Metronomic Oral Cyclophosphamide Chemotherapy Possibly Contributes to Stabilization of Disease in Patients With Metastatic Castration-Resistant Prostate Cancer: A Prospective Analysis of Consecutive Cases

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Abstract

We evaluated activity of metronomic cyclophosphamide chemotherapy in metastatic castration-resistant prostate cancer (CRPC) patients who had shown resistance to continuous dexamethasone. The median prostate-specific antigen (PSA) progression-free and overall survival were 5.0 and 19.0 months, respectively, and favorable PSA decrease had no predictive value. The metronomic regimen is a safe option for patients, but we must identify the predictive factors of response other than the known factors.

Introduction/Background: Castration-resistant prostate cancer remains a therapeutic challenge, even after establishing the survival benefits of docetaxel chemotherapy. Metronomic chemotherapy stabilizes various cancers through antiangiogenic and immunomodulatory effects. We evaluate the activity of metronomic oral cyclophosphamide chemotherapy in metastatic CRPC patients, and assess predictive factors for clinical outcomes. **Patients and Methods:** Twenty-four patients with metastatic CRPC received an oral cyclophosphamide and dexamethasone regimen. Of those, 11 patients (45.8%) had been exposed and resistant to previous docetaxel chemotherapy. Six patients had refused to receive docetaxel chemotherapy, and 7 patients could not receive the therapy because of deteriorated performance status. All patients had already shown resistance to continuous dexamethasone therapy. Demographic and clinical data were collected prospectively. **Results:** A total of 16 patients (66.7%) experienced a reduction in PSA levels, and PSA decrease $\geq$ 50% was observed in 8 patients (33.3%). The median PSA progression-free and overall survival were 5.0 months and 19.0 months, respectively. The favorable PSA decrease had no associations with the progression-free and overall survival, but 7 patients (29.2%) in whom response had exceeded 8 months achieved long overall survival of 28 months in median. None of the patients discontinued therapy because of the presence of toxicities. **Conclusion:** Metronomic cyclophosphamide is an active and well tolerated chemotherapy and can be an option for metastatic CRPC patients. The benefit of this regimen could not always be evaluated according to a favorable PSA decrease; thus, we must identify the predictive factors of response other than known clinical factors.

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Introduction

The current standard treatment for castration-resistant prostate cancer (CRPC) is chemotherapy based on docetaxel, which has a confirmed survival benefit of approximately 2 months in randomized controlled clinical trials.[1,2] However, more than half of the patients experience Grade $\geq$ 3 toxicities,[2] and the docetaxel-based regimen is contraindicated in elderly patients with comorbidities

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or patients with deteriorated performance status. Recent understanding of the progression mechanism of CRPC in which persistent ligand activation of the androgen receptor (AR) remains in substantial proportion has led to the development of novel agents targeting AR signaling, such as abiraterone acetate and enzalutamide. These new agents showed additional survival advantage when used after docetaxel chemotherapy,[3,4] and have been used in clinical settings in Western countries, but have not been approved in our country. Despite these new targeted agents making paradigm changes and becoming a second-line or new standard treatment in the post-docetaxel era,[5] CRPC still remains a therapeutic challenge.

Metronomic chemotherapy is low daily dosing of chemotherapy without a break period. The oldest alkylating agent, cyclophosphamide, can be administered on a metronomic schedule and has been demonstrated to involve antiangiogenic and immunomodulatory effects in various tumor types.[6] In human prostate cancer, there are several retrospective studies that achieved respectable prostate-specific antigen (PSA) response with minimal toxicity; reports of these studies have suggested metronomic oral cyclophosphamide as a possible alternative therapeutic method in patients with metastatic CRPC.[7-11] In this study, we evaluated the efficacy and toxicity of a metronomic oral chemotherapy with low-dose cyclophosphamide and dexamethasone in metastatic CRPC patients who acquired resistance to continuous dexamethasone therapy, and assessed predictive factors for clinical outcomes, and briefly reviewed the recent literature published in the docetaxel era to discuss the current and future position of this oldest chemotherapy agent.

Table 1 Patient Characteristics at Baseline

Characteristic	Value
Age, Years	75.0 (67.8-79.3)
PSA Before Treatment, ng/mL	61.0 (22.1-246.3)
ALP Before Treatment, IU/L	395 (251-1364)
Hb Before Treatment, g/dL	11.9 (10.5-12.7)
CRP Before Treatment, mg/dL	0.24 (0.12-0.51)
Gleason Score	
≤7	4 (16.7)
≥8	20 (83.3)
Response to Hormonal Therapy, Months	27 (12.8-56.3)
ECOG Performance Status	
0-1	11 (45.8)
2	9 (37.5)
3	4 (16.7)
Metastatic Disease Site	
Bone	21 (87.5)
Lymph node	10 (41.7)
Bone and lymph node	8 (38.1)
Liver	1 (4.2)
Brain	1 (4.2)

Data are presented as median (interquartile range) or n (%).
Abbreviations: ALP = alkaline phosphatase; CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; Hb = hemoglobin; PSA = prostate-specific antigen.

Patients and Methods

Patients Enrolled in the Study

Twenty-four patients with metastatic CRPC received oral metronomic chemotherapy at Dokkyo Medical University Hospital and St Luke's International Hospital between September 2009 and December 2013. The criteria for enrollment of this study were CRPC patients who developed resistance to docetaxel chemotherapy, or who did not receive docetaxel chemotherapy because of refusal or comorbidities; an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤ 3; a life expectancy of > 3 months; and adequate bone marrow, liver, and renal function. All patients had received continuous dexamethasone therapy just before study enrollment and had already shown resistance to the therapy. The CRPC status was confirmed as 2 or more consecutive increases of PSA level at least 2 weeks apart and castrated level of serum testosterone < 50 ng/dL at any point during hormonal therapy. Demographic and clinical data were collected prospectively.

Patient characteristics and previous treatments are shown in Tables 1 and 2. The median age was 75 years, including 6 patients older than 80 years, and more than half of the patients presented with an ECOG PS of 2 or 3. The median baseline PSA and alkaline phosphatase levels were 61.0 ng/mL (interquartile range, 22.1-246.3 ng/mL) and 395 IU/L (interquartile range, 251-1364 IU/L), respectively. Twenty-one patients had bone metastases, 10 had lymph node disease, 8 had involvement of both, and 1 each had massive liver metastases and brain metastasis. Twenty patients (83.3%) had been exposed to estramustine phosphate, and 11 patients (45.8%) had been exposed to docetaxel-based chemotherapy of 5 cycles at median and then become resistant. Six patients had refused to receive docetaxel chemotherapy despite 5 having been fit enough for the therapy, and 7 patients could not receive the therapy because of deteriorated performance status. One patient had tried abiraterone acetate obtained by personal import.

Treatment

Patients received oral cyclophosphamide 50 mg daily and dexamethasone 1.0 mg daily on an outpatient basis without a rest

Table 2 Previous Treatments

Treatment	n (%)
LHRH Analogue	22 (91.7)
First Antiandrogen	24 (100)
Second Antiandrogen	22 (91.7)
Surgical Castration	2 (8.3)
Prostatectomy	3 (12.5)
Radiotherapy	4 (16.7)
Bisphosphonates	14 (58.3)
Dexamethasone	24 (100)
Chemotherapy	
EMP	20 (83.3)
Docetaxel	11 (45.8)[a]
Others (UFT, paclitaxel, carboplatin, abiraterone acetate)	4 (16.7)

Abbreviations: EMP = estramustine phosphate; LHRH = luteinizing hormone-releasing hormone; UFT = uracil with tegafur.
[a]Five cycles at median.