Medical Oncology (2019) 36:80
https://doi.org/10.1007/s12032-019-1304-y

ORIGINAL PAPER

Metronomic chemotherapy with cyclophosphamide plus low dose of corticosteroids in advanced castration-resistant prostate cancer across the era of taxanes and new hormonal drugs

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Received: 5 February 2019 / Accepted: 5 August 2019 / Published online: 9 August 2019

Abstract
The aim of our study is to investigate the efficacy of metronomic cyclophosphamide plus low dose of corticosteroids in advanced or metastatic castration-resistant prostate cancer (CRPC) before, between, and after standard chemotherapy, such as docetaxel and cabazitaxel, and new hormonal treatments, such as abiraterone and enzalutamide. A retrospective analysis was performed on 37 patients. Cyclophosphamide was given orally 50 mg per day together with low dose of corticosteroids, namely dexametasone orally 1 mg per day or prednisone 10 mg per day. Seventeen patients (51%) showed a PSA decline≥ 50%. Median progression-free survival (PFS) and overall survival (OS) were 11 and 28 months, respectively. Median PFS and OS in the subgroup of patients with a PSA decline ≥ 50% were 14 and 35 months, respectively. Treatment was very well tolerated. We suggest that oral metronomic cyclophosphamide plus low dose of oral dexamethasone or prednisone may be a good and safe therapeutic option not only in those CRPC patients unfit for standard treatments but also in those heavily pre-treated patients.

Keywords Prostate cancer · Castration-resistant · Cyclophosphamide · Metronomic chemotherapy

Introduction

Prostate cancer is the most common malignant tumor in men with incidence increasing by age. Androgen deprivation therapy with luteinizing hormone-releasing hormone (LHRH) analogue is the gold standard in those patients with advanced or metastatic disease, whereas patients with castration-resistant prostate cancer (CRPC) can still respond to either conventional cytotoxic chemotherapy with docetaxel and cabazitaxel or to the new hormonal drugs, such as abiraterone and enzalutamide. In the last decade, enough emphasis has been dedicated to the role of neoangiogenesis and immune system in the pathogenesis of several malignancies, including CRPC and, despite new molecules under investigation, some well-known chemotherapeutic drugs are experienced a renaissance. Metronomic cyclophosphamide is administered orally at daily low dose and has been shown to exert significant anti-tumor activity through inhibition of neoangiogenesis and stimulation of immune response rather than through cytotoxic mechanisms of action [1–4]. Importantly, metronomic cyclophosphamide is a very well tolerated treatment also in elderly patients with co-morbidities [5]. In clinical practice corticosteroids are commonly used in the treatment of CRPC although their exact role is still debated. The aim of our study is to investigate the efficacy of metronomic cyclophosphamide plus low dose of corticosteroids in advanced or metastatic CRPC before, between, and after standard chemotherapy and hormonal treatments.

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Methods

A retrospective analysis was performed for patients with advanced or metastatic CRPC who received metronomic cyclophosphamide plus low dose of corticosteroids at the four Italian oncology centers of A. Perrino Hospital in Brindisi, V. Fazzi Hospital in Lecce, IRCCS Casa Sollievo della Sofferenza in San Giovanni Rotondo, and IRCCS Giovanni Paolo II in Bari. Cyclophosphamide was given orally 50 mg per day together with low dose of corticosteroids, namely dexametasone orally 1 mg per day or prednisone 10 mg per day. Treatment was continued until disease progression, death, or intolerable toxicity. All patients continued androgen deprivation therapy with LHRH analogue.

The primary endpoint was the proportion of patients with a decline of ≥ 50% in their PSA level. Progression-free survival (PFS) was defined as the time from the start of therapy to disease progression, discontinuation due to intolerance, or death, and patients lost to follow-up were censored. Disease progression was defined as: PSA increase ≥ 25% and 2 ng/ml above the nadir; and/or onset of ≥ 2 new lesions on bone scan; and/or bone pain worsening and significant clinical status deterioration. Patients with measurable disease as assessed by CT scan and/or MRI were evaluated according to the RECIST criteria. Finally, overall survival (OS) was defined as the time from administration of study therapy to death for any cause, and patients lost to follow-up were censored. PFS and OS were estimated with the Kaplan–Meier method. Adverse events were classified according to the NCI CTCAE version 5.

Results

Thirty-seven patients were included into the study. Twenty-one patients (57%) received dexamethasone in conjunction with metronomic cyclophosphamide whereas the remaining 16 patients (43%) received prednisone.

Baseline demographic and clinical characteristics are described in Table 1. Age of patients ranged from 56 to 87 years with a median of 75 years. Most of patients had bone metastases and an ECOG performance status (PS) of 2. Median PSA and serum testosterone levels at baseline were 64.5 ng/ml and 10 ng/dl, respectively. Good prognostic features were long duration of response to initial hormonal treatment, with a median of 24 months, and Gleason's score of 7 or less in 52% of patients. Prior treatments are shown in Table 2. About half of our patients received a primary local treatment, whether radiotherapy or radical prostatectomy. All patients were treated with at least one line of hormonal therapy and most of them received chemotherapy with docetaxel. Only 7 patients (19%) received a sequential treatment with docetaxel, abiraterone and or cabazitaxel before the start of study therapy. Almost all patients with bone metastases were also treated with zoledronic acid or denosumab. Fourteen patients (38%) suffered of significant co-morbidities,

Table 1 Baseline patient characteristics

Number of patients	37
Median age, years (range)	75 (56–87)
Median pre-treatment PSA, ng/ml (range)	64, 5 (0–1230)
Median pre-treatment testosterone level, ng/dl (range)	10 (5–21)
Median duration of response to initial hormonal treatment, months (range)	24 (6–180)
ECOG PS[a] [n (%)]	
0	5 (14)
1	12 (32)
2	18 (49)
3	2 (5)
Gleason's score of primary tumor[b] [n (%)]	
≤ 7	15 (52)
8	7 (24)
≥ 9	7 (24)
Metastatic sites [n (%)]	
Bone	29 (78)
Lymph node	9 (24)
Liver	1 (3)
Lung	2 (6)

[a]Performance status according to the Eastern Cooperative Oncology Group

[b]Gleason's score was not available for 8 patients

Table 2 Prior treatments

Number of patients	37
Local therapy [n (%)]	
Radical prostatectomy	12 (32)
Primary radiotherapy	7 (19)
Post-surgery radiotherapy	7 (19)
Palliative bone radiotherapy	23 (62)
Hormonal therapy [n (%)]	
LHRH analogue	37 (100)
Bicalutamide	36 (97)
Abiraterone	5 (13)
Chemotherapy [n (%)]	
Docetaxel	23 (62)
Cabazitaxel	6 (16)
Estramustine	6 (16)
Zoledronic acid or denosumab [n (%)]	27 (72)

including cardiovascular diseases, renal and liver dysfunctions. Co-morbidities along with age over 75, and/or a poor PS or the lack of a valid treatment option, were the main reasons which led the investigators to choose the study treatment.

Median follow-up from start of metronomic cyclophosphamide plus low dose of corticosteroids was 10 months (range 2–35). One patient was not evaluable because lost to follow-up after first prescription, 1 patient had 0 as basal PSA and 2 patients had not recorded data on PSA. Seventeen patients (51%) showed a PSA decline≥ 50%. Median PFS and OS were 11 and 28 months, respectively. Median PFS and OS in the subgroup of patients with a PSA decline≥ 50% were 14 and 35 months, respectively. At the time of analysis, 13 patients (34%) were still on follow-up with a continued response. Data are summarized in Table 3. Of 12 patients with measurable disease, 3 showed a partial response according to RECIST (2 patients with lymph node metastasis and 1 patient with lymph node and soft tissue metastasis of left eye's orbit cavity). Twenty-seven patients (73%) showed an improvement in pain with a better or not worsened PS and most of PS 2 patients (11/18, 61%) moved to a PS 1. Subsequent treatments were abiraterone in 5 patients (13%), cabazitaxel in 3 patients (8%), docetaxel in 3 patients (8%), cabozantinib in 1 patient (3%), vinorelbine in 2 patients (6%), and ezalutamide in 2 patients (6%).

Twenty-three patients received metronomic cyclophosphamide plus low dose of corticosteroids post-docetaxel chemotherapy, and 8 of 19 evaluable patients (42%) showed a PSA decline ≥ 50% with a median PFS and OS of 11 and 20 months, respectively. Thirteen patients were docetaxel naive when started the study therapy. Interestingly, 9 of them (69%) had a PSA decline ≥ 50% with a median PFS of 19 months and a median OS of 35 months. Seven patients were treated after docetaxel and abiraterone and/or cabazitaxel. Two of these patients showed a PSA decline ≥ 50% (50% of 4 evaluable patients). Among the 23 post-docetaxel patients, 8 patients received the study therapy prior of subsequent lines of treatment, such as abiraterone or cabazitaxel or enzalutamide, and 5 of them (62%) had a PSA decline ≥ 50%. Data are summarized in Table 4.

Metronomic cyclophosphamide plus low dose of corticosteroids was a very well tolerated treatment. Not serious adverse events occurred. Three patients reported G2 anemia (8%) and 2 patients G1 thrombocytopenia (6%). None of these patients discontinued the treatment due to toxicity and only 1 patient required a dose reduction of cyclophosphamide to 50 mg three times a week. One diabetic patient had G3 hyperglycemia (3%) and required a temporary suspension of the corticosteroid.

Table 3 Main results

n tot = 37		
PSA decline > 50%		17/33* (51%)
Median follow-up		10 months (range 2–35)**
Median PFS		11 months**
Median OS		28 months**
Median PFS in pts. with PSA decline > 50%	*n* = 17	14 months
Median OS in pts. with PSA decline > 50%		35 months
pts. still on follow-up with a continued response		13/36** (34%)

*1 pt. lost to follow-up after first prescription, 1 pt with basal PSA 0 and 2 pts. without available PSA data

**1 pt. lost to follow-up after first prescription

Table 4 Subgroup results

	Post DOC *n* = 23	DOC naive *n* = 13	Post DOC and post ABI and/or CBX *n* = 7	Post DOC and pre ABI or CBX or ENZ[a] *n* = 8
PSA decline > 50%	8/19[b] (42%)	9/13 (69%)	2/4[b] (50%)	5/8 (62%)
Median PFS	11 mo.[c]	19 mo.	11 mo.[c]	11 mo.
Median OS	20 mo.[c]	35 mo.	NR[c]	28 mo.

DOC docetaxel, *ABI* abiraterone, *CBX* cabazitaxel, *ENZ* enzalutamide, *NR* not reached

[a]Among the 23 post-docetaxel patients, 8 patients received the study therapy prior of subsequent lines of treatment, such as abiraterone or cabazitaxel or enzalutamide

[b]1 pt. lost to follow-up after first prescription, 1 pt with basal PSA 0 and 2 pts. without PSA data

[c]1 pt. lost to follow-up after first prescription

Discussion

This study shows the efficacy of metronomic chemotherapy with cyclophosphamide given at 50 mg per day plus low dose of corticosteroids in patients with advanced CRPC. Overall, treatment resulted in a PSA decline more than half of basal level in 51% of patients and a good control of the disease over time with 50% of patients free of progression at 11 months and still alive at 28 months. Although PS is not a validated marker for cancer-related pain, most of patients had an improvement in pain associated with an improvement/no worsening of the PS also in virtue of the excellent toxicity profile with no significant adverse events. This is particularly important when considering that the primary aim in this setting of disease is palliation.

In other trials of metronomic cyclophosphamide, as single agent or combined with low dose of corticosteroids, 24–68% of patients with CRPC showed a PSA decline ≥ 50% and symptomatic responses have also been reported [6–11]. In particular, Glode et al. treated 34 patients with oral cyclophosphamide 50 mg/day plus oral dexametasone 1 mg/day reporting in 64.7% of them a decrease in PSA greater than 50% with median time to progression and survival of 9 and 14 months, respectively [6]. It is noteworthy that 21 out of 34 enrolled patients were chemotherapy naive. In our study 13 out of 37 evaluated patients were docetaxel naive. Interestingly, this subgroup of patients had the greatest benefit from the study treatment. Nine of them (69%) showed a PSA decline ≥ 50%, whereas the median PFS and OS were 19 and 35 months, respectively.

In our study the combination of metronomic cyclophosphamide plus low-dose corticosteroids in patients who progressed after docetaxel demonstrated relevant clinical activity yelding a PSA decrease ≥ 50% in 42% of patients with median PFS and OS of 11 and 20 months, respectively. Similar results were also found when considering the subgroup of heavily pre-treated patients, which received the study therapy after docetaxel and abiraterone and/or cabazitaxel. On the other hand, the subgroup of patients receiving the study therapy post-docetaxel but before abiraterone or cabazitaxel or enzalutamide showed better results with a PSA decline ≥ 50% in 62% of patients with median PFS and OS of 11 and 28 months, respectively. Ladoire et al. treated 23 metastatic CRPC patients after docetaxel failure with oral cyclophosphamide 50 mg/day plus prednisone 10 mg/day reporting in 26% of them a decrease in PSA greater than 50% with median PFS and OS of 6 and 11 months, respectively [12]. The higher PSA response rate and the longer median PFS and OS we found could be explained by the fact that our patients were less heavily pre-treated since proportion of patients receiving the metronomic chemotherapy after docetaxel was 70% versus 43%.

The biological bases of metronomic chemotherapy have been initially discovered by Folkmann and Kerbel [1, 13]. This peculiar modality of chronic low-dose drug delivery has been shown to exert anti-tumor activity through inhibition of neoangiogenesis and stimulation of immune response rather than through cytotoxic mechanisms of action. Cyclophosphamide has been the first compound to be used in experimental models. The administration of cyclophosphamide at doses lower than the maximum tolerated dose and more frequently than standard schedule resulted in better anti tumor effects in Lewis lung carcinoma, murine mammary carcinoma EMT-6 cell line, L1210 leukemia as well as in PC-3 human prostate cancer xenografts otherwise resistant to cyclophosphamide [14, 15]. The importance of the angiogenic process in prostate cancer progression has been widely described in the literature and the clinical activity of metronomic cyclophosphamide has been significantly associated with a decrease in plasma/serum vascular endothelial growth factor (VEGF) levels [16]. Rozados et al. reported the immune-modulatory effect of metronomic cyclophosphamide in euthymic rats but not in nude mice bearing a rat B cell lymphoma [17]. Moreover, a depletion in CD4 + CD25 + regulatory T cell Has been shown in cancer patients, with subsequent restored activity of NK cells and T killer cells [18]. Interestingly, Wada et al. showed that low-dose cyclophosphamide was associated with increased expression of dendritic cell maturation markers in a murine system based on the transgenic adenocarcinoma of the mouse prostate (TRAMP) model [19].

The effects of glucocorticoids on prostate cancer remain to be elucidated. Venkitaraman et al. investigated the utility of low-dose dexamethasone versus prednisolone in CRPC with a PSA response rate of 41 versus 22% and a median time to PSA progression of 9.7 versus 5.1 months [20]. Glucocorticoids inhibit androgen production by exerting a negative feedback on the pituitary gland [21]. Moreover, steroids have supplementary antiangiogenic and immunomodulatory activities by acting against VEGF and interleukin-8 production [22]. Thus, the rationale of combining low-dose dexamethasone to metronomic cyclophosphamide in CRPC is supported by their synergistic activities. However, we can not assert that association of the two drugs is better than the use of the same in monotherapy since we lack evidences from controlled trials. Finally, in terms of efficacy, we are not able to define the specific weight of the individual drugs as part of their combination use.

We acknowledge that our study has several limitations due to its retrospective nature. In particular, the study size is relatively small ($n = 37$) and the subgroups studied are even smaller ($n = 7, 8, 13, 23$). The latter makes the interpretation of the subgroup outcome data difficult to appreciate. However, few data are now available about the use of metronomic cyclophosphamide plus low dose of corticosteroids

in patients with advanced CRPC across the era of taxanes and new hormonal drugs. Recently, Dabkara et al. published data on 18 metastatic CRPC patients treated with cyclophosphamide 50–100 mg/day ± prednisolone after failure or not fit for docetaxel and/or abiraterone. Overall PSA response rate was 44% with a median PSA PFS of 4.7 months [23]. More substantial data are expected from a larger retrospective Italian study recently completed on post-docetaxel setting (Caffo O. et al. accepted for publication). In conclusion, our findings suggest that oral metronomic cyclophosphamide plus low dose of oral dexamethasone or prednisone may be a good and safe therapeutic option not only in those CRPC patients unfit for standard treatments but also in those heavily pre-treated patients. On the other hand, we also suggest a role in combination with standard treatments as an hypothesis to be explored in a randomized prospective trial.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This study was approved by the Independent Medical Ethics Committee of ASL Brindisi. Because this was a retrospective study, formal consent was required only for those participants still alive at the time of data collection.

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