Metronomic Oral Cyclophosphamide Prednisolone Chemotherapy after Docetaxel failure in Metastatic Hormone-refractory Prostate Cancer

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Abstract: Background*:* treatment for patients with hormone refractory prostate cancer (HRPC) after failure of docetaxel-based chemotherapy remains controversial. The aim of this study was to assess the efficacy and tolerance of metronomic cyclophosphamide plus prednisolone in those patients. **Patients and Methods**: From June 2012 to December 2015, 29 patients with HRPC who failed on docetaxel-based chemotherapy received metronomic cyclophosphamide-prednisolone regimen. Twenty-nine patients received 50 mg oral cyclophosphamide and 10 mg Prednisolone daily until disease progression**. Results**: Nine patients (31.03%) had stable disease with<50% reduction of PSA level, 8 (27.58%) patients had ≥50%, while 12 (41.37%) patients showed progressive disease. The median overall survival was 11 months (5.5-21 months) and the median progression free survival was 4 months (3-5.5 months). Treatment was well tolerated. **Conclusion***:* low dose metronomic cyclophosphamide- prednisolone was well tolerated with modest activity in HRPC who failed on docetaxel-based chemotherapy.

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Key words: hormonal refractory metastatic prostate cancer, metronomic chemotherapy.

1. Introduction:

Prostate cancer is the most commonly diagnosed cancer in men in the western world and the second leading cause of cancer related deaths in men worldwide. [1].

The standard initial treatment for metastatic prostate cancer is androgen suppression but most patients eventually become resistant to hormonal manipulation and develop hormone-refractory prostate cancer (HRPC).[2].

Two large randomized trials reported a significant improvement in prostate specific antigen (PSA) response, pain control, time to disease progression and, for the first time, a survival benefit, with docetaxel-based chemotherapy compared with mitoxantrone. Since then, docetaxel-based chemotherapy has been adopted as the new standard treatment in HRPC. Although the use of taxanes represents a significant milestone in the treatment of hormone-refractory metastatic disease, most patients experience progression within several months, and there is currently no generally accepted and effective second-line treatment after docetaxel failure. [3, 4].

Hanahan *et al.* coined the term metronomic chemotherapy for continuous administration of low-dose chemotherapeutic agents with no prolonged drug-free breaks[5]. Although the exact mechanisms in which metronomic chemotherapy inhibits tumor growth is not established, there is an increasing evidence suggest that, metronomic chemotherapy has antiangiogenic effect [6]. Also, this type of regimen may help to restore anticancer immune response, through decreasing the number of regulatory T cells blocking its suppressive functions [7-8]. Alkylating agent cyclophosphamide given orally in metronomic regimens has been most frequently used in metastatic castration-resistant prostate cancer (mCRPC) and breast cancer [9-10].

Several phase III studies showed that cyclophosphamide administered in metronomic schedule has significant activity and is capable of positively altering PSA kinetics without significant toxicity thus constituting a therapeutic option in HRPC.(11-17).

The aim of this study was to evaluate the safety and efficacy of oral cyclophosphamide combined with Prednisolone, given as metronomic schedules for mCRPC patients after docetaxel failure.

2. Patients and Methods:

This study was conducted at Clinical Oncology Department Tanta University Hospital from June 2012 to December 2015 on 29 patients with metastatic HRPC. All patients were castrated either surgically (orchiectomy) or medically (LHRH-analogue)with evidence of disease progression on docetaxel based chemotherapy based on raising prostate-specific antigen (PSA) or radiographic evidence of disease progression in soft tissue and/or bones. Patients had performance status 0-3 according to European Collaborative Oncology Group (ECOG) performance scale, adequate bone marrow function (hemoglobin ≥8.5 g/dL, absolute neutrophil count ≥1,500/mm3, platelet count ≥100,000/mm3). Antiandrogen therapy was discontinued at least 3 months in all patients before cyclophosphamide initiation, whereas luteinizing hormone-releasing hormone (LHRH)

analogs and bisphosphonates were continued. None of the patients had previously received cyclophosphamide.

Treatment plan:

All patients received 50 mg oral cyclophosphamide, and 10 mg prednisolone on daily basis. Chemotherapy was renewed every 4 weeks if the granulocyte count was ≥1,500 $mm^3$and platelet count ≥100,000/mm^3 and hemoglobin ≥8.5 g/dL. The treatment was continued without interruption until unacceptable toxicity, disease progression, or until the patient refused further therapy. Red blood cell transfusions and/or recombinant erythropoietin were used if required.

PSA response defined as ≥ 50% reduction from initial level. 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 ng/mL). [(19)]Progressive disease was also defined for those patients with documented new sites of disease. Progression-free survival (PFS) was estimated from the start of treatment to the first sign of progression documented by rising PSA and/or clinical evidence by examination or radiological. Overall survival (OS) was calculated from the start of treatment until the date of death or the last follow-up. National Cancer Institute Common Toxicity Criteria (NCICTC) version 3.0 was used to monitor treatment related toxicity.

Statistical analysis:

Patient's characteristics were analyzed by Descriptive statistics (mean, median, 95% confidence intervals). Kaplan-Meier method was used to calculate OS and PFS. Quantitative variables were compared using the Student *t*-test and categorical variables using the Chi-square or Fisher's exact test as appropriate. A p-value ≤0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software version 21.

3. Results:

Twenty nine (29) patients were evaluated in this study from June 2012 to Dec. 2015. All patients were treated at Tanta university hospital, clinical oncology department. Table (1) showed patients' characteristics. The mean age was 65.9 ± 8.3 years and the median age was 66 years (range: 56 –79). The performance status (PS) according to Eastern Cooperative Oncology Group (ECOG), was 1 in 14 patients, 2 in 9 patients and 3 in 6 patients. All patients had been castrated and received antianderogen treatments. Seventeen (58.6%) patients received 2 lines while 12 (41.4%) patients received more than 2 lines of hormonal treatment. Being hormonal refractory, patients then received docetaxel based chemotherapy. The median serum level of pretreatment PSA was 1067 (8-2119) and the mean PSA level was 1032.41±709.9 ng/ml.

Table (2) showed the PSA response where 9 (31.03%) patients had stable disease with<50% reduction of PSA level, 8 (27.59%) patients had ≥50%, while 12 (41.38%) patients showed progressive disease.

The median overall survival was 11 months (5.5-21 months) and the median progression free survival (was 4 months (3-5.5 months) as shown in Figure 1&2 respectively. Subjective decrease in pain level recorded in 15 (51.72%) patients.

Table (3) showed treatment toxicity, metronomic cyclophosphamide plus prednisone regimen was well tolerated where 7 (24.14%) patients showed grade 3 lymphopenia while grade 3 anemia and neutropenea was reported in only 1(3.4%) patient with no patients had grade 4 toxicity.

Table (1): Patients characteristics

Patients characteristics	N0(%)
Age (years) Median 66 (56-79) Mean 65.9 ± 8.3	
Initial PSA level Mean 1032.41±709.9 Median 1067(8--2119)	
Performance status (ECOG) 1 2 **3**	 14(48.3) 9 (31) 6 (20.7)
Hormonal lines 2 lines >2 lines	 17(58.6) 12(41.4)
chemotherapy regimens docetaxel based	 29(100)
Site of metastases: **Bone** **LN and/or visceral**	 29(100) 19(65.5%)
Gleason Score: **< 7** **≥ 7**	 3(10.34%) 26(89.66%)
Palliative radiotherapy: **Yes** **No**	 24(82.75%) 5(17.25%)

Table (2): Clinical treatment response

PSA Response	No. (%)
≥50% decline	8(27.59%)
Stable disease	9 (31.03%)
Progressive disease	12 (41.38%)
Decrease in pain level	15 (51.72%)

Table (3): Treatment-related toxicities

Toxicity	Grade 1No. (%)	Grade 2No. (%)	Grade 3No. (%)	Grade 4No. (%)
Anaemia	29 (100)	7 (24.14)	1(3.44)	-
Neutropenia	4 (13.79)	1 (3.44)	1(3.44)	-
Lymphopenia	10 (34.48)	9 (31.03)	7 (24.14)	-
Thrombocytopenia	2 (6.89)	1 (3.44)	-	-
Nausea	2 (6.89)	1 (3.44)	-	-
Vomiting	1 (3.44)	3 (10.34)	-	-
Diarrhea	2 (6.89)	1 (3.44)	-	-
Stomatitis	2 (6.89)	1 (3.44)	-	-
Hepatic	6 (20.69)	2 (6.89)	-	-
Renal	3 (10.34)	-	-	-

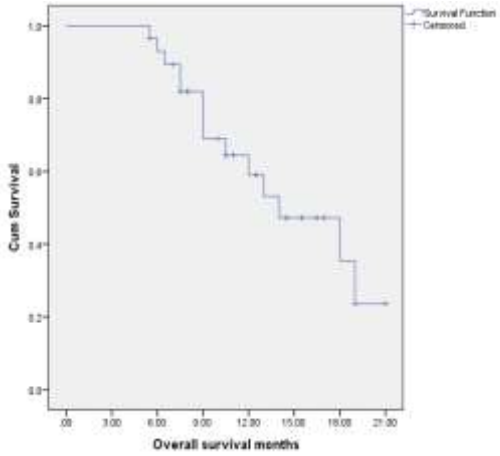

Fig.(1) Overall survival in months.

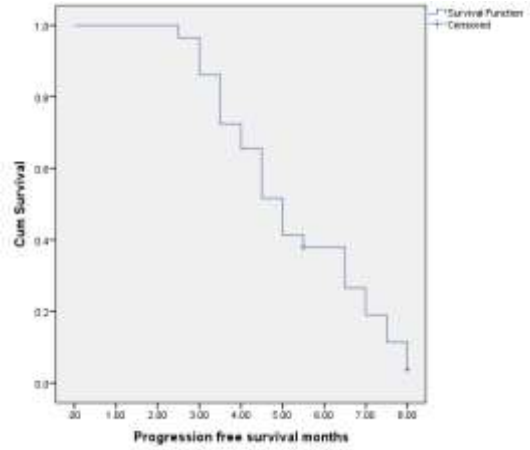

Fig. (2) Progression free survival in months.

4. Discussion

Low-dose metronomic (LDM) chemotherapy represents an emerging concept in the treatment of cancer. Directed against tumor cells and other types of cells, such as endothelial and immune cells, this treatment regimen alters the tumor microenvironment and suppresses innate features which support tumor growth.[20]

In the present study, among twenty nine (29) patients, the mean age was 65.9 ± 8.3 and the median age was 66 years (range: 56 –79). The performance status (PS) according to Eastern Cooperative Oncology Group (ECOG was 1 in 14 patients, 2 in 9 patients and 3 in 6 patients. All patients had castration and received hormonal treatments, 17 (58.6%). patients received 2 lines and 12 patients more than 2 lines (41.4%).

Being hormonal refractory, all patients received docetaxel based chemotherapy. The median serum level of pretreatment PSA was 1067 (8-2119) ng/ml and the mean PSA level was 1032.41 ±709.9 ng/ml. Nine patients (31.03%) had stable disease, 8 patients (27.59%) had ≥50% reduction of PSA level, while 12 (41.38%) patients showed progressive disease. The median overall survival was 11 months (5.5-21 months) and the median progression free survival was 4 months (3-5.5 months). Metronomic cyclophosphamide plus prednisolone regimen was well tolerated where just 7 (24.14%) patients showed grade 3 lymphopenia.

Ladoire et al 2010 evaluated 23 patients with refractory metastatic prostatic carcinoma. Patients received 50 mg cyclophosphamide and 10 mg prednisolone daily until disease progression. Metronomic cyclophosphamide prednisolone was safe, well tolerated, and demonstrated interesting clinical activity, yielding a prostate specific antigen decrease by ≥50% in 26% of patients and decrease by ≥30% in 48% of patients. Also favorable palliative effects on pain in 43% of patients . The median progression free survival was 6 months (95% CI: 4-8 months) and the median overall survival was 11 months (95% CI: 7-19 months).[21]

Nelius et al 2011 reviewed and analyzed relevant articles and references between 1962 and 2010 to evaluate the efficacy and toxicity of oral/metronomic cyclophosphamide in the treatment of patients with castration-refractory prostate cancer. They revealed

that oral cyclophosphamide is active in the treatment for castration-refractory prostate cancer even in patients treated with previous chemotherapy including docetaxel. It yields symptomatic and objective remissions. The side effects are usually grade 1–2 and easy to manage. Grade three to four side effects are less common. [10]

Gebbia et al., 2012 investigated 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. A PSA decrease ≥50% was recorded in 15 of 58 evaluable patients (25.86%), and objective partial response in 3 (18%) and stable disease in 4 (24%) of 17 patients with measurable disease. Disease progressed in 10 patients (59%). Pain intensity decreased in 16 (30%). Grade 3 leukopenia was observed in 4 cases (7%), grade 3 thrombocytopenia in 2 (3%), and grade 2 anemia in 4 (7%). 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.[21]

Dickinson et al., 2012 studied 28 patients with metastatic castration refractory carcinoma of the prostate who received cyclophosphamide 50 mg and dexamethasone 2 mg daily, until disease progression. A total of 13 out of 28 (46%) patients achieved a nadir PSA response below the baseline value. At 12 weeks, 12 out of 28 (43%) patients had a PSA reduction of 25%, 11 out of 28 (39%) had a PSA rise of25% and 5 out of 28 (18%) had a PSA within 25% of the baseline value. The median time to progression was 16 weeks. Four patients had clinical improvement of symptoms. Treatment was generally well tolerated and toxicities were mild or potentially attributable to the disease process.[22]

Glode et al., 2003 evaluated the efficacy and toxicity of the continuous oral administration of a combination of cyclophosphamide (50 mg/day given in the morning) and dexamethasone (1 mg/day given in the evening) in patients with (PSA) progression,29% of patients were found to have a > or = 80% reduction in PSA, 39% were found to have a 50-79% reduction in PSA, 6% were found to have a < 50% decrease in PSA, and 26% experienced disease progression. The duration of response was 8 months. The treatment was reported to be well tolerated effictive as salvage therapy in the treatment of patients with hormone-refractory prostate carcinoma.[15]

Romualdo et al., 2015 evaluated the metronomic oral cyclophosphamid (CTX) and prednisone in metastatic castration-resistant prostate cancer (mCRPC) patients previously treated with docetaxel. 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). The PSA response rate (≥50%) was achieved in eight (20.0 %) out of 40 patients. The median TTF was 3 months (ranged 2.5–3.5). The treatment was well tolerated. Grade 3 lymphopenia was reported in 11 (27.5 %) patients and was the only grade 3 toxicity reported. They concluded that metronomic oral CTX showed activity and safety in docetaxel-pretreated mCRPC patients.[23]

Conclusion: low dose metronomic cyclophosphamide prednisolone was well tolerated regimen with modest activity in HRPC who failed on docetaxel-based chemotherapy. Further study with large number of patients may be needed for more conclusive evaluation of treatment activity and patient's tolerability for this regimen.

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