Salvage Therapy With Oral Metronomic Cyclophosphamide and Methotrexate for Castration-refractory Metastatic Adenocarcinoma of the Prostate Resistant to Docetaxel

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OBJECTIVE To investigate the activity and toxicity of metronomic chemotherapy with low-dose oral cyclophosphamide (CTX) and methotrexate (MTX) in patients with metastatic CRPC that progresses after docetaxel. Patients with castration-resistant prostate cancer (CRPC) that progresses after docetaxel may benefit from receiving further chemotherapy.

METHODS Patients were treated with CTX 50 mg/d p.o. plus MTX 2.4 mg p.o. twice per week without rest periods. All patients received simultaneous luteinizing hormone-releasing hormone analogue. Prostate-specific antigen (PSA) response was defined as a 50% reduction on 2 evaluations at least 4 weeks apart. Objective response was measured according to the RECIST criteria. Pain relief was analyzed with the McGill-Melzack Pain Questionnaire. Simon's 2-stage design for phase II study was used. Time to progression and progression-free and overall survival were computed. Toxicity was recorded according to the CTC-NCCN criteria.

RESULTS A PSA decrease ≥50% was recorded in 15 of 58 evaluable patients (25%), and objective partial response in 3 (18%) and stable disease in 4 (24%) of 17 patients with measurable disease. Disease in 10 patients (59%) progressed. Pain intensity decreased in 16 (30%), increased in 18 (33%), and remained stable in 18 (33%) patients. Five patients discontinued narcotic analgesics for a mean duration of 12 weeks. Transitory grade 3 leukopenia was observed in 4 cases (7%), grade 3 thrombocytopenia in 2 (3%), and grade 2 anemia in 4 (7%).

CONCLUSION This study demonstrates the feasibility, activity, and tolerability of oral low-dose CTX and MTX given on a metronomic schedule in patients with CRPC progressing after docetaxel-based chemotherapy. UROLOGY 78: 1125–1130, 2011. © 2011 Elsevier Inc.

In the last decade, docetaxel-based chemotherapy has been shown to achieve a survival benefit for patients with castrate-resistant prostate carcinoma (CRPC)[1,2] However, even responding patients undergo clinical, serologic, and objective progression. Second-line chemotherapy may be difficult to administer in a pretreated population often represented by elderly patients with several comorbidities. The search for new nontoxic schedules is a major challenge for oncologists.

Metronomic chemotherapy (MC) refers to the long-period administration of low-dose chemotherapeutic agents.[3,4] In this setting, antitumor drugs are used at doses far below their maximum tolerated dosage without therapy-free intervals.[5,6] MC presents many potential advantages, such as the low rate of severe toxicity, the delivery of a dose-dense but not necessarily dose-intense treatment, and the reduction in both patient and family burden. Oral cyclophosphamide (CTX)-based MC has been successfully used in metastatic CRPC[7] as well as in breast carcinoma,[8] myeloma,[9] soft-tissue sarcoma,[10] and ovarian carcinoma.[11] Adding MTX to CTX has been shown to deeply inhibit vascular endothelial growth factor levels in humans. This combination has been used for several solid tumors with remarkable results, particularly in metastatic breast cancer when given on a metronomic schedule with only a slight increase of toxicity.[4,6-8]

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Moreover, MC still represents the basis for the development of experimental trials.[12] The all-oral MC of daily CTX and twice-weekly low-dose MTX have been shown to be very well tolerated and active in treating metastatic breast cancer.[8] Moreover, patients' preference for oral treatment has been widely reported.[11] A recently published paper of our group demonstrated the tolerability and efficacy of low-dose oral combination of etoposide and estramustine phosphate in patients unfit for hospital admittance.[12] The primary goal of this study was to evaluate the safety and efficacy of a regimen combining low-dose oral CTX/MTX in patients with metastatic CRPC progressing after docetaxel.

MATERIAL AND METHODS

Patients with histologically proven CRPC progressing after docetaxel were enrolled. Main eligibility was increase in serum prostate-specific antigen (PSA) level >50% confirmed by a second measurement after 2 weeks and/or development of new metastatic lesions and/or increase in cancer-related pain of 50%; PSA level >5 ng/mL; serum testosterone level <50 ng/mL; performance status <2 accordingly to the Eastern Cooperative Oncology Group scale; life expectancy >3 months; adequate bone marrow function (leukocytes 3000/dL, absolute neutrophil count <1500/dL, platelets >100 000/mL); total bilirubin and serum transaminases within normal limits; creatinine within normal limits or creatinine clearance >60 mL/min; absence of cerebral or leptomeningeal involvement; no history of nephritic syndrome or arterial thromboembolic events; absence of severe uncontrolled cardiovascular or gastrointestinal diseases; ability to complete pain and quality-of-life questionnaires; medical history negative for cancer other than prostatic carcinoma with the exception of nonmelanotic skin tumors; and no radiopharmaceuticals administration within 2 months.

Previous radiotherapy was allowed. Measurable disease was not a necessary prerequisite. Ethical committee approval was obtained and written informed consent was required. At entry, patients were staged with medical history, physical examination, serum PSA, blood counts, serum chemistry tests, bone scan, abdomen and pelvis computed tomography scan, and chest radiograph. PSA was recorded within 1 week before treatment. Complete blood counts, serum chemistry tests, PSA, coagulation tests and assessment of adverse events were recorded every three weeks to monitor therapy. Radiographic studies were repeated every three months for patients with documented objective response. Bone scans were repeated as clinically needed. The patients received CTX 50 mg per os daily at 10:00 AM plus MTX 2.5 mg per os twice weekly without a rest period, as previously described.[10] In case of nausea, patients were prescribed oral metoclopramide. During MC all patients were also receiving luteinizing hormone–releasing hormone agonists. Patients were monitored with hemocromocytometric and routine serum chemistry tests and were asked to report toxicity every 3 weeks. Toxicity was graded according to NCI Common Toxicity Criteria, version 3.20.[13] CTX and MTX were reduced or stopped in case of grade >2 hematologic toxicity until recovery, gastrointestinal side effects, cystitis, or hand-foot syndrome. Treatment was administered until progression, patient request to withdraw, or unacceptable toxicity. Both agents were withheld if platelet counts were <75,000/mm^3 or neutrophil count was <1000/mm^3. The dose of CTX and MTX was reduced by 50% if recovery of platelet or neutrophil count took longer than 1 week, if multiple consecutive doses needed to be withheld, or if patients experienced febrile neutropenia. MTX was reduced by 50% for increase of transaminases. Dose reduction for fatigue was permitted at the discretion of the treating physician. To achieve a 50% dose reduction, CTX was administered as one 50-mg tablet every other day, and MTX to 1 weekly administration. In case of liver toxicity, MTX was omitted until resolution of toxicity.

Re-evaluation of disease was carried out after 6 weeks of treatment. The primary end point was PSA response defined as a >50% reduction in PSA maintained at 2 consecutive evaluations at least 4 weeks apart according to the guidelines for phase II trials in CRPC.[14] Secondary end points included response in measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) criteria,[15] time to progression, toxicity, progression-free survival (PFS) and overall survival (OS).

Secondary endpoints also included pain reduction measured by the McGill-Melzack Pain Questionnaire.[16,17] Patients were asked to rank their average pain level during the previous 24 hours according to the following criteria: 0 = no pain, 1 = mild pain, 2 = discomforting pain, 3 = distressing pain, 4 = horrible pain, and 5 = excruciating pain. A positive response was a 2-point decrease in the 6-point pain intensity scale, or complete loss of pain if initially 1+, to be maintained on 2 consecutive evaluations at least 3 weeks apart without an increase in analgesic use. A positive pain response was also a >50% decrease in analgesic consumption without an increase in pain maintained for 2 consecutive evaluations at least 3 weeks apart. Duration of palliative response was calculated from the start of chemotherapy to the last assessment visit for which response criteria were met.

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), progression in measurable disease as defined by RECIST criteria, or the appearance of new lesions on bone scan. Patients with severe worsening of cancer-related symptoms requiring an increase in analgesics or bone radiation were considered to have PD. Time to progression was calculated from the first day of treatment until the first finding subsequently confirmed to be PD or the last date the patient was known to be alive.

PFS was defined as the time from enrollment in the study until either measurable PD or 25% increase in PSA from nadir confirmed at least 4 weeks later, clinical deterioration (decline in performance score), increase in opiate requirements, or death from any cause. Time to PSA progression was defined from the first treatment day until the date PSA levels increased. If clinical progression occurred before PSA progression, the date of clinical progression was used. Duration of PSA response is measured from the time at which PSA declined to 50% to the time when PSA rose by 25% above the nadir. OS was defined as the time from enrollment on study until death from any cause.

Statistics

The trial was designed according to the Simon's 2-stage phase II study. PSA response rate to the combination of CTX and MTX in patients with CRPC progressing after docetaxel was evaluated. If the combination of CTX and MTX had a PSA response rate of <35%, then the regimen would not be con-

Table 1. Demographic and clinical characteristics of enrolled patients

Number of enrolled patients	60 (100%)
Age, years (median)	72 (56-83)
ECOG performance status	
0	17 (28%)
1	27 (45%)
2	16 (27%)
Site of disease	
Bone	57 (95%)
Node	15 (25%)
Liver	3 (5%)
Lung	2 (3%)
Local recurrence	5 (8%)
PSA (serum concentration, ng/dL)	
Median	156
Range	45-478
Previous treatments	
Surgery	16 (27%)
Radiotherapy to primary	12 (20%)
LHRH	60 (100%)
Bicaludamide	51 (85%)
Flutamide	9 (15%)
Docetaxel + prednisone	60 (100%)
Palliative radiotherapy	5 (8%)
Radionuclides	1 (2%)
Zoledronic acid	52 (87%)
Pain intensity	
0	5 (8%)
1	14 (23%)
2	35 (58%)
4	6 (10%)
Analgesic score	
Median	3
Range	0-5

LHRH = luteinizing hormone-releasing hormone.

Table 2. Outcome results

Biological response (number of evaluable patients)	58 (100%)
PSA decrease ≥50% and <80%	9 (15%)
PSA decrease ≥80%	6 (10%)
PSA decrease <50%	22 (38%)
PSA increase ≥25%	21 (36%)
Objective response (number of evaluable patients)*	17 (100%)
Complete response	0
Partial response	3 (18%)
Stable disease	4 (24%)
Progressive disease	10 (59%)
Pain relief (number of of evaluable patients)	54 (100%)†
Pain decreased	16 (30%)
Stabilization	18 (33%)
Pain increased	18 (33%)

* Evaluated according to the RECIST criteria.
† Only patients with pain score from 1-4 were included and 1 patients was not evaluable for pain because of incomplete data; McGill-Melzack Pain Questionnaire.

sidered worth testing in a phase III trial. Sample size was chosen with the goal of detecting an increase in the PSA response rate from 15% overseen with single-agent CTX to an estimated 25%. A 2-stage study mini-max design, with alpha < 0.05 and power beta of 80% would reject the regimen if fewer than 6 of 33 patients responded in the first stage, and it would require 58 patients. Objective responses were reported as relative rates with their 95% confidence intervals (95% CI). The 2-sided Fisher exact test was used for comparisons. Survival data analysis was performed using the Kaplan–Meier analysis. Calculation of dose intensity was carried out according to Hryniuk et al.[18]

Table 3. Toxicity

NCCN-CTC Type	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	8 (14%)	4 (7%)	5 (9%)	1 (2%)*
Thrombocytopenia	5 (9%)	2 (3%)	2 (3%)	0
Anemia	4 (7%)	4 (7%)	0	0
Nausea	5 (9%)	0	1 (2%)*	0
Liver	3 (5%)	2 (3%)	0	0
Diarrhea	3 (5%)	0	0	0
Stomatitis	3 (5%)	0	0	0
Cystitis	2 (3%)	1 (2%9	0	0
Hand foot syndrome	1 (2%)	0	0	0

n, Evaluable patients = 58.
* The patient developed hydroureteronephrosis caused by disease progression.

RESULTS

Of 111 screened patients, 60 (54%) fulfilled entry criteria and were enrolled between 2002 and 2007 in 4 institutions. The demographic and clinical characteristics are outlined in Table 1. Seventeen patients had measurable disease. Pain intensity score was 1 in 14 patients (23%), 2 in 35 (58%), and 4 in 6 (10%).

All patients but 2 were evaluable for outcomes and toxicity. Results are shown in Table 2. A PSA decrease of >50% was recorded in 15 (25%, 95% CI 14-36) of 58 evaluable patients. Six (10%, 95% CI 2-18) had a PSA decrease >80%. PSA nadir was reached after a median of 60 days (range 21-84) of administration. The median duration of PSA response was 4.2 months (range 2-11.2). Stable PSA response was reported in 22 patients (38%, 95% CI 26-50) and progressive PSA increase was recorded in 21 cases (36%, 95% CI 24–48).

Seventeen patients had measurable disease involving lymph nodes, liver, and lung. Partial response was observed in 3 patients (18%, 95% CI 4-31) with a duration of 5.4, 6, and 7.5 months, respectively. Of the remaining patients, 4 (24%, 95% CI 4-44) had SD and 10 (59%, 95% CI 36-82) had PD. The median duration of SD was 5 months (range 4-8.2). All responding patients and 1 of 4 with stable disease had a concomitant decrease in PSA >50%. Progression was first detected by PSA and by increase in cancer-related symptoms in all patients. Median PFS was 5.2 months (range 1.5-12.5) with a 6-month PFS rate of 36%. Median OS was 11.5 months (range 4-25.3). OS at 1 year was 44%.

At study entry, 55 patients required analgesics for bone pain. Five patients were not evaluable because of the absence of pain (score 0). Pain intensity decreased in 16 (30%, 95% CI 18-42), increased in 18 (33%, 95% CI 21-45), and remained stable in 18 patients (33%, 95% CI

Table 4. CTX-based metronomic chemotherapy in metastatic CRPC

Reference*	Number of patients	Previous chemotherapy, number of patients (%)	Regimen	PSA response rate >50%, number of pts (%)	Objective response rate, number of patients (%)	Median duration of response, PFS, OS (months)	Subjective improvement, number of patients (%)
Raghavan et al, 1993	30	None	CTX 100 mg/m^2 14 d q 4 wks	NR	6 (20%)	NR	18 pt (60%)
Wozniak et al, 1993	52	None	CTX 100 mg/m^2 5-Fluorouracil Methotrexate	NR	2/29 (7%)	3.2 mo	NR
Maulard-Durdux et al, 1996	20	7/20 (35%)	CTX 100 mg/d 14 d w 4 wks Etoposide	1/20 (5%)	1/6 (35%)	8 mo	14/20 (71%)
Bracarda et al, 2000	32	11 (34%)	CTX 2 mg/kg/d 14 d q 4 wks	14 pt (44%)	2/12 (17%)	10.7 mo	NR
Nishimura et al, 2001	21	7 (33%)	CTX 100 mg/d* Tegafur/uracil	12 (57%)	2/3 (67%)	7 mo	2/10 improved 1 stable
Glode et al, 2003	34	13 (38%)	CTX 50 mg/d Corticosteroids	22 (65%)	NR	8 mo	NR
Hellerstedt et al, 2003	37	15 (41%)	CTX 100 mg/d 20 d q 4 wks	15/36 (42%)	1/16 (6%)	4.5 mo	17 (46%)
Di Lorenzo et al, 2007	16	16 (100%)	CTX 50 mg/d Thalidomide	2/13 (15%)	0	NR	2/13 (15%)
Lord et al, 2007	58	NR	CTX 50 mg/m^2/d	34%, including objective responses		7.5 mo	NR
Fontana et al, 2009	28	19 (68%)	CTX 50 mg/d CTX iv, celecoxib Corticosteroids	9/28 (32%)	1/5 (25%)	9.8 m 3 m PFS 21 m OS	8/10 (80%)
Nelius et al, 2009.	17	17 (100%)	CTX 50 mg/d Corticosteroids	4/17 (24%)	NR	NR	5/17 (29%)
Ladoire et al, 2010	23	23 (100%) D	CTX 50 mg/d Corticosteroids	6/23 (26%)	NR	NR 6 m PFS 11 m OS	10/23 (43%)
Gebbia et al, present paper	58	58 (100%) D	CTX 50 mg/d Methotrexate p.o.	15/58 (25%)	3/17 (18%)	4.2 m 5.2 m PFS	16/58 (30%) 11.5 m OS

NR = not reported, E = estramustine, D = docetaxel.

* Raghavan D, Cox K, Pearson BS, et al. Oral cyclophosphamide for the management of hormone-refractory prostate cancer. Br J Urol 1993;72:625-628.

Wozniak AJ, Blumenstein BA, Crawford ED, et al. Cyclophosphamide, methotrexate, and 5-fluorouracil in the treatment of metastatic prostate cancer. A Southwest Oncology Group study. Cancer 1993;71:3975-3978.

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Ladoire S, Eymard JC, Zanetta S, et al. Metronomic oral cyclophosphamide prednisolone chemotherapy is an effective treatment for metastatic hormone-refractory prostate cancer after docetaxel failure. Anticancer Res. 2010;30:4317-4323.

21-45). Narcotic analgesics were discontinued in 5 patients (8%) for a mean duration of 12 weeks (range 3-18).

Overall, 58 patients were assessable for toxicity (Table 3). The median time of MC was 18 weeks. The median dose density of CTX and MTX was 95% and 88%, respectively. Dose reduction or delay was necessary in 18 patients (31%) because of grade 2 leukopenia (10 cases, 19%); thrombocytopenia (4 cases, 7%); and liver toxicity (transaminases, 5 cases, 8%). Grade 4 febrile leukopenia was recorded in 1 patient in whom hydroureteronephrosis developed as a result of rapid PD, possibly the cause of reduced drug clearance and increasing toxicity.

COMMENT

In patients with metastatic CRPC, chemotherapy may provide a positive impact on cancer-related symptoms and survival.[3,4] The patients with metastatic CRPC are often elderly, with significant comorbidities, and are particularly vulnerable to the toxicity of first-line docetaxel-based chemotherapy. Moreover, patients progressing after first-line chemotherapy may still require second-line treatment, which should be devoid of potentially severe side effects in view of the limited evidence of an advantage in survival or quality of life.[19-21]

To date, mitoxantrone is considered an accepted second-line chemotherapy with response rates up to 20% in few retrospective studies and in one randomized trial.[22-24]

Abiraterone acetate, an orally administered pregnenolone analog, is able to further reduce androgen levels in patients with CRPC via the inhibition of CYP17, a rate-limiting enzyme in androgen biosynthesis, with acceptable toxicity. A large phase III randomized trial showed a significant improvement in OS, time to PSA progression, radiographic PFS, and PSA response for metastatic CRPC patients who had previously received docetaxel.[25] Although median OS with oral metronomic chemotherapy had similar results to that of the prednisone-only arm in the aforementioned study, it should be noted that all our patients had a worse performance.

A more recent option is represented by cabazitaxel, which showed a statistical advantage in survival vs mitoxantrone in a large prospective phase III trial in patients pretreated with docetaxel-based fist-line chemotherapy.[26] Cabazitaxel is, however, associated with a high rate of severe hematological toxicity with febrile neutropenia in up to 7.5% of patients.

Preclinical investigations demonstrated the antineoplastic and anti-angiogenetic activity of CTX[6-8] as well the inhibition of endothelial cell proliferation by low-dose MTX.[27] In humans, oral metronomic CTX has shown clinical activity against CRPC given both as single agent or in combination with corticosteroid and/or other chemotherapeutic drugs.[9] Unfortunately, most of the published data were obtained in unselected patients mixing first- and second-line therapy. Nelius et al[28] reported a PSA decrease >50% in 24% of 17 patients with docetaxel-pretreated metastatic CRPC receiving oral metronomic CTX plus dexamethasone. Most published trials report excellent tolerability and impressive improvements in symptomatic patients (Table 4).

The schedule of oral MC adopted in our patients was successfully tested in various neoplasms.[9,11] MTX had already shown activity against metastatic CRPC in some phase II trials.[28,29] To our knowledge, this is the largest series of docetaxel-pretreated patients receiving second-line metronomic oral chemotherapy. A PSA decrease >50% was observed in 25% and a decrease >80% in 15% of our patients. Moreover, an objective partial response was achieved in 18% and a stabilization in 24% of cases. These responses corresponded to significant relief in pain intensity in 30% of patients. Moreover, tolerability was very good, with grade 3-4 toxicity rare.

The PSA response rate in our trial was in the range previously reported for second-line mitoxantrone trials in a similar patient population.[21-24] The median overall survival of 11.5 months (range 4-25.3) is somewhat lower than that reported with other agents but falls in the range of 10-12 months reported in second-line mitoxantrone studies.[21-24] Although comparison of different phase II studies is not recommended, our results are in line with those reported in several smaller studies with metronomic oral chemotherapy with CTX alone or in combination with corticosteroids or other chemotherapeutic agents.

This regimen may be adopted in patients unfit for docetaxel-based chemotherapy or when treating physicians want to avoid i.v. chemotherapy–related side effects or in those countries where abiraterone is not available.

CONCLUSIONS

Our study shows the feasibility, activity, and good tolerability of the oral combination of low-dose CTX and MTX given on a metronomic schedule in patients with CRPC progressing after docetaxel-based chemotherapy. Our results suggest the possible role of such therapy in frail and/or elderly patients in which the potential risks of severe toxicity should be avoided. Moreover, it can be useful for patients unwilling to leave their own home.

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