Major Response to Cyclophosphamide and Prednisone in Recurrent Castration-Resistant Prostate Cancer

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Abstract
Prostate cancer is the most common noncutaneous cancer among men. This case report describes a 43-year-old man with rapidly progressing castration-resistant prostate cancer (CRPC) that responded initially to docetaxel and did not tolerate cabazitaxel. He subsequently received a third line of chemotherapy with cyclophosphamide and prednisone, and experienced a dramatic clinical and radiographic response in his liver metastases. This therapeutic intervention led to a significant clinical benefit and confirms the potential use of cyclophosphamide in patients with CRPC, particularly those with liver metastases. (JNCCN 2013;11:911–915)

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Learning Objectives
Upon completion of this activity, participants will be able to:
- Describe current treatment options for metastatic prostate cancer
- Discuss the potential for major response to cyclophosphamide and prednisone in recurrent CRPC

Most patients with locally advanced or metastatic prostate cancer become resistant to androgen deprivation therapy (ADT) within 18 to 24 months of treatment.¹² Inevitably, patients with castration-resistant prostate can-
Prostate cancer (CRPC) tend to have disease progression with effective but limited treatment options. This case report describes a patient with CRPC who experienced a dramatic response to cyclophosphamide and prednisone.

**Case Report**

A 43-year-old man noted urinary frequency and hesitancy, with incomplete voiding. His prostate-specific antigen (PSA) level was 387 ng/mL. A transrectal ultrasound revealed an enlarged prostate gland. Transurethral resection of the prostate showed prostatic adenocarcinoma, Gleason score 9 (5+4). The bone scan revealed diffuse abnormal signal throughout the skeleton. Repeat PSA testing showed a level of 873 ng/mL. MRI of the pelvis revealed extensive bony metastases and an irregular tumor protruding into the bladder lumen with bilateral pelvic lymphadenopathy. ADT was initiated with leuprolide, 30 mg, subcutaneously, and bicalutamide, 50 mg, orally daily. A biochemical response occurred, with a nadir PSA of 6 ng/mL, after 6 months.

At 9 months, the PSA level rose to 31.6 ng/mL. Bicalutamide was discontinued and led to a short-lived reduction of PSA levels. In the interim, the patient experienced severe right leg pain. Repeat MRI of the pelvis showed extensive metastatic disease in all vertebral bodies and extradural extension of blastic metastases in the posterior aspect of L1 and L3, with mild compression of the anterior sac. He underwent palliative radiation to the lumbar spine. He was then started on docetaxel at 75 mg/m² and prednisone and completed 13 cycles with clinical benefit. This treatment was followed by a short drug holiday.

Unfortunately, restaging CT revealed new liver lesions. A second line of chemotherapy with cabazitaxel was then initiated but discontinued after one cycle due to liver toxicity. At that time, he was referred to the authors’ institution with a PSA level of 102.3 ng/mL and rising liver enzymes, and was started on low-dose cyclophosphamide, 100 mg orally, for 14 days on a 2 weeks on, 2 weeks off schedule, and prednisone was continued at 5 mg orally daily.3 While on therapy, the patient denied any fatigue and reported only intermittent right leg pain from metastases. Repeat PSA level at 6 months of cyclophosphamide therapy was 8 ng/mL and his liver enzymes normalized (Figure 1A and B). A CT scan at that time revealed almost resolution of his liver lesions (Figure 2). Eventually his PSA started to increase again and the patient complained of severe back pain. MRI of the spine confirmed progressive metastatic bone lesions of the spine and rib cage. Cyclophosphamide was therefore discontinued and he underwent another course of palliative radiation to the thoracic spine. After radiation treatment, the androgen synthesis inhibitor abiraterone became available and was prescribed to the patient (1000 mg orally daily). Unfortunately, his PSA levels continued to rise and his treatment was switched to cabazitaxel at 25 mg/m² intravenously every 3 weeks. However, no clinical response was observed and, ultimately, treatment with mitoxantrone was initiated without control of the disease. The patient passed away 4 months later under hospice care.

**Discussion**

Prostate cancer is the most common cancer in men. In 2012, an estimated 241,740 new cases were diagnosed and 28,170 men died of the disease.4 Metastatic CRPC significantly affects the quality of life of patients and remains an incurable disease. In fact, the median survival for this patient population is approximately 12 months without further therapy.5 Docetaxel-based chemotherapy is the current standard of care in CRPC and has been shown to significantly improve survival and the quality of life of patients.6,7 In the present case report, the patient had derived clinical benefit from docetaxel for more than 11 months with acceptable toxicities. However, despite the initial response, CRPC eventually develops drug resistance and additional therapies are needed.5,8 Several therapeutic options are now available, including second-line chemotherapy involving cabazitaxel and hormone therapies with the androgen synthesis inhibitor abiraterone and the antiandrogen enzalutamide. In this setting, cyclophosphamide may also be a possible therapeutic option. It is, in general, well tolerated and its efficacy has been previously reported in CRPC.9 For example, 30 patients with CRPC were treated with cyclophosphamide alone at a dose of 100 mg/m²/day for 14 days, with 2 weeks off before the next cycle.10 Responses were partial, stable, and progressive disease in 6 (20%), 13 (43%), and 10 (33%) patients, respectively. Interestingly, a major reduction of tumor-associated symptoms was seen in almost two-thirds of these patients. The major reported adverse event was myelosuppression, and anemia was the predominant feature. No case of
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hemoaggous cystitis was noted. The median survival was 33.3 months from diagnosis and 12.7 months from the beginning of cyclophosphamide. Similarly, the patient in the present case experienced an approximately 95% reduction of his PSA level while on cyclophosphamide. His overall survival was 37 months from diagnosis and 15 months from the start of cyclophosphamide. Additionally, he experienced a major improvement in his symptoms, including overall performance status, while on cyclophosphamide.

The concomitant use of steroids is generally based on the evidence of their clinical efficacy as single agents in CRPC. In fact, low-dose corticosteroids inhibit adrenocorticotropic hormone secretion by activating a negative feedback loop. This, in turn, results in decreased adrenal hormone production, which includes androgens. Thus, a confounder in this anecdotal observation is the potential effect of prednisone. Therefore, the clinical impact of cyclophosphamide alone is difficult to discern in this setting. However, the patient was on prednisone before starting cyclophosphamide and he remained on it. Another potential confounding element is that the patient had one cycle of cabazitaxel before starting cyclophosphamide. However, the authors believe that it is unlikely that this intervention had a significant contribution to the durable response seen in this patient.

Cyclophosphamide can be administered at metronomic dosing, such as chronic administration of low doses at close regular intervals without prolonged drug-free interruptions. Preclinical and clinical studies have reported the efficacy of this strategy in prostate cancer. In 2 studies, a 50% reduction in PSA was noted in 23.5% and 64.7% of the patients, respectively. Stable disease corresponding to a PSA response of less than 50% was reported in 29% and 60% of the patients, respectively, with a median survival after starting cyclophosphamide and dexamethasone treatment of 24 and 14 months, respectively. In other studies, oral cyclophosphamide was combined with different drugs, including thalidomide, uracil with tegafur, estramustine, etoposide, and methotrexate with 5-FU.

Despite the favorable toxicity profile, long-term administration of an alkylating agent such as cyclophosphamide may cause significant side effects, including acute promyelocytic leukemia, even when given at low doses. This risk seems to be directly
related to the cumulative exposure to cyclophosphamide and is generally observed approximately 2 years after initiation of therapy. Thus, the risk of this complication should be weighed against the potential benefit when considering use of this drug.

The significant and rapid response of the liver metastases in this patient is intriguing. Anecdotal experience of this drug in patients with CRPC and liver metastases suggests a specific response for these visceral lesions. The reason for the organ-specificity of this response remains unclear, but the rapid onset may suggest a direct antitumor effect rather than an immunologic modulation that has also been observed with this drug in solid tumors. It is possible that a progressive accumulation (increased tissue penetration and/or retention) of cyclophosphamide in the liver may result in increased tumor exposure to the drug and an associated cytotoxic effect. Interestingly, preclinical data suggest that tumors with acquired resistance to low-dose metronomic cyclophosphamide retain sensitivity to the drug at the maximum tolerated dose. Further preclinical and clinical testing of this hypothesis should be considered.

**Conclusions**

Cyclophosphamide represents an “old” drug whose potential role in prostate cancer has not been fully exploited. This treatment may have a clinical benefit in heavily pretreated patients who are eligible for additional treatments. CRPC provides an ideal setting to apply this therapeutic strategy, particularly in patients who experienced progression on taxanes. An additional application of oral/metronomic cyclophosphamide therapy may be during treatment holidays of docetaxel in view of its low toxicity profile; in elderly patients; or in patients who have comorbid conditions and are unfit for cytotoxic chemotherapy regimens.

**References**

Case Report

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Instructions for Completion

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Posttest Questions

1. Most patients with locally advanced or metastatic prostate cancer become resistant to ADT within 18 to 24 months of treatment.
   a. True
   b. False

2. The following therapies are currently available to treat docetaxel-resistant CRPC:
   a. Second-line chemotherapy with cabazitaxel
   b. Hormone therapy with abiraterone, an androgen synthesis inhibitor
   c. Hormone therapy with enzalutamide, an antiandrogen
   d. All of the above

3. The following statements are true regarding the administration of cyclophosphamide:
   a. Cyclophosphamide can be administered by metronomic dosing
   b. Cyclophosphamide has been used in combination with other drugs such as thalidomide, estramustine, and methotrexate with 5-FU
   c. Long-term exposure to cyclophosphamide may cause significant side effects including acute promyelocytic leukemia, even when given at low doses
   d. All of the above