Med Oncol (2015) 32:443
DOI 10.1007/s12032-014-0443-4

ORIGINAL PAPER

Metronomic oral cyclophosphamide plus prednisone in docetaxel-pretreated patients with metastatic castration-resistant prostate cancer

Romualdo Barroso-Sousa · Leonardo Gomes da Fonseca · Karla Teixeira Souza · Ana Carolina Ribeiro Chaves · Ariel Galapo Kann · Gilberto de Castro Jr · Carlos Dzik

Received: 4 December 2014 / Accepted: 6 December 2014 / Published online: 18 December 2014

Abstract We evaluated the efficacy and safety of metronomic oral cyclophosphamide (CTX) and prednisone in metastatic castration-resistant prostate cancer (mCRPC) patients. We analyzed retrospectively patients with mCRPC previously treated with docetaxel, and who received metronomic CTX (from 50 mg PO daily to 150 mg PO, 14 days/7 days off) and prednisone 10 mg PO daily between September 2009 and April 2014 were analyzed. The primary endpoint was prostate-specific antigen (PSA) decrease ≥50 %. Secondary analysis included PSA decrease ≥30 %, time-to-treatment failure (TTF) and toxicity. Demographics and baseline characteristics were summarized using descriptive statistics. PSA response and adverse events were reported as relative rates. Kaplan–Meier estimates were calculated and plotted for time-to-event endpoints. Forty patients were evaluated. The median age was 69 years old (52–86), 12 (30.0 %) patients presented a Karnofsky performance status (KPS) of <80 %, and 34 (85 %) presented with bone with or without nodal metastases. Median pretreatment PSA was 192 ng/dL (7–2696 ng/dL). All patients were previously exposed to docetaxel, including 33 (82.5 %) with docetaxel-refractory disease. PSA response rate was achieved in eight (20.0 %) out of 40 patients. Additionally, PSA declines of ≥30 % occurred in 14 (35.0 %) patients. The median TTF was 3 months (95 % confidence interval 2.5–3.5). The treatment was well tolerated. Grade 3/4 lymphopenia was reported in 11 (27.5 %) patients and was the only grade 3–4 toxicity reported. Metronomic oral CTX showed activity and safety in docetaxel-pretreated mCRPC patients. This regimen deserves further investigation in this setting.

Keywords Prostate cancer · Cyclophosphamide · Metronomic chemotherapy · Docetaxel

R. Barroso-Sousa (✉) · L. G. da Fonseca · K. T. Souza · A. C. R. Chaves · A. G. Kann · G. de Castro Jr · C. Dzik
Division of Medical Oncology, Instituto do Câncer do Estado de São Paulo (ICESP), Hospital das Clínicas da Faculdade de Medicina, Universidade de São Paulo, Av. Dr. Arnaldo 251, 5o andar, São Paulo 01246-000, São Paulo, Brazil
e-mail: romualdo.sousa@icesp.org.br

Introduction

Prostate cancer is the second leading cause of cancer-related deaths in men worldwide [1]. The standard initial treatment for metastatic prostate cancer is androgen suppression. Nevertheless, all patients invariably progress after a median time of 18–24 months to a castration-resistant status [2]. Despite the emergence of new alternatives, including antiandrogenic [3, 4], cytotoxic [5], immunologic [6] and bone-targeted agents [7], these therapies provide short-term response.

At the end of last century, Hanahan et al. [8] coined the term metronomic chemotherapy for continuous administration of low-dose chemotherapeutic agents with no prolonged drug-free breaks [9]. Although the exact mechanisms in which metronomic chemotherapy inhibits tumor growth is not completely elucidated, increasing evidence suggest that, besides antiangiogenic mechanism [10], this type of regimen may help to restore anticancer immune response, through decreasing the number of regulatory T cells (Treg) blocking its suppressive functions [11, 12]. In this context, the classical bifunctional alkylating agent cyclophosphamide (CTX) given orally in metronomic regimens has been most frequently used in metastatic castration-resistant prostate cancer (mCRPC) and breast cancer [13, 14].

The aim of this study was to evaluate the efficacy and safety of oral CTX combined with prednisone, given in metronomic schedules for mCRPC patients pre-exposed to docetaxel.

Materials and methods

Patients

This study is a retrospective chart review of patients with mCRPC treated at Instituto do Câncer do Estado de São Paulo (ICESP), Hospital das Clínicas da Faculdade de Medicina, Universidade de São Paulo, Brazil. We included in this analysis patients with mCRPC who were treated with oral metronomic CTX in association with prednisone, for at least 4 weeks, with the following eligibility criteria: 1—castrate levels of testosterone or prior orchiectomy; 2—prior docetaxel exposure and 3—disease progression based on raising prostate-specific antigen (PSA) (defined as two consecutive increases in PSA value at least 2 weeks apart from each value) or radiographic evidence of disease progression in soft tissue or bone with or without disease progression on the basis of the PSA value). 4—Karnofsky performance status (KPS) $\geq$ 60 % and 5—adequate bone marrow function (hemoglobin >8.5 g/dL, absolute neutrophil count 1,500/mm^3, platelet count 100,000/mm^3). Patients were eligible for analysis if docetaxel was discontinued due to limiting toxicity, regardless of antitumoral efficacy. As exclusion criteria, we selected out 1—patients with central nervous system metastasis; 2—second cancer diagnosed 5 years before starting CTX (except non-melanoma skin cancer or superficial bladder cancer) and those who received CTX in combination with other antineoplastic drugs. Institutional Review Board approval was given to conduct this retrospective review.

Treatment, assessment and outcomes

Patients received different schedules of oral metronomic CTX treatment and prednisone 10 mg PO daily according to treating physician's choice. Treatment was maintained until progression of disease (PD) or significant toxicity. All patients without previous orchiectomy received continuing (LHRH) analog and were monitored for castration levels of testosterone. Patients underwent clinical and laboratorial evaluation, including complete blood cell counts, blood chemistry and PSA levels usually every 4 weeks. The primary end point was PSA response defined as a $\geq$50 % reduction in PSA levels that was confirmed by another measurement at least 4 weeks later (following PSA Working Group criteria) [15]. Stable disease (SD) was defined as a <50 % decrease in PSA from baseline. Progressive disease (PD) was defined as an increase in PSA of 25 % above nadir (minimum increase of 5.0 ng/mL). Progressive disease was also defined for those patients with documented new sites of disease and/or worsening of bone pain.

Patients with severe worsening of cancer-related symptoms requiring an increase in analgesics or bone irradiation were considered to have PD. A waterfall plot was provided for the maximum decline in PSA at any point after treatment with combined oral CTX and corticosteroids for each patient. Increases in PSA levels of >100 % were reported and registered as 100 %. Duration of PSA response was defined as the time from the first 50 % PSA decrease to confirmed PSA progression. Progression-free survival (PFS) was calculated from the time of treatment initiation to the first sign of progression documented by either PSA, clinical examination or imaging. Overall survival (OS) was calculated from the time of treatment initiation until the date of death or the last follow-up.

Secondary end points included time-to-treatment failure (TTF), toxicity and overall survival (OS). TTF was defined as time from beginning of therapy with CTX until either measurable PD, symptomatic progression, 25 % increase in PSA from nadir, confirmed at least 4 weeks later, increase in opioid requirements, and radiotherapy for palliation or death from any cause. Patients who lost follow-up were censored for survival analysis based on last outpatient visit. Safety outcomes included the numbers and proportion of patients who experienced adverse events (AEs) of any grade. We retrospectively assessed AEs and assigned grade levels based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Statistics

Demographics and baseline characteristics were summarized using descriptive statistics. PSA responses and AEs were reported as relative rates. Kaplan–Meier estimates were calculated and plotted for time-to-event end points including TTF and OS.

Results

Patients

Forty eligible patients were identified. These patients initiated CTX from June 2009 to October 2013 and were followed until July 2014. They received different regimens of oral CTX, in combination with oral prednisone 5 mg twice daily continuously. The median age was 69 years (range 52–86), and the median baseline PSA at treatment

initiation was 192 (range 7–2,696 ng/mL). At initiation of CTX, 12 (30.0 %) patients were classified as KPS < 80 %, and 34 (85 %) patients had bone with or without lymph node disease, six (15.0 %) had lymph node only metastatic disease, and one (2.5 %) patient had liver and lymph node disease. Furthermore, 36 (90.0 %) presented pain and 23 (57.5 %) received palliative radiotherapy before started CTX. All patients were previously exposed to docetaxel, including 33 (82.5 %) with docetaxel-refractory disease. The median number of previous docetaxel cycles was 7 (range 1–17). Demographic and clinical characteristics are outlined in Table 1.

Table 1 Population characteristics

	Characteristics ($n = 40$)
Age (years)	
Median (range)	69 (52–86)
>75 years old, *n* (%)	12 (30.0)
KPS, *n* (%)	
≥80	28 (70.0)
<80	12 (30.0)
PSA (serum concentration, ng/dL)	
Median (range)	192 (7–2,696)
Sites of metastasis, *n* (%)	
Bone/bone with nodes	34 (85.0)
Nodes only	6 (15.0)
Visceral organs	1 (2.5)
Pain present, *n* (%)	32 (80.0)
Prior palliative radiotherapy, *n* (%)	20 (50.0)
Prior hormonal manipulation	
Castration	42 (100)
2 lines	38 (95)
>2 lines	28 (70.0)
Ketoconazole	7 (17.5 %)
Prior chemotherapy	
Docetaxel plus prednisone	42 (100)
Median docetaxel cycles (range)	7 (3–17)
Disease progression relative to docetaxel administration	
During treatment	16 (40.0)
<3 months from last dose	12 (30.0)
≥3 months from last dose	5 (12.5 %)
Not progression[a]	7 (17.5 %)
Metronomic cyclophosphamide schedule, *n* (%)	
100 mg once daily 21 days on 7 off	28 (72.5)
100 mg once daily 14 days on 7 off	9 (22.5)
50 mg once daily continuously	4 (10.0)

[a] Patients presented grade 3 AEs and were discontinued of docetaxel

PSA response, TTF and OS

At the time of analysis, 37 patients had discontinued treatment, 27 died, and two were lost to follow-up. The median follow-up time after treatment initiation was 9.1 months. PSA response rate was achieved in eight (20.0 %) out of 40 patients. Additionally, PSA declines of ≥30 % occurred in 14 (35.0 %) patients (Table 2). The waterfall plot with the maximal percentage of change in PSA from baseline is shown in Fig. 1. The median TTF was 3.0 months (2.5–3.5), and OS was 11.9 months 6 (95 % CI 4.8–19.0) (Table 2).

Toxicity

In general, metronomic oral CTX and prednisone was well tolerated. The most common adverse event was lymphopenia, (grade 1 = 8 (20.0 %), grade 2 = 11 (27.5 %), grade 3 = 10 (25.0 %) and grade 4 = 1 (2.5 %). No major clinical events, including opportunistic infections, were observed. Other hematological and non-hematological toxicities chart reported are listed in Table 3. Importantly, neither hematuria nor secondary malignancy has been reported in any patient. Furthermore, none of the patients interrupted treatment because AEs.

Discussion

This analysis showed that metronomic oral CTX plus prednisone can be safely administered and has antitumour activity in mCRPC previously treated with docetaxel. Post-treatment declines in PSA of ≥50 and ≥30 % were observed, respectively, in 20 and 35 % of patients. Furthermore, none of patients interrupted treatment due to toxicity and lymphopenia was the only AE ≥grade 3 reported.

Historically, metronomic chemotherapy is thought to have antineoplastic activity mainly by inhibiting tumor angiogenesis [9]. The paradigm proposed by Folkman and

Table 2 Outcomes results

Efficacy criterion	Result
PSA decrease ≥50 %	8 (20.0 %)
PSA decrease ≥30 %	14 (35.0 %)
Progressive disease	17 (42.5 %)
Time-to-treatment failure	
Median, months (95 % CI)	3.0 (2.5–3.5)
Overall survival	
Median, months (95 % CI)	11.9 (4.8–19.0)

PSA prostate-specific antigen

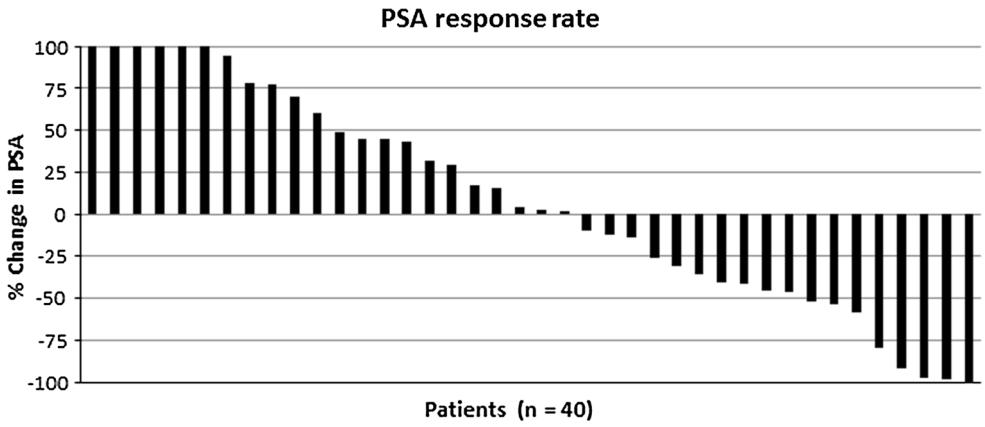

Fig. 1 Maximal PSA change from baseline after the metronomic chemotherapy regimen

Table 3 Toxicities

Toxicity	Grade		
	1 *n* (%)	2 *n* (%)	3–4[a] *n* (%)
Anemia	24 (70)	4 (10)	–
Neutropenia	–	–	–
Lymphopenia	8 (20)	11 (27.5)	11 (27.5)
Thrombocytopenia	5 (12)	–	–
Nausea	1 (2.5)	4 (10)	–
Vomiting	–	4 (10)	–
Asthenia	5 (12.5)	2 (5)	–
Stomatitis	–	1 (2.5)	–
Diarrhea	–	1 (2.5)	–

[a] One patient presented grade 4 lymphopenia

Kerbel determine that by targeting tumor endothelial cells, metronomic chemotherapy should be able to indirectly kill drug-naïve and drug-resistant cancer cells by inducing hypoxia and starvation upon tumor cells [16, 17]. In fact, in preclinical models, it was demonstrated the antiangiogenic and cytotoxic activity of continuous low dose of CTX [18, 19]. More recently, some evidence suggest that restoration of antitumor immune response is an important additional mechanism of action related to antineoplastic activity of metronomic CTX regimens. Preclinical and clinical data demonstrated that this approach both reduces the number of Treg cells as well as causing its functional impairment [11, 20–23]. In addition, reducing Treg cells seems to occur only after low-dose CTX as compared to higher doses, in which depletion of all lymphocyte subpopulations is observed.

The primary objective of our analysis was PSA response rate. In our study, eight (20 %) and 14 (35 %) patients achieved declines in PSA of ≥50 and ≥30 %, respectively. Our data are in line with other trials that have demonstrated clinical activity of oral metronomic CTX given alone or in combination with other agents in mCRPC, either in patients pretreated or not with docetaxel [24–27]. Gebbia et al. [28] published a single-arm phase II trial reporting a PSA decrease ≥50 % in 26 % of 58 patients with docetaxel-pretreated mCRPC receiving oral metronomic CTX plus methotrexate. Other groups reporting on metronomic chemotherapy in only docetaxel-pretreated mCRPC patients showed PSA response rates ranging between 15 and 36 % [24, 25, 29, 30]. Although our PSA response rate was 20 %, this is comparable to mitoxantrone-based chemotherapy as second-line treatment [5]. Furthermore, it is important to notice that 30 % of patients were >75 years old and 30 % presented with KPS < 80.

Despite the significant proportion of patients older than 75 years old and low KPS, the treatment was safe. As previously highlighted, no patients discontinued therapy due to major toxicities and lymphopenia was the only grade 3 or 4 AEs reported. This finding is consistent with other previous studies showing good tolerability of metronomic CTX [14].

Furthermore, several studies have evaluated the role of metronomic cyclophosphamide combination with other therapeutic modalities. Recently, Derosa et al. [31] reported the results of a phase II trial evaluating the combination of docetaxel plus metronomic cyclophosphamide in mCRPC chemo-naïve patients. This regimen showed a PSA response rate of 82 % and a similar toxicity profile as compared to docetaxel alone. Beyond this, metronomic cyclophosphamide as an immunotherapy tool has been combined with hormonal therapy or vaccines [12, 20].

Since 2010, new treatments for mCRPC after docetaxel progression were approved based on significant improvements in overall survival, namely cabazitaxel, abiraterone, enzalutamide and RAD-223 [3–5, 7]. However, abiraterone and enzalutamide, both with antiandrogen mechanisms of action, may not be widely available, especially in low-income and middle-income countries, as the case of Brazil. Additionally, both cabazitaxel and radium-223 dichloride

presented considerable rates of grade 3 or 4 hematologic events and a significant proportion of patients are not fit enough for these drugs [5, 7]. In a context of an incurable disease, it is clear that new therapies are needed for mCRPC patients.

Despite our study limitations, mainly due to its small sample size and its retrospective and single-center nature, we showed that CTX and prednisone given on a metronomic schedule are feasible, active and presented a favorable toxicity profile, in docetaxel-pretreated patients with mCRPC. Therefore, exploring the concept of drug repositioning, which consists of using old drugs for new indications, prospective randomized trials are needed to better evaluate oral CTX, alone or in combination with other agents, in both frontline and salvage settings for patients with mCRPC [32].

Conflict of interest None.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359–86.
2. Eisenberger MA, Walsh PC. Early androgen deprivation for prostate cancer? N Engl J Med. 1999;341:1837–8.
3. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB Jr, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Flechon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364:1995–2005.
4. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de WR, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Flechon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367:1187–97.
5. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, Gravis G, Bodrogi I, Mackenzie MJ, Shen L, Roessner M, Gupta S, Sartor AO. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376:1147–54.
6. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB, Xu Y, Frohlich MW, Schellhammer PF. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363:411–22.
7. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, Chodacki A, Wiechno P, Logue J, Seke M, Widmark A, Johannessen DC, Hoskin P, Bottomley D, James ND, Solberg A, Syndikus I, Kliment J, Wedel S, Boehmer S, Dall'Oglio M, Franzen L, Coleman R, Vogelzang NJ, O'Bryan-Tear CG, Staudacher K, Garcia-Vargas J, Shan M, Bruland OS, Sartor O. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213–23.
8. Hanahan D, Bergers G, Bergsland E. Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice. J Clin Invest. 2000;105:1045–7.
9. Pasquier E, Kavallaris M, Andre N. Metronomic chemotherapy: new rationale for new directions. Nat Rev Clin Oncol. 2010;7:455–65.
10. Kerbel RS, Kamen BA. The anti-angiogenic basis of metronomic chemotherapy. Nat Rev Cancer. 2004;4:423–36.
11. Ghiringhelli F, Menard C, Puig PE, Ladoire S, Roux S, Martin F, Solary E, Le CA, Zitvogel L, Chauffert B. Metronomic cyclophosphamide regimen selectively depletes CD4+ CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients. Cancer Immunol Immunother. 2007;56:641–8.
12. Wada S, Yoshimura K, Hipkiss EL, Harris TJ, Yen HR, Goldberg MV, Grosso JF, Getnet D, Demarzo AM, Netto GJ, Anders R, Pardoll DM, Drake CG. Cyclophosphamide augments antitumor immunity: studies in an autochthonous prostate cancer model. Cancer Res. 2009;69:4309–18.
13. Colleoni M, Orlando L, Sanna G, Rocca A, Maisonneuve P, Peruzzotti G, Ghisini R, Sandri MT, Zorzino L, Nole F, Viale G, Goldhirsch A. Metronomic low-dose oral cyclophosphamide and methotrexate plus or minus thalidomide in metastatic breast cancer: antitumor activity and biological effects. Ann Oncol. 2006;17:232–8.
14. Nelius T, Rinard K, Filleur S. Oral/metronomic cyclophosphamide-based chemotherapy as option for patients with castration-refractory prostate cancer: review of the literature. Cancer Treat Rev. 2011;37:444–55.
15. Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, Figg WD, Freidlin B, Halabi S, Hudes G, Hussain M, Kaplan R, Myers C, Oh W, Petrylak DP, Reed E, Roth B, Sartor O, Scher H, Simons J, Sinibaldi V, Small EJ, Smith MR, Trump DL, Wilding G. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol. 1999;17:3461–7.
16. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med. 1971;285:1182–6.
17. de Castro JG, Puglisi F, de AE, El Saghir NS, Awada A. Angiogenesis and cancer: a cross-talk between basic science and clinical trials (the "do ut des" paradigm). Crit Rev Oncol Hematol. 2006;59:40–50.
18. Browder T, Butterfield CE, Kraling BM, Shi B, Marshall B, O'Reilly MS, Folkman J. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. Cancer Res. 2000;60:1878–86.
19. Man S, Bocci G, Francia G, Green SK, Jothy S, Hanahan D, Bohlen P, Hicklin DJ, Bergers G, Kerbel RS. Antitumor effects in mice of low-dose (metronomic) cyclophosphamide administered continuously through the drinking water. Cancer Res. 2002;62:2731–5.
20. Le DT, Jaffee EM. Regulatory T-cell modulation using cyclophosphamide in vaccine approaches: a current perspective. Cancer Res. 2012;72:3439–44.
21. Lutsiak ME, Semnani RT, De PR, Kashmiri SV, Schlom J, Sabzevari H. Inhibition of CD4(+)25+ T regulatory cell function implicated in enhanced immune response by low-dose cyclophosphamide. Blood. 2005;105:2862–8.
22. Loeffler M, Kruger JA, Reisfeld RA. Immunostimulatory effects of low-dose cyclophosphamide are controlled by inducible nitric oxide synthase. Cancer Res. 2005;65:5027–30.
23. Ghiringhelli F, Larmonier N, Schmitt E, Parcellier A, Cathelin D, Garrido C, Chauffert B, Solary E, Bonnotte B, Martin F. CD4+ CD25+ regulatory T cells suppress tumor immunity but are sensitive to cyclophosphamide which allows immunotherapy of

established tumors to be curative. Eur J Immunol. 2004;34: 336–44.
24. Ladoire S, Eymard JC, Zanetta S, Mignot G, Martin E, Kermarrec I, Mourey E, Michel F, Cormier L, Ghiringhelli F. Metronomic oral cyclophosphamide prednisolone chemotherapy is an effective treatment for metastatic hormone-refractory prostate cancer after docetaxel failure. Anticancer Res. 2010;30:4317–23.
25. Nelius T, Klatte T, de RW, Haynes A, Filleur S. Clinical outcome of patients with docetaxel-resistant hormone-refractory prostate cancer treated with second-line cyclophosphamide-based metronomic chemotherapy. Med Oncol. 2010;27:363–7.
26. Glode LM, Barqawi A, Crighton F, Crawford ED, Kerbel R. Metronomic therapy with cyclophosphamide and dexamethasone for prostate carcinoma. Cancer. 2003;98:1643–8.
27. Lord R, Nair S, Schache A, Spicer J, Somaihah N, Khoo V, Pandha H. Low dose metronomic oral cyclophosphamide for hormone resistant prostate cancer: a phase II study. J Urol. 2007;177:2136–40.
28. Gebbia V, Serretta V, Borsellino N, Valerio MR. Salvage therapy with oral metronomic cyclophosphamide and methotrexate for castration-refractory metastatic adenocarcinoma of the prostate resistant to docetaxel. Urology. 2011;78:1125–30.
29. Di LG, Autorino R, De LM, Forestieri V, Romano C, Prudente A, Giugliano F, Imbimbo C, Mirone V, de PS. Thalidomide in combination with oral daily cyclophosphamide in patients with pretreated hormone refractory prostate cancer: a phase I clinical trial. Cancer Biol Ther. 2007;6:313–7.
30. Meng LJ, Wang J, Fan WF, Pu XL, Liu FY, Yang M. Evaluation of oral chemotherapy with capecitabine and cyclophosphamide plus thalidomide and prednisone in prostate cancer patients. J Cancer Res Clin Oncol. 2012;138:333–9.
31. Derosa L, Galli L, Orlandi P, Fioravanti A, Di DT, Fontana A, Antonuzzo A, Biasco E, Farnesi A, Marconcini R, Francia G, Danesi R, Falcone A, Bocci G. Docetaxel plus oral metronomic cyclophosphamide: a phase II study with pharmacodynamic and pharmacogenetic analyses in castration-resistant prostate cancer patients. Cancer. 2014;120:3923–31.
32. Andre N, Banavali S, Snihur Y, Pasquier E. Has the time come for metronomics in low-income and middle-income countries? Lancet Oncol. 2013;14:e239–48.