizumab (7.5 mg/m²). 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 (Borgenovo et al., 2016).

Based on these data metronomic chemotherapy, especially capeci-
tabine, should probably be taken into major consideration as a reason-
able 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 avail-
ability of new anti-androgen 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 pro-
gressed 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 effi-
cacy 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).

Fee 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 (Fee 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% thrombocytopenia, 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 corticoste-
roids, diethylstilbestrol or celecoxib 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 naïve 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 chemo-
therapy 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 pharma-
cologic 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 anti-
inflammatory 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 cyclophos-
phamide 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
Main toxicities reported with metronomic chemotherapy in patients with prostate cancer.

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

(CP: cyclophosphamide; Estra: estramustina; L: lenalidomide; V: vinorelbine; E: etoposide; U: uracil; T: tegafur; DEX: dexamethasone; PD: prednisone; PL: prednisolone; 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 (Jedezko 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-fluorouracil and temozolomide have given similar results (Kerbel, 2007; Bhattacharyya et al., 2017).

MC with some antiangiogenic 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 metastatic 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; Sanchez-Munoz et al., 2010; Alvarez et al., 1999; Jurado et al., 2008; Chura et al., 2007).

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) |
|-------------------|------|----------------|----------|------|---------------------|
| Bellumt           | 2010 | 44             | Cape-Gem-Sor | 0 | 1 (PE) |
| Walter            | 2012 | 45             | Cape-IFN-Pi,Eto | 0 | 16 (Hand and foot Syndrome) |
| Tupikovsky        | 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.
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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 (NSCLC) 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 (Kontopoulos et al., 2013).

For NSCLC metronomic regimens were tested in first line treatment and for maintenance or salvage therapy. Recently, a well conducted metaanalysis 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 (Pujoil 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. Temozolomide was studied as MC in advanced stage NSCLC with brain metastases. The low dose temozolomide schedule reported a response rate of about 50% in association with RT (Adddeo et al., 2008).

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

Metronomic cyclophosphamide plus RT shows a significantly higher PFS clinical benefit as radiosensitizer in NSCLC 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 celecobix 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 4

Main toxicities reported with metronomic chemotherapy in lung cancer.

| Author                        | Year of patient | Drug     | FN N | SAE N (worst event) |
|-------------------------------|-----------------|----------|------|---------------------|
| Beck (Beck and Boyes, 1968)   | 1968            | CP       | 0    | N                  |
| Markman (Markman et al., 1992)| 1992            | E        | 0    | 2 (neutropenia)    |
| Chura (Chura et al., 2007)    | 2007            | CP-Beva  | 0    | 0                  |
| Garcia (Garcia et al., 2008)  | 2008            | CP-Beva  | 0    | 2 (leucopenia)     |
| Jurado (Jurado et al., 2008)  | 2008            | CP-Beva  | 0    | 0                  |
| Ferrandina (Ferrandina et al., 2014) | 2014 | CP    | 0 | 0 |
| Handolias (Handolias et al., 2016) | 2016 | CP | 0 | 2 (non-hematological) |
| Wong (Wong and Liu, 2017)     | 2017            | CP       | 0    | 0                  |
| Sharma (Sharma et al., 2019)  | 2019            | Pa-CP    | 0    | d.n.r (mild toxicity/well tolerated), 5 G3/4 mucositis |
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 weeks (Bhatt 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 temozolomide. 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 temozolomide, 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).

Temozolomide was safe with radiotherapy and the overall survival was about 7 months (Clarke et al., 2009); moreover, metronomic temozolomide 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 temozolomide schedule seems to get a worse response (Omuro et al., 2013).

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

In 2013 Chen conducted a metanalysis comparing metronomic and standard temozolomide 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 antiinflammatory celecoxib, temozolomide 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 temozolomide; 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 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., 2015) | 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: celecoxib; Erlo: erlotinib; d.n.r: details not reported; FN: febrile neutropenia; SAE: severe adverse event, defined as any grade 4 toxicity or treatment interrupted.

### Table 6

Main toxicities reported with metronomic chemotherapy in patients with melanoma.

| Author                  | Year | No. of patient | Drug | FN N | SAE N (worst event) |
|-------------------------|------|----------------|------|------|---------------------|
| Bhatt (Bhatt et al., 2010) | 2010 | 20             | Pacli- cell | 0 | d.n.r (mild toxicity/well tolerated); G4 evthypreibungofcoagulation |
| Borne (Borne et al., 2010) | 2010 | 13             | CP | 0 | 1 linopения |
| Ellebaek (Ellebaek et al., 2012) | 2012 | 28             | CP- IL2 | 0 | 0 |
| Simeone (Simeone et al., 2009) | 2016 | 33             | TMZ- Col- Cis | 0 | 0 |

d.n.r: details not reported; 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 neupenia |
| Omuro (Omuro et al., 2013) | 2013 | 47             | TMZ | 0 | 1 linopenia, thromboictopenia |
| Zustovich (Zustovich et al., 2013) | 2013 | 43             | TMZ- SO | 0 | 0 |
| Welzel (Welzel et al., 2015) | 2015 | 146            | TMZ- EBR- Col- Bev cape | 0 | 0 |
| Preereboom (Preereboom et al., 2019) | 2019 | 11             | TMZ- Col- Bev cape | 0 | 0 |

GB: glioblastoma; CP: cyclophosphamide, TMZ: temozolomide; E: etoposide; Beva: bevacizumab; SO: sorafenib; Col: celecoxib; 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 utmost importance in palliative situations. In general there was no life-threatening adverse event or major risk of infection with metronomic regimen.

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 inclusion, exclusions 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 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 Fanelli: writing – original draft preparation. Saverio Cinieri, Nicola Calvani: visualization, supervision. Palma Fedele, Valeria Sanna: writing – reviewing and editing.

Funding

None.

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.

Acknowledgement

We thank Antonio Guadalupe for his assistance with the manuscript.

References

Adddeo, R., De Rosa, C., Faio, V., et al., 2008. Phase 2 trial of temozolomide using protracted low-dose and whole-brain radiotherapy for non-small cell lung cancer and breast cancer patients with brain metastases. Cancer 113 (9), 2524–2531.
Adddeo, R., Sgambato, A., Cennamo, G., et al., 2010. Low-dose metronomic oral administration of vinorelbine in the first-line treatment of elderly patients with metastatic breast cancer. Clin. Breast Cancer 10, 301–306.
Alagizi, H.A., Shehata, M.A., Hashem, T.A., et al., 2015. Metronomic capcitabine as extended adjuvant chemotherapy in women with triple negative breast cancer. Hematol. Oncol. Stem Cell Ther. 8, 22–27.
Alvarez, A.A., Krigman, H.R., Whitaker, R.S., et al., 1999. The prognostic significance of angiogenesis in epithelial ovarian carcinoma. Clin. Cancer Res. 5 (3), 587–591.
Aurilio, G., Munzone, E., Bottieri, E., et al., 2012. Oral metronomic cyclophosphamide and methotrexate plus fulvestrant in advanced breast cancer patients: a mono-institutional case-cohort report. Breast J. 18 (5), 470–474.
Banna, G., Anile, G., Castaing, M., et al., 2017. Palliative chemotherapy with oral metronomic vinorelbine in advanced non-small cell lung cancer (NSCLC) patients unsuitable for chemotherapy. J. Thorac. Oncol. 12, S907–S908.
Barrosso-Souza, R., da Fonseca, L.G., Souza, K.T., et al., 2015. Metronomic oral cyclophosphamide plus prednisone in docetaxel pretreated patients with metastatic castration-resistant prostate cancer. Med. Oncol. 32, 443–444.
Beck, R.E., Boyes, D.A., 1968. Treatment of 126 cases of advanced ovarian carcinoma with cyclophosphamide. Can. Med. Assoc. J. 98 (11), 539–541.
Bellmunt, J., Trigo, J.M., Calvo, E., et al., 2010. Activity of a multitargeted chemo-switch regimen (sorafenib, gemcitabine, and metronomic capcitabine) in metastatic renal cell carcinoma: a phase 2 study (SOGUG-02-06). Lancet Oncol. 11 (4), 350–357.
Bhatt, R.S., Merchant, J., Parker, R., et al., 2010. A phase 2 pilot trial of low-dose, continuous infusion, or ‘metronomic’ paclitaxel and oral celecoxib in patients with metastatic melanoma. Cancer 116 (7), 1751–1756.
Bhattacharyya, G.S., Malhotra, H., Parikh, P.M., et al., 2017. Phase II study of metronomic cyclophosphamide and temozolomide in platinum resistance ovarian cancer. ASCO Annual Meeting Proceedings. J. Clin. Oncol. 33 (15S), e16575.
Bilir, C., Durak, S., Kizilkaya, B., et al., 2017. Efficacy of metronomic vinorelbine in elderly patients with advanced non-small cell lung cancer and poor performance status. Curr. Oncol. 24, e199–e204.
Borgonovo, K.F., Petrelli, F., Cabiddu, M., et al., 2016. Mono-institutional retrospective analysis of metronomic cyclophosphamide (MC) schedule in the treatment of metastatic colorectal cancer European Society for Medical Oncology Congress Proceedings. Ann. Oncol. 27 (4S), D48.
Borne, E., Desmedt, E., Duhamel, A., et al., 2010. Oral metronomic cyclophosphamide in patients with metastatic melanoma. Investig. New Drugs 28, 684–689.
Bracarda, S., Tomato, M., Rosi, P., et al., 2000. Oral estramustine and cyclophosphamide in patients with metastatic hormone refractory prostate carcinoma: a phase II study. Cancer 88, 1438–1444.
Budman, D.R., Moropol, N.J., Reigner, B., et al., 1998. Preliminary studies of a novel oral fluoropyrimidine carbamate: capecitabine. J. Clin. Oncol. 16, 1795–1802.
Caffo, O., Facchini, G., Bisaccio, E., et al., 2019. Activity and safety of metronomic cyclophosphamide in the modern era of metastatic castration-resistant prostate cancer. Future Oncol. 15 (10), 1115–1123.
Calcagno, F., Mouillet, G., Adotevi, O., et al., 2016. Metronomic cyclophosphamide therapy in hormone-naive patients without-metastatic biochemical recurrent prostate cancer: a phase II trial. Med. Oncol. 33, 8.
Calvan iN, Morelli, F., Naglieri, E., 2019. Metronomic chemotherapy with cyclophosphamide plus low dose of corticosteroids in advanced castration-resistant prostate cancer across the era of taxanes and new hormonal drugs. Med. Oncol. 36 (9), 80.
Camerini, A., Puccetti, C., Donati, S., et al., 2015. Metronomic oral vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer: results of a phase II trial (MOVE trial). BMC Cancer 15, 1–6.
Carrozza, Bellomo, I.U., Pernici, F.M., et al., 2013. Metronomic (M), capcitabine (C), and oxaliplatin (O) plus bevacizumab (B) as treatment of advanced colorectal cancer (ACRC) in very elderly people (M-COB: efficacy and safety (E&S) evaluation-A 2-year monitoring. ASCO Annual Meeting Proceedings. J. Clin. Oncol. 29 (15S), S986–S986.
Cazzaniga, M.E., Torri, V., Villa, F., et al., 2014. Efficacy and safety of the all-oral schedule of metronomic vinorelbine and capcitabine in locally advanced or metastatic breast cancer patients: the Phase I-II VICTOR-1 Study. Int. J. Breast Cancer 769–790.
Cazzaniga, M.E., Cortesi, L., Ferzi, A., et al., 2016. Metronomic chemotherapy with oral vinorelbine (mVNR) and capcitabine (mCAPE) in advanced HER2-negative breast cancer patients: is it a way to optimize disease control? Final results of the VICTOR-2 study, Breast Cancer Res. Treat. 160 (3), 501–506.
Chen, C., Xu, T., Lu, Y., et al., 2013. The efficacy of temozolomide for recurrent glioblastoma multiforme. Eur. J. Neurol. 20, 223–230.
Chu, J.C., Iseghem, K., Van, Downs, L.S., et al., 2007. Bevacizumab plus cyclophosphamide in hormone-refractory patients treated with recurrent ovarian cancer. Gynecol. Oncol. 107 (2), 326–330.
Clarke, J.L., Iwamoto, F.M., Sul, J., et al., 2009. Randomized phase II trial of chemoradiation followed by either dose-dense metronomic temozolomide for newly diagnosed glioblastoma. J. Clin. Oncol. 27 (23), 3861–3867.
Colleoni, M., Rocca, A., Sandri, M.T., et al., 2002. Low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer: antitumor activity and correlation with vascular endothelial growth factor levels. Ann. Oncol. 13, 73–80.
Colleoni, M., Orlando, L., Sanna, G., et al., 2006. A Metronomic low-dose oral cyclophosphamide and methotrexate plus or minus thalidomide in metastatic breast cancer: antitumor activity and biological effects. Ann. Oncol. 17, 232–238.
Colleoni, M., Gray, K.P., Gelber, S., et al., 2016. Low-dose oral cyclophosphamide and methotrexate maintenance for hormone receptor-negative early breast cancer: the International Breast Cancer Study Group Trial 22-00. J. Clin. Oncol. 34 (28), 3400–3408.
Corrado, P., Cerretani, D., Remondo, C., et al., 2006. A novel metronomic chemotherapy regimen of weekly platinumb and daily oral etoposide in high-risk non-small cell lung cancer patients. Oncol. Rep. 16, 133–140.
Jeong, Y., Lee, J.L., 2017. Efficacy of metronomic oral cyclophosphamide with low dose Jurado, J.M., Sanchez, A., Pajares, B., et al., 2008. Combined oral cyclophosphamide and Jellvert, A., Lissbrant, I.F., Edgren, M., et al., 2011. Effective oral combination Jedeszko, C., Paez-Ribes, M., Di Desidero, T., et al., 2015. Postsurgical adjuvant or Hashimoto, K., Man, S., Xu, et al., 2010. Potent preclinical impact of metronomic low- Ferrandina, G., Corrado, G., Mascilini, F., et al., 2014. Metronomic oral Dabkara, D., Ganguly, S., Ghosh, J., et al., 2018. Metronomic cyclophosphamide in Juri, D., Krohe, M., Mazar, I., et al., 2016. Patient-reported preferences for oral versus Garcia-Saenz, J.A., Martin, M., Calles, A., et al., 2008. Bevacizumab in combinationwith Derosa, L., Galli, L., Orlandi, P., et al., 2014. Docetaxel plus oral metronomic metronomic chemotherapy with bevacizumab in hormone-refractory prostate cancer. Br. J. Cancer 104, 1822-1827. Kontopidis, E., Hatzidaki, D., Varthalitis, et al., 2013. A phase II study of metronomic oral vinorelbine administered in the second line and beyond in non-small cell lung cancer (NSCLC): a phase II study of the helicent oncology research group. J. Chemother. 25, 49–55. Kouroussis, C., Yamvakas, L., Vardakis, N., et al., 2009. Continuous administration of low-dose metronomic temozolomide in pre-treated patients with advanced small-cell lung cancer: a phase II study. Oncology 72 (6), 112–117. Kucukoner, M., Isikdogan, A., Yaman, S., et al., 2012. Oral etoposide for platinum-resistant and recurrent epithelial ovarian cancer: a study by the anatolian society of medical oncology. Asian Pac. J. Cancer Prev. 13, 3973–3976. Lee, S., Eymard, J.C., Zeng, W., et al., 2009. Docetaxel plus oral metronomic prednisolone chemoprevention is an effective treatment for metastatic hormone-refractory prostate cancer after docetaxel failure. Anticancer Res. 30, 4317–4323. Lamberti, M., Toss, A., Passaro, A., et al., 2020. Cancer care during the spread of coronavirus disease 2019 (COVID-19) in Italy: a pathway from perspective. ESMO Open 5 (2). https://doi.org/10.1136/esmoopen-2020-000759. Langkjer, S.T., Kenholm, J., Jensen Dupont, J., et al., 2019. The NAME trial: a direct comparison of classical oral Navelbine versus Metronomic Navelbine in metastatic breast cancer. Future Oncol. 15 (22), 2561–2570. Liang, W., Guan, W., Chen, R., et al., 2020. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 21 (3), 335–337. Lokich, J., 2004. Capcitabine: fixed daily dose and continuous (nonycyclic) dosing. Lancet 207, 1717. Lord, R., Nair, S., Schache, A., et al., 2007. Low dose metronomic oral cyclophosphamide for hormone resistant prostate cancer: a phase II study. J. Urol. 177, 2136–2140. Metronomic Chemotherapy of Catecholamine after Standard Adjuvant Chemotherapy in Operable Triple Negative Breast Cancer (MACRO). ClinicalTrials.gov identifier: NCT02012634. Markman, M., Hakes, T., Reichman, B., et al., 1992. Phase 2 trial of chronic low-dose oral etoposide as salvage therapy of platinum refractory ovarian cancer. J. Cancer Res. Clin. Oncol. 119, 55–57. Maulard-Durzicz, D., Cufour, B., Hennquin, C., et al., 1996. Phase II study of the oral cyclophosphamide and oral etoposide combination in hormone refractory prostate cancer patients. Cancer 77, 1138–1148. Mayer, E.L., Inkoff, S.J., Klement, G., et al., 2012. Combination antiangiogenic therapy in advanced breast cancer: a phase 1 trial of vandetanib, a VEGFR inhibitor, and metronomic chemotherapy, with correlative platelet proteomics. Breast Cancer Res. Treat. 136, 169–179. Mayer, E.L., Liggibl, J.A., Burstien, H.J., 2016. TRBCR 0122. ABCDE, a phase II randomized study of oral bevacizumab, metronomic chemotherapy (CM), diet and exercise as preparative chemotherapy for breast cancer. ASCO Annual Meeting Proceedings. J. Clin. Oncol. 28 (15), 103. Mencoboni, M., Filiberti, R.A., Tavegga, P., et al., 2017. Safety of first-line chemotherapy with metronomic single-agent oral vinorelbine in elderly patients with NSCLC. Anticancer Res. 37 (6), 3189–3194. Meng, L.J., Wang, J., Fan, W., et al., 2012. Evaluation of oral chemotherapy with capcitabine and cyclophosphamide plusplasidomide and prednisone in prostate cancer patients. J. Cancer Res. Clin. Oncol. 138, 333–339. Metronomic Treatment Option in Advanced BreastAner (METOEA-II). ClinicalTrials. Identifier: NCT02095075. Montagna, E., Bagnardi, V, Cancello, G., et al., 2018. Metronomic chemotherapy for first-line treatment of metastatic triple-negative breast cancer: a phase II trial. Breast Care 13 (3), 177–181. Muraki, C., Ohga, N., Hida, Y., et al., 2012. Cyclooxygenase-2 inhibition causes antiangiogenic effects on tumor endothelial and vascular progenitor cells. Int. J. Cancer. 130, 59–70. Nair, O.A., Oman, M., Elkady, M.S., et al., 2015. Metronomic methotrexate and cyclophosphamide after carboplatin included adjuvant chemotherapy in triple negative breast cancer: a phase III study. Ann. Transl. Med. 3, 284. Nelson, T., Klatte, T., De Riese, W., et al., 2010. Clinical outcome of patients with metastatic hormone-refractory prostate cancer treated with second-line metronomic chemotherapy-based metronomic chemotherapy. Med. Oncol. 27 (2), 363–367.
COVID-19 rapid guideline: delivery of systemic anticancer treatments NICE guideline, 2020. https://www.nice.org.uk/guidance/ng161 (Accessed 20 March 2020).

Nishihara, K., Nonomura, N., Ovu, Y., et al., 2001. Oral 22-nitrohinolone of cyclophosphamide, uracil plus tegafur and estramustine for hormone-refractory prostate cancer. Oncology 60, 49–54.

Noronha, V., Joshi, A., Marfatia, S., et al., 2016. Health-related quality of life in patients with metastatic, non-small cell inoperable squamous cell carcinoma of the head and neck in India. Support Care Cancer 24, 1595–1602.

Omuro, A., Chan, A., Abrey, L.E., et al., 2013. Phase II trial of continuous low-dose temozolomide for patients with recurrent malignant glioma. Neuro-oncology 15 (2), 242–250.

Ontario Health, Cancer Care Ontario, 2020. Pandemic Planning Clinical Guideline for Patients with Cancer. https://www.accn-cancer.org/docs/document/cancer-progr

Patel, V.M., Noronha, V., Joshi, A., et al., 2015. Metronomic chemotherapy in platinum-non-squamous lung cancer: a randomized phase II trial of cisplatin, docetaxel and bevacizumab vs cisplatin, docetaxel, and bevacizumab plus oral metronomic etoposide and bevacizumab (mPEBev). Oncotarget 8 (44), 79504–79519.

Patt, V.M., Noronha, V., Joshi, A., et al., 2015. Metronomic chemotherapy in platinum-resistant failures and/or early failures postmodality management in oral cancers. Indian J. Med. Paediatr. Oncol. 36, 161–165.

Patt, V.M., Noronha, V., Joshi, A., et al., 2019. Phase II I/II study of palliative triple metronomic chemotherapy in platinum refractory oral cancer. J. Clin. Oncol. 37 (32), 3032–3041.

Peereboom, D.M., Alban, T.J., Grabowski, M.M., et al., 2019. Metronomic capecitabine as an immune modulator in glioblastoma patients reduces myeloid-derived suppressor cells. JCI Insight 4 (22), 1–15.

Perry, J.R., Belanger, K., Mason, W.P., et al., 2010. Phase II trial of continuous dose-prednisone in the treatment of hormone-refractory metastatic prostate cancer. J. Med. Oncol. 3, 54.

Perea, A., Vignat, D., Eolin, V., et al., 2016. Chemotherapy in frail elderly patients with advanced oral squamous cell cancers: a matched-pair analysis. Indian J. Cancer 50 (15s), 618.

Pai, P.S., Vaidya, A.D., Prabhash, K., et al., 2013. Oral metronomic scheduling of anticancer therapy-based treatment compared to existing standard of care in locally advanced oral squamous cell cancers: a matched pair analysis. Indian J. Cancer 50 (2), 135–141.

Paney, A., Abbay, D., Sunny, J., et al., 2016a. Outcomes of advanced epithelial ovarian cancer with integration of metronomic chemotherapy: an Indian ovarian cancer centre experience. South Asian J. Cancer 5, 54.

Paney, A., Desai, A., Ostwal, V., et al., 2016b. Outcome of operable oral cavity cancer and impact of maintenance metronomic chemotherapy: a retrospective study from rural India. South Asian J. Cancer 5, 52–55.

Patini, J., Fratoni, S., Balec, C., et al., 2018. Oral Metronomic Vinorelbine (OMV) in elderly or pretreated patients with advanced non small cell lung cancer: outcome and pharmacokinetics in the real world. Invest. New Drugs 36 (5), 927–932.

Pastina, P., Nardone, V., Botta, C., et al., 2017. Radiotherapy prolongs the survival of advanced non-small cell lung cancer patients undergone to an immune-modulating treatment with dose-fractioned cisplatin and metronomic etoposide and bevacizumab (m-PEBVE). Oncotarget 8 (44), 75904–75913.

Patil, V.M., Noronha, V., Joshi, A., et al., 2015. Metronomic chemotherapy in platinum-resistant failures and/or early failures postmodality management in oral cancers. Indian J. Med. Paediatr. Oncol. 36, 161–165.

Patil, V.M., Noronha, V., Joshi, A., et al., 2019. Phase II I/II study of palliative triple metronomic chemotherapy in platinum refractory oral cancer. J. Clin. Oncol. 37 (32), 3032–3041.

Pujol, J.L., Pujol, C., Camerini, A., et al., 2019. An individual patient data meta-analysis of metronomic oral Vinorelbine in metastatic non small cell lung cancer. PLOS ONE 14 (8), e0220988.

Reardon, D.A., Desjardins, A., Vredenburgh, J.J., et al., 2009. Metronomic chemotherapy with daily, oral etoposide plus bevacizumab for recurrent malignant gliomas: a Phase II study. J. Neuro-Oncol. 101 (12), 1893–1994.

Reardon, D.A., Desjardins, A., Peters, K., et al., 2011. Phase II study of metronomic chemotherapy with bevacizumab for recurrent glioblastoma after progression on bevacizumab therapy. J. Neuro-Oncol. 103, 371–379.

Revenant-Reid, S., Agra, D., Pandey, R.C., et al., 2003. The results with the addition of metronomic cyclophosphamide to palliative radiotherapy for the treatment of non-small cell lung carcinoma. Ann. Transl. Med. 3 (20), 1–7.

Robles, C., Furst, A.J., Sriratana, P., et al., 2015. Continuous, low-dosecapcitabine for patients with recurrent colorectal cancer. Med. Oncol. 32, 54.

Romi, A., Falcone, R., Roberto, M., et al., 2017. Current achievements and future perspectives of metronomic chemotherapy. Invest. New Drugs 35 (3), 359–374.

Salem, D.A., Gado, N.M., Abdelaziz, N.N., et al., 2008. Phase II trial of metronomic chemotherapy as salvage therapy for patients with metastatic breast cancer. J. Egypt Natl. Cancer Inst. 20, 134–140.
metastatic castration resistant prostate cancer: a prospective analysis of consecutive cases. Clin. Genitourinary Cancer 12 (5), e197-e203.
Yoshimoto, M., Takao, S., Hirata, M., et al., 2012. Metronomic oral combination chemotherapy with capecitabine and cyclophosphamide: a phase II study in patients with HER2-negative metastatic breast cancer. Cancer Chemother. Pharmacol. 70, 331–338.

You, B., Ravaud, A., Canivet, A., et al., 2020. The official French guidelines to protect patients with cancer against SARS-CoV-2 infection. Lancet Oncol. S1470-2045(20): 30204-7.
Zustovich, F., Landi, L., Lombardi, G., et al., 2013. Sorafenib plus daily low-dose temozolomide for relapsed glioblastoma: a phase II study. Anticancer Res. 33 (8), 3487-3494.