Indian J Hematol Blood Transfus (Jan-Mar 2019) 35(1):50–56
https://doi.org/10.1007/s12288-018-0995-0

ORIGINAL ARTICLE

Outcomes of Oral Metronomic Therapy in Patients with Lymphomas

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Received: 4 May 2018 / Accepted: 21 July 2018 / Published online: 2 August 2018

Abstract Oral Metronomic chemotherapy (OMC) is used in patients with lymphoma who may not tolerate intravenous chemotherapy or have refractory disease. It is cheaper, less toxic and easy to administer. Adult patients with lymphoma who received OMC (combination of cyclophosphamide, etoposide and prednisolone) were included in this retrospective analysis. Response assessment was clinical with limited use of radiology. Progression free and overall survival (PFS and OS) were calculated from the time of start of OMC until documentation of disease progression or death. Between 2007 and 2017, 149 patients were given OMC [median age: 62 years (19–87); 94 patients (63.1%) male]. Majority [112 patients (75.2%)] had stage III/IV disease. The most common subtype of lymphoma was diffuse large B cell lymphoma (40.9%). OMC was used at diagnosis in 41 patients (27.5%) and after relapse in 108 patients (72.5%). Overall response rates were 43.9 and 41.7% with clinical CR in 14 (34.1%) and 21 (19.4%) in patients given first line and later lines of OMC respectively. After a median follow up of 12 months (range 1–123 months), median PFS and OS were 10.5 (95% CI 8.6–12.5) and 18.8 (95% CI 12.1–25.5) months respectively. PFS and OS at 12 months were 47.6 and 64.2% respectively. Though OMC is used in many centers in India, there is scanty published information on its efficacy in lymphoma. In this analysis, we demonstrate its activity in a subset of patients with predominantly high-grade and advanced stage NHL. OMC is a useful option in frail patients and a small proportion can achieve deep and long lasting responses.

Keywords Oral metronomic chemotherapy · Lymphoma · Survival · Diffuse large B cell lymphoma · Outcomes

Introduction

Metronomic chemotherapy (MC) is the chronic administration of chemotherapy at low, minimally toxic doses with no prolonged drug-free intervals [1]. Metronomic chemotherapy acts through anti-angiogenic and immunomodulatory effects leading to tumor dormancy and immune mediated eradication of cancer cells [2, 3]. Metronomic treatment is cost-effective, has low rate of complications and may help to palliate symptoms in patients with advanced disease [3, 4]. Most MC protocols prefer orally administered (OMC) medications due to ease of administration, especially in patients treated with palliative intent.

OMC has been tried in multiple tumor types like metastatic breast cancer, advanced hepatocellular carcinoma, metastatic prostate cancer and soft tissue sarcomas with varying results [5–8]. Excellent responses have been noted in lymphomas, especially indolent non-Hodgkin's lymphomas (NHL) [9, 10].Though there are multiple treatment options for relapsed lymphomas, their usage is limited due to considerations of availability, affordability and patient's fitness to withstand some of the intensive drugs. OMC becomes relevant in resource-challenged situations and when patient is unfit for intensive intravenous medications due to age, comorbidities or persistent effects of previous therapies [4].We report our experience with the use of OMC in lymphomas. In contrast to the available

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literature, our experience consists predominantly of patients with aggressive subtypes of NHL.

Methods

Adult patients with a histologically confirmed diagnosis of lymphoma who received OMC with etoposide, cyclophosphamide and prednisolone between 2007 and 2017 were included in this retrospective analysis. The details of clinical presentation, pathological subtype, blood investigations, indications for oral metronomic chemotherapy and patient status at follow up were retrieved from the patient records. Staging of disease was performed with contrast enhanced CT scans (CECT) of the chest and abdomen in most cases. A few patients were staged with chest X-ray and ultrasound of the abdomen and pelvis. All patients underwent bone marrow (BM) studies at baseline. In patients who relapsed and received OMC as second treatment or later, the details of the prior treatment were captured.

Schedule of OMC and Follow Up

OMC regimen at our center consisted of cyclophosphamide 50 mg BD for 14–21 days per cycle, etoposide 50 mg OD (afternoon) for 7–14 days, and Prednisolone 20 mg BD for 10–14 days. Cycles were repeated Q 3–4 weekly. Patients usually started with a shorter duration of medications and doses were escalated depending on tolerance. Similarly, duration of cycles was adjusted as three- or four-weekly depending on individual patient's tolerance and convenience. The dosage adjustment was carried out as per the treating oncologists' discretion. OMC was continued till progression of disease, stopped when palliation was achieved or according to patient choice. Patients were followed up in the outpatient clinic before each cycle and a complete hemogram was performed before starting the next cycle to ensure that the white cell counts were above 4000/cmm and platelet counts were above 100,000/cmm (unless they were low due to disease involvement of the BM, in which case OMC was continued as per the discretion of the treating oncologist).

Response Evaluation and Analysis

As OMC was largely a palliative measure, the assessment of response was not stringent. Responses were assessed by clinical evaluation (prior to each cycle) and use of radiology was limited to the rare patient with pure intra-abdominal disease. Complete response (CR) was documented when there was disappearance of all clinical and radiologically assessable disease as well as marrow negativity if it was involved earlier. Since exact radiological measurements were not available for most patients, all patients who had documented reduction in size of lymph nodes were considered as having partial response (PR) while documented increases were considered progressive disease (PD). Progression free survival (PFS) was calculated from the date of start of treatment till progression of disease or death and overall survival (OS) was calculated from the date of start of treatment till death due to any cause. Patients who were lost to follow up were actively contacted by phone calls or by letters through the tumor registry to ascertain their status (wherever possible). Our institute has a very robust system of tracking lost to follow up patients; hence the status of patients (whether alive or dead) is known for majority of the patients even when the patients are lost to follow up from the clinic. Follow up data was censored in December 2017. Actuarial probability of survival was estimated using the Kaplan–Meier method and baseline parameters compared using log rank test using SPSS version 13.0 (IBM inc.)

Results

We identified 172 adult patients with lymphoma who were prescribed OMC between January 2007 and November 2017. Of these, 23 patients had not come for follow up after receiving the prescription; no data is available regarding their response or outcomes and they were excluded from analysis (Fig. 1). One hundred and forty-nine patients were evaluable [median age at diagnosis: 62 years (19–87); 94 patients (63.1%) were male] (Table 1). Sixty-seven patients (45%) had ECOG PS $\geq$ 2 at baseline and 112 patients (75.2%) had stage III/IV disease. The most common subtype of lymphoma was diffuse large B cell lymphoma (DLBCL, N = 61, 40.9%) followed by other high-grade lymphomas (N = 49, 32.9%), low-grade lymphomas (N = 21, 14.1%) and Hodgkin's lymphoma (N = 18, 12.1%).

Treatment and Outcomes

OMC was used as the initial therapy (at diagnosis) in 41/149 (27.5%), second line therapy in 74/149 (49.7%), third line therapy in 22/149 (14.8%) patients and later lines (fourth line in 4 patients, fifth line in 7 patients and eighth line in one patient) in 12 patients (8.1%). Seven patients had undergone prior high dose chemotherapy with stem cell rescue. The indications for using OMC as first-line treatment were older age (N = 24/41, 58.5%) followed by poor performance status (12/41 patients, 29.2%) and HIV infection (5/41 patients, 12.2%). The indications for starting later-lines of OMC were poor performance status in

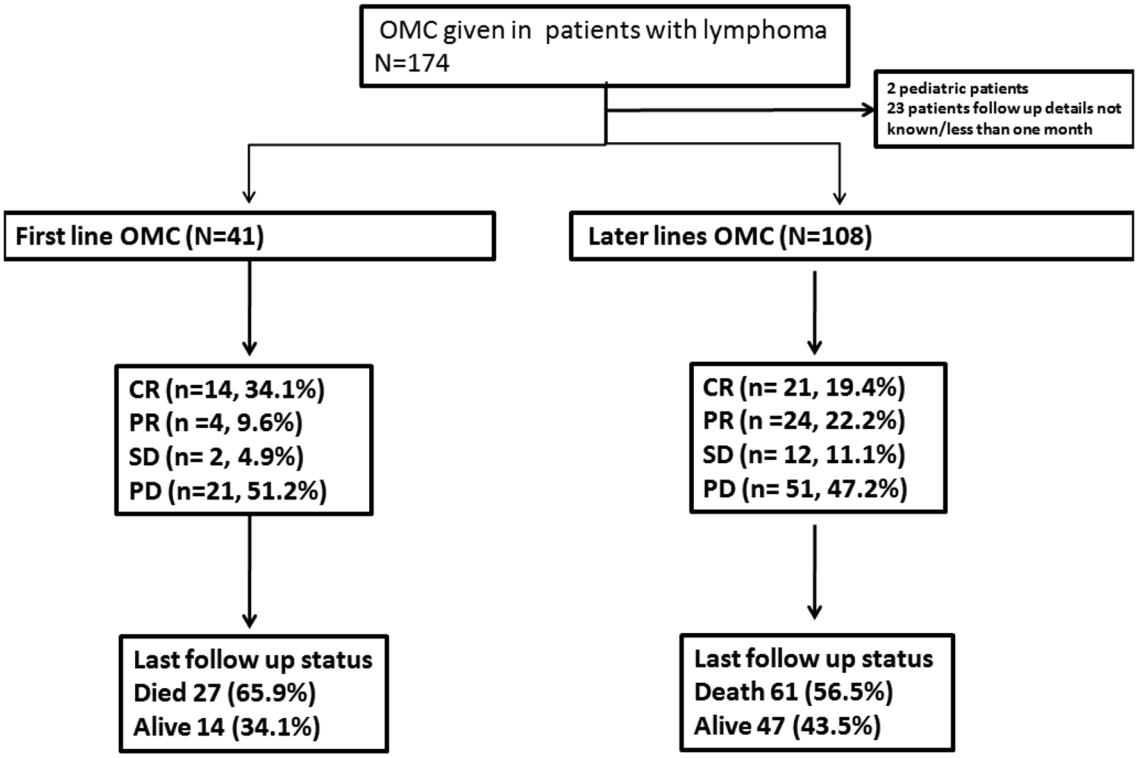

Fig. 1 Flow chart depicting the patient inclusion and outcomes

58/108 patients and treatment toxicity or unwillingness to continue intravenous therapy in 50/108 patients. Median duration of treatment was 6.1 months (1–49 months). OMC was stopped in 72 (48.3%) patients due to progressive disease. In the remaining patients, it was stopped due to achievement of good response/disease stability, patient desired treatment break or default from therapy. Since doses were reduced for side-effects, OMC was discontinued specifically for toxicity only in 3 patients. Median duration of follow up was 12 months (1–123 months). The chemotherapeutic regimens used at diagnosis in patients who were given OMC as 2nd line or later are detailed in Table 2.

Response Rates

Overall response rates (CR + PR) with OMC were 43.9% (first-line) and 41.7% (later-lines) (Fig. 1). Clinical CR was attained in fourteen patients (34.1%) who had OMC as initial therapy and 21 patients (19.4%) who had OMC after relapse.

Survival Outcomes

After a median follow up of 12 months (range 1–123 months), median PFS was 10.5 months (95% CI 8.6–12.5) and median OS was 18.8 months (95% CI 12.1–25.5) (Fig. 2). Median PFS was similar for first and second line use of OMC [10.3 (5.9–14.8) months vs. 12.1 (9.9–14.2) months, $p = 0.668$, NS]. PFS at 12 months was 47.6% (n = 149); 43.3 and 48.9% for first and later lines of OMC respectively. OS at 12 months was 64.2% (n = 149); 62.9% for first line and 64.9% for later lines of OMC. Factors associated with OS are shown in Table 3. At last follow up, 61 patients (40.9%) patients were alive.

Toxicity

Since this was a retrospective analysis among patients treated with palliative intent, it was not possible to reliably capture lower grades of toxicities. Further, treatment was usually started at a lower dose and adjusted depending on tolerance. Hence, the therapy was well tolerated for the most part. Only 3 patients discontinued OMC due to side effects. Of the 28 patients (18.8%) patients who developed significant side effects; 13 patients had asymptomatic drop in the blood counts, 8 patients had infectious complications, 7 patients had other complications including mucositis in 4 patients, skin rash in one patient, anorexia and fatigue in one patient and hemorrhagic cystitis in one patient.

Table 1 Baseline characteristics (at time of diagnosis) of patients prescribed OMC

Baseline characteristic	All patients (N = 149)	1st line OMC (N = 41)	≥ 2nd line (N = 108)
Age[a] (years)	62 (19–87)	72 (32–87)	58.5 (19–77)
Male sex	94 (63.1%)	25 (60.9%)	69 (63.9%)
ECOG PS			
0/1	82 (55%)	14 (34.1%)	68 (63%)
≥ 2	67 (45%)	27 (65.9%)	40 (37%)
Stage of disease			
1	10 (6.7%)	5 (12.2%)	5 (4.6%)
2	27 (18.1%)	10 (24.4%)	17 (15.7%)
3	40 (26.8%)	10 (24.4%)	30 (27.8%)
4	72 (48.3%)	16 (39%)	56 (51.9%)
Hemoglobin[a] (g/dL)	11 (5.5–15)	11 (6–15)	11 (5.5–16.5)
WBC (/cmm)[a]	8200 (1900–56,800)	7300 (3600–28,000)	8500 (1900–56,800)
Platelet count[a] (× 100,000/mm)^3	2.54 (0.19–7.4)	2.52 (0.5–5.9)	2.56 (0.19–7.4)
Albumin[a] (g/dl) (N = 56)	3.2 (1.4–5.2)	3.05 (1.4–4.1)	3.25 (1.6–5.2)
LDH (U/L)[a] (N = 65)	702 (169–3221)	848 (187–2920)	687 (169–3221)
Type of lymphoma			
DLBCL	61 (40.9%)	16 (39.0%)	45 (41.7%)
High grade[b]	49 (32.9%)	17 (41.5%)	32 (29.6%)
Low grade[c]	21 (14.1%)	6 (14.6%)	15 (13.9%)
Hodgkins lymphoma	18 (12.1%)	2 (4.9%)	16 (14.8%)

[a]Data presented as median (range); other data presented as N (%)

[b]Unspecified subtype high grade B lymphoma (N = 25), PTCL (N = 11), Follicular lymphoma high grade (N = 3), anaplastic large cell lymphoma (N = 4), Burkitt's lymphoma (N = 2), NK/T cell lymphoma (N = 3), Hepatosplenic T cell lymphoma (N = 1)

[c]Follicular lymphoma (N = 6), Low grade NHL NOS (N = 9), SLL (N = 5), CTCL (N = 1)

Table 2 Chemotherapy regimens used in the initial treatment of patients

Regimen used	No of patients (percentage) N = 108
CHOP	22 (20.4)
R CHOP	33 (30.6)
COP	13 (12)
R COP	13 (12)
ABVD/AVD	12 (11.1)
BR or BOP	9 (8.3)
CEOP	3 (2.8)
COPP	1 (0.9)
MACOP B	1 (0.9)
VIPD	1 (0.9)

CHOP cyclophosphamide, doxorubicin, vincristine and prednisolone, *R CHOP* Rituximab CHOP, *COP* cyclophosphamide, vincristine and prednisolone, *COPP* COP and procarbazine, *BR* bendamustine rituximab, *BOP* bendamustine, vincristine and prednisolone, *ABVD or AVD* adriamycin, bleomycin, vinblastine and dacarbazine, *CEOP* etoposide replacing doxorubicin in CHOP, *MACOP B* methotrexate, adriamycin, cyclophosphamide, vincristine, prednisolone and bleomycin, *VIPD* etoposide, ifosphamide, cisplatin and dexamethasone

Discussion

Oral low-dose chemotherapy was effective in lymphomas and produced a response rate of 42.3% including 34.3% CR when used as first line therapy in patients unfit to receive standard chemotherapy. Even among those with relapsed aggressive lymphomas, the response rate was over 40% with 65% being alive at the end of 1 year. A tailored regimen with a careful escalation and de-escalation strategy with scheduled short treatment breaks yielded a patient friendly treatment with minimal toxicity. We believe that this is one of the first reports on the use of OMC as the initial therapy in unfit patients with lymphoma.

There are very few studies that have evaluated OMC in aggressive lymphomas like DLBCL and PTCL. In heavily pre-treated patients, a study with 35 patients described a response rate of 37% with 22% stable disease rate and a median OS of 14.4 months [11]. Similar response rates (33%) were described in the subset of patients with aggressive NHL in another paper [9]. These studies used a continuous schedule of cyclophosphamide, etoposide, prednisolone and procarbazine (PEPC). Also, OMC was not used in treatment naïve patients in the other studies.

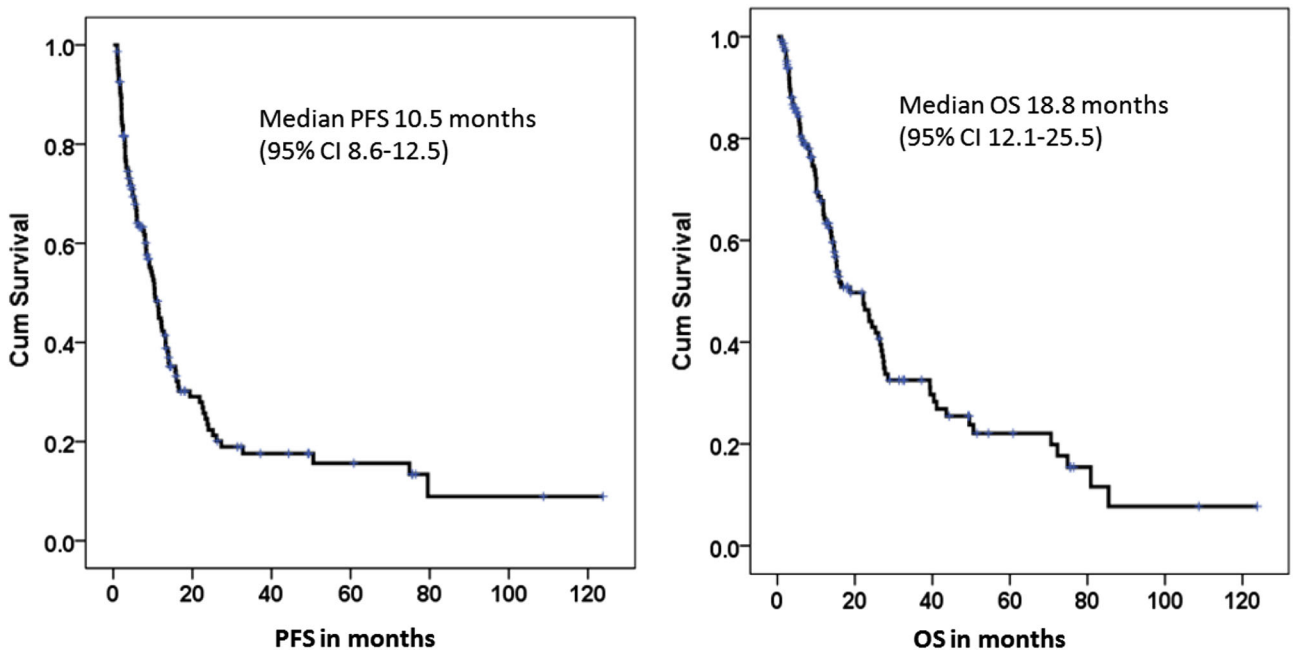

Fig. 2 Progression free (PFS) and overall survival (OS) with oral metronomic chemotherapy in lymphomas

Table 3 Factors associated with OS on univariate analysis

Parameter	N	Median OS in months (95% CI)	*p* value
Age			
> 60 years	81	22.2 (13.3–31)	0.766
< 60 years	68	16.0 (5.6–26.3)	
Sex			
Male	94	22.5 (12.9–32.1)	0.32
Female	55	15.9 (10.3–21.4)	
ECOG PS			
0–1	82	24.4 (20.2–28.6)	0.395
2–4	67	14.7 (11.2–18.1)	
Hemoglobin			
< 10	52	14.9 (13.2–16.6)	0.297
> 10	95	23.6 (13.5–33.6)	
Stage			
I/II	37	14.9 (3.1–26.7)	0.125
III/IV	112	22.2 (11.4–33)	
LDH			
> 2 times the ULN	82	14.7 (11.5–17.8)	0.341
< 2 times the ULN	47	23.6 (12.7–34.4)	
Type of lymphoma			
High grade	129	15.3 (8.5–22.1)	0.07
Low grade	20	27.5 (25.0–29.9)	
Albumin (g/dl)$^{(N=72)}$			
< 4	62	14.5 (11.4–17.7)	0.608
> 4	10	27.4 (0–61.8)	

Our regimen had an intermittent schedule and we had similar results, but we included both treatment naïve and pre-treated patients. A randomized trial comparing OMC with conventional salvage in patients with relapsed/

refractory NHL demonstrated a 6.5-month PFS advantage with OMC along with superior response rates (47.8 vs. 19%) [12]. Among patients with Hodgkin's lymphoma, novel oral regimens combining anti-inflammatory agents have demonstrated higher response rates but these are small studies with limited number of patients [13].

The common side effects reported in studies with OMC are infections, gastrointestinal problems, skin rashes, fatigue and cytopenias [9–11]. We believe that the dose adjusted delivery of treatment with the intermittent scheduling greatly increases the tolerability of the regimen. In one report, 64% patients had hematological side effects and 13% needed to stop therapy due to toxicity [9]. Another concern with continuous scheduling of medications is the long-term toxicity of prednisolone which was not observed by us. The other potential advantage of the intermittent schedule is better activation of the innate antitumor immunity and better anti-tumor effects [14].

Though other studies have reported chemosensitivity, subtype of lymphoma and elevated LDH to be significantly associated with survival outcomes, we could not identify any specific prognostic factors for survival [9, 11]. Response rates are reportedly higher with the addition of rituximab and thalidomide in patients with mantle cell lymphoma; however more data is needed to identify the exact role of incorporating rituximab and anti-angiogenic agents like lenalidomide to oral metronomic therapy [10].OMC is particularly suited for Indian conditions where availability of costly therapies and access to clinical trials is limited. Treatment centers are situated far apart and there is very little back-up to treat toxicities, hence it is vital to keep the side-effects to a minimum. In a patient treated with palliative intent, quality of life is paramount importance. Our way of delivering OMC with an escalation strategy, with intermittent scheduling was based on these philosophies. The general principle of use of tolerable doses by dose/duration alteration was followed during dosing of OMC though this was done at the discretion of the treating oncologist. It is surprising that despite these advantages, there are few reports in the literature from India on the use of oral therapy in lymphomas. Only 7 patients had lymphomas out of a large report on the use of metronomic therapy in India, with 1390 patients with various advanced malignancies [15]. Though used frequently, the outcomes of OMC regimen in lymphomas have not been formally analyzed before.

Our study has many limitations like its retrospective nature, non-capture of toxicity data, and missing data on the reasons for stopping OMC. Also, there has been variability in the exact OMC schedules used since this analysis included patients treated at our institute for the last 10 years and the dose adjustments of OMC schedules were based largely on individual oncologists' decisions and not based on a uniform protocol. Despite these concerns, our data is important in highlighting the effectiveness of this approach in a providing reasonable therapy to patients with limited options. Unique features of our study are the way the oral therapy was planned and delivered with a goal of minimal toxicity. A minority of patients derive significant benefit from this therapy with deep and long-lasting responses. It is time for prospective studies using these approaches to better define populations who derive maximum benefit. Combination of this approach with immunotherapy like rituximab and immunomodulators like lenalidomide needs to be evaluated.

Acknowledgements Ms. Vanitha N for helping with collection of data.

References

1. Kerbel RS, Klement G, Pritchard KI, Kamen B (2002) Continuous low-dose anti-angiogenic/metronomic chemotherapy: from the research laboratory into the oncology clinic. Ann Oncol Off J Eur Soc Med Oncol 13(1):12–15
2. Browder T, Butterfield CE, Kräling BM, Shi B, Marshall B, O'Reilly MS et al (2000) Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. Cancer Res 60(7):1878–1886
3. Hanahan D, Bergers G, Bergsland E (2000) Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice. J Clin Invest 105(8):1045–1047
4. André N, Banavali S, Snihur Y, Pasquier E (2013) Has the time come for metronomics in low-income and middle-income countries? Lancet Oncol 14(6):e239–e248
5. Fedele P, Marino A, Orlando L, Schiavone P, Nacci A, Sponziello F et al (2012) Efficacy and safety of low-dose metronomic chemotherapy with capecitabine in heavily pretreated patients with metastatic breast cancer. Eur J Cancer 48(1):24–29
6. Mir O, Domont J, Cioffi A, Bonvalot S, Boulet B, Le Pechoux C et al (2011) Feasibility of metronomic oral cyclophosphamide plus prednisolone in elderly patients with inoperable or metastatic soft tissue sarcoma. Eur J Cancer Oxf Engl 47(4):515–519
7. Gebbia V, Serretta V, Borsellino N, Valerio MR, GSTU Foundation (2011) Salvage therapy with oral metronomic cyclophosphamide and methotrexate for castration-refractory metastatic adenocarcinoma of the prostate resistant to docetaxel. Urology 78(5):1125–1130
8. Ang S-F, Tan S-H, Toh H-C, Poon DYH, Ong SYK, Foo K-F et al (2012) Activity of thalidomide and capecitabine in patients with advanced hepatocellular carcinoma. Am J Clin Oncol 35(3):222–227
9. Coleman M, Martin P, Ruan J, Furman R, Niesvizky R, Elstrom R et al (2008) Prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) oral combination chemotherapy regimen for recurring/refractory lymphoma: low-dose metronomic, multidrug therapy. Cancer 112(10):2228–2232
10. Ruan J, Martin P, Coleman M, Furman RR, Cheung K, Faye A et al (2010) Durable responses with the metronomic rituximab and thalidomide plus prednisone, etoposide, procarbazine, and cyclophosphamide regimen in elderly patients with recurrent mantle cell lymphoma. Cancer 116(11):2655–2664
11. Buckstein R, Kerbel RS, Shaked Y, Nayar R, Foden C, Turner R et al (2006) High-dose celecoxib and metronomic "low-dose"

cyclophosphamide is an effective and safe therapy in patients with relapsed and refractory aggressive histology non-Hodgkin's lymphoma. Clin Cancer Res Off J Am Assoc Cancer Res 12(17):5190–5198

12. Zeng J, Yang L, Huang F et al (2016) The metronomic therapy with prednisone, etoposide, and cyclophosphamide reduces the serum levels of VEGF and circulating endothelial cells and improves responserates and progression-free survival in patients with relapsed or refractory non-Hodgkin lymphoma. Cancer Chemother Pharmacol 78(4):801–808
13. Ugocsai P, Wolff D, Menhart K et al (2016) Biomodulatory metronomic therapy induces PET-negative remission in chemo- and brentuximab-refractory Hodgkin lymphoma. Br J Haematol 172(2):290–293
14. Chen C-S, Doloff JC, Waxman DJ (2014) Intermittent metronomic drug schedule is essential for activating antitumor innate immunity and tumor xenograft regression. Neoplasia 16(1):84–96
15. Parikh PM, Hingmire SS, Deshmukh CD (2016) Selected current data on metronomic therapy (and its promise) from India. South Asian J Cancer 5(2):37–47