Prolonged Remission of Fulminant Castrate-Resistant Prostate Cancer: A Case Report

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Clinical Practice Points

- Castrate-resistant prostate cancer (CRPC) is the main cause of prostate cancer (PC) morbidity and mortality.
- Newer therapies have provided modest survival benefits.
- CRPC patients' various comorbidities mean one must treat them judiciously and cautiously.
- Cyclophosphamide, vincristine, and dexamethasone (CVD) therapy has a favorable benefit-risk profile.
- Diethylstilbestrol (DES) is a useful therapeutic option in selected patients with CRPC.
- The patient that we described had multiple bony metastases, disseminated intravascular coagulopathy, and dural metastases. He responded remarkably well to a combination treatment regimen containing CVD plus DES.
- The patient experienced minimal toxic effects. He is still alive and well nearly 3 years after his initial treatment.
- CVD plus DES is efficacious for the treatment of selected patients with advanced CRPC who are otherwise too ill to tolerate or benefit from most therapies.

Clinical Genitourinary Cancer, Vol. 9, No. 2, 133-6
Keywords: Cyclophosphamide vincristine dexamethasone chemotherapy, Diethylstilbestrol, Disseminated intravascular coagulation, Dural metastasis, Low prostate-specific antigen level, Prostate cancer

Introduction

Prostate cancer (PC) is the most common cancer among American men.[1] When PC progresses despite androgen-deprivation therapy in the setting of low serum testosterone concentrations, it is considered castrate-resistant PC (CRPC). In the United States, nearly all deaths from PC (approximately 28,000 annually) occur among men with CRPC.[1]

New therapies for CRPC have emerged as we have gained better understanding of the molecular mechanisms underlying PC progression and its development of castration resistance. Despite various new treatment options however these men survive for a median of only 1-2 years.[2] Chemotherapy has a proven palliative role in treating metastatic CRPC, but to date the overall survival benefit has been modest (ie, several months) in randomized trials.[3-5] Most men with CRPC are elderly and have clinically significant comorbidities (eg, cardiovascular disease, hypercoagulability, myelosuppression, neurologic problems). Thus to avoid serious toxicity, one must choose from among the treatment options cautiously, considering a patient's underlying risk factors for morbidity and mortality. One regimen—cyclophosphamide, vincristine, and dexamethasone (CVD)—was associated with very mild hematologic, neurologic, and cardiovascular toxicity when used for CRPC in a phase II clinical trial.[6] Diethylstilbestrol (DES) has also been used successfully for treating patients with CRPC.[7]

This article describes the case of a patient with fulminant CRPC, multiple comorbidities, and metastases in the bone and dura who experienced a very gratifying response to a regimen of CVD plus DES.

Case Report

A 77-year-old white man had seen his local physician for urinary frequency and nocturia; a prostate biopsy in December 2005 revealed Gleason score 9 (5 + 4) prostatic adenocarcinoma. At that time, his prostate-specific antigen (PSA) concentration was 1.1 μg/L and bone scanning showed no metastases. He was treated with androgen-ablation therapy (bicalutamide and leuprolide acetate) followed by intensity-modulated radiotherapy (total dose, 7540 cGy). This treatment resulted in an undetectable PSA level.

In March 2008 he transferred to The University of Texas MD Anderson Cancer Center for care. The staging work-up identified multiple bony lesions involving the calvarium, spine, ribs, hemipelvis, and scapula. His PSA concentration was 0.8 μg/L and his testosterone level was 23 nmol/L.

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Submitted: Mar 29, 2011; Accepted: Apr 12, 2011

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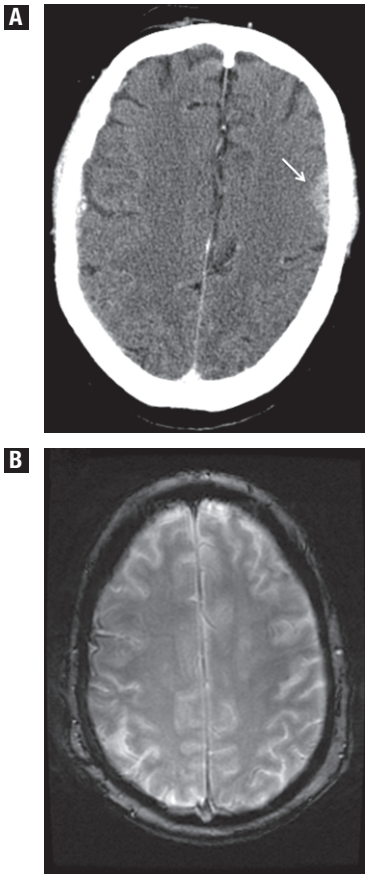
1558-7673/$ - see frontmatter
doi: 10.1016/j.clgc.2011.04.003

Figure 1 **(A) Cranial Computed Tomographic Image Obtained Before Treatment Illustrates One of the Contrast-Enhanced Extraaxial Lesions *(Arrow)* Found Bilaterally Along the Cerebral Hemispheres of the Patient's Brain. (B) Cranial Magnetic Resonance Image Obtained After Treatment with Cyclophosphamide, Vincristine, and Dexamethasone plus Diethylstilbestrol Shows Resolution of the Previously Identified Lesion**



In May 2008 the patient was hospitalized with symptoms of clinically significant fatigue, worsening memory, and altered mental status. Cranial computed tomography revealed contrast-enhanced extraaxial lesions located laterally along both cerebral hemispheres, with slight focal sclerosis of the overlying calvarium, findings consistent with a diagnosis of dural metastases (Figure 1A). Bone scanning revealed diffuse bony metastases.

At that time, the complete blood count results indicated pancytopenia: white blood cell count, 2.9×10^9/L; hemoglobin count, 6.5 mmol/L; and platelet count, 51×10^9/L. His fibrinogen concentration was $>$ 20.5 μmol/L owing to acute-phase response, and D-dimer level was elevated to 27.4mol/L. A bone marrow specimen was not obtained, although tumor infiltration into the marrow, complicated by smoldering disseminated intravascular coagulation (DIC), was suspected.

Additionally because of his rapidly deteriorating condition (performance status score 4 on the Eastern Cooperative Oncology Group [ECOG] performance scale), possibly attributable to his fulminant PC, he was given 1 dose of CVD (cyclophosphamide [300 mg/m^2 I.V.], vincristine [1 mg I.V.], and dexamethasone [0.75 mg p.o. b.i.d.]) plus DES (1 mg p.o. b.i.d.). He was discharged and recommended for home hospice care. His condition perceptibly improved.

At his first follow-up visit in June 2008 his performance status score had improved. The DIC picture had resolved, with platelet count increased to $89{,}000 \times 10^9$/L, D-dimer level decreased to 5 nmol/L, and fibrinogen level decreased to 6.2 μmol/L. Maintenance CVD (cyclophosphamide, 150 mg/day p.o. for 21 days every 28 days; vincristine, 1 mg I.V. weekly; dexamethasone, 0.5 mg p.o. b.i.d.) plus DES, 1 mg p.o. b.i.d., was then started and continued for 5 months. During treatment, his PSA concentration remained undetectable.

In August 2008 after completion of the 5 months of chemotherapy, his blood cell counts had recovered and his performance status score had improved. He was then given 2 doses of docetaxel (35 mg/m^2 I.V. every 2 weeks). His platelet count continued to show an increasing trend during his subsequent outpatient follow-up visits (Figure 2).

In March 2009 he was considered eligible to participate in an ongoing randomized phase III clinical trial of abiraterone acetate plus prednisone vs. placebo plus prednisone. In November 2010, it was found that he had been receiving placebo to that point, and he was switched to the abiraterone treatment arm.

In January 2011, when this article was written, he was still alive and well.

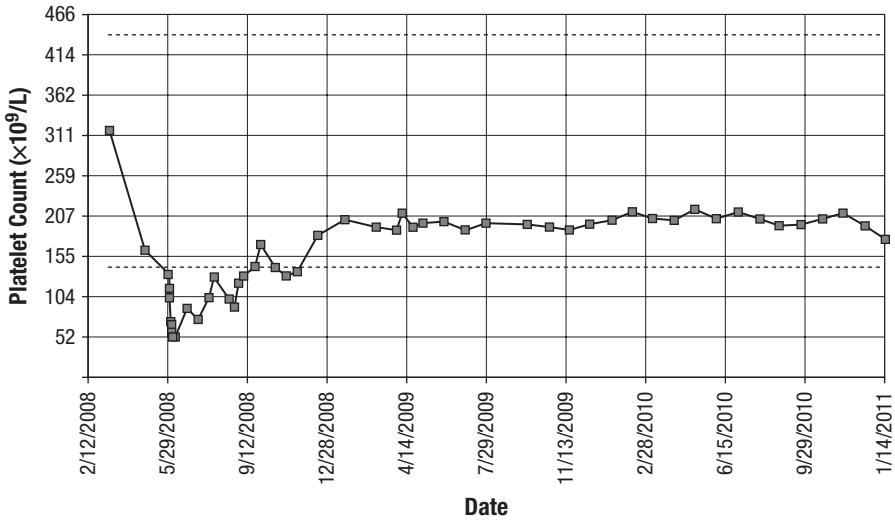
Discussion

Overall, this patient's initial clinical picture was poor, with very short life expectancy because of his advanced CRPC, poor performance status, diffuse bone metastases, symptomatic dural metastases, and DIC. Soon after his treatment with CVD plus DES began however his condition improved remarkably. In January 2011, nearly 3 years after treatment began, he was still alive with completely recovered performance status.

Dural metastasis of PC is uncommon and rarely seen in men with CRPC. Some case reports have suggested that the longer survival achievable since docetaxel was introduced in 2004 has resulted in metastases seen more often in uncommon sites, including the cranial dura.[8] Indeed Tremont-Lukats et al[9] showed that the dura is the most common intracranial site of PC metastasis. Dural metastasis is associated with very poor prognosis in PC patients. Lawton et al[8] reported median survival of about 6 months in a group of CRPC patients with dural metastases.

A picture of overwhelming DIC, a serious manifestation of advanced PC, occurs in about 25% of patients.[10] In the setting of DIC and possible complete bone marrow infiltration in patients with CRPC, as evidenced by pancytopenia in our patient, overall survival is predicted to be less than 3 months.[11] Some agents—including DES, ketoconazole, and docetaxel—are reportedly effective in PC-associated DIC,[12-14] but the essence of its management is treatment of the underlying condition.

Figure 2 Changes in Patient's Platelet Counts During Nearly 3 Years of the Course of his Disease. Dotted Lines Indicate the Upper and Lower Limits of the Normal Range at The University of Texas MD Anderson Cancer Center



Even though the use of PSA as a surrogate marker for PC detection is not satisfactorily sensitive or specific (nor is follow-up of this marker), it has been used to guide treatment decisions for individual patients.[2] In some 5%-10% of patients, the serum PSA is naturally low however and elevation of its concentration cannot be used as an indicator of disease progression.[2,15] Further, substantial numbers of patients with low PSA levels display features of aggressive tumor, including high Gleason score and extracapsular invasion.[16,17] Indeed Bonet et al[18] showed that the prognosis for patients with low PSA levels was not better than that for patients with elevated levels. Our patient's PSA concentration became undetectable after initial androgen-ablation therapy and has remained undetectable or low despite multiple widespread metastases, including diffuse bony and cranial dural metastases. This low PSA in the setting of metastatic disease suggested that the patient harbored a poorly differentiated carcinoma, although we found no evidence of tumor transformation into a neuroendocrine or small-cell prostate carcinoma.

Oral cyclophosphamide is active against CRPC both alone and in combination regimens,[19] and vincristine has modest single-agent activity against it.[20] Dexamethasone has significantly reduced PSA levels, and a substantial percentage of patients whose PSA levels decreased also had radiographic evidence of disease regression,[21] as did our patient. Additionally glucocorticoids (eg, dexamethasone, prednisone, and hydrocortisone) produce some benefit for CRPC patients, partly because inhibiting adrenal androgen production suppresses the pituitary.[22] Glucocorticoids can also interfere with the activity of several transcription factors (eg, NF-κB, AP-1) and thus have considerable local regulatory effect on the tissue.[23]

DES has also been widely used for PC. In patients with non-CRPC, it suppresses the hypothalamic-pituitary-testicular axis and testosterone production.[24] According to published reports, DES additionally suppresses adrenal androgen production; this may be the mechanism underlying its usefulness in treating patients with CRPC.[24,25]

These facts led us to try CVD plus DES as a last resort in the case of this patient. His DIC improved substantially, as evidenced by normalization of his coagulation parameters. He also experienced notable improvement of the metastases, including the cranial dural lesions (Figure 1B), and the pancytopenia resolved soon after treatment was begun. His overall clinical picture improved remarkably as his performance status score improved from 4 to 0. Despite his devastating clinical status, he tolerated this treatment extremely well, with no clinically significant adverse effects.

Conclusion

From our success with this patient, we conclude that CVD plus DES may help certain selected patients with advanced, fulminant CRPC who have multiple bony metastases, dismal performance status, altered mental status in the setting of dural metastasis, and frank DIC accompanied by bone marrow failure. Such patients are too ill to tolerate other therapy, especially standard chemotherapy, which may cause more harm than good. This CVD plus DES treatment is advantageous because it is generally well tolerated, causes minimal bone marrow suppression, and may improve patients' overall performance status, quality of life, and possibly clinical outcome.

Acknowledgments

The study was supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant, CA016672. We thank Karen F. Phillips, ELS, for editorial assistance.

Disclosures

The authors made no disclosures.

References

1. Jemal A, Siegel R, Xu J, et al. Cancer statistics. *CA Cancer J Clin* 2010; 60:277-300.
2. Vishnu P, Tan WW. Update on options for treatment of metastatic castration-resistant prostate cancer. *Onco Targets Ther* 2010; 3:39-51.
3. Tanimoto T, Hori A, Kami M. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010; 363:411-22.
4. Tannock IF, de Wit R, Berry WR, et al. for the TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; 351:1502-12.
5. Tu S-M, Millikan RE, Mengistu B, et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *Lancet* 2001; 357:336-441.
6. Daliani DD, Assikis V, Tu S-M, et al. Phase II trial of cyclophosphamide, vincristine, and dexamethasone in the treatment of androgen-independent prostate carcinoma. *Cancer* 2003; 97:561-7.
7. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* 1941; 1:293-7.
8. Lawton A, Sudakoff G, Dezelan LC, et al. Presentation, treatment, and outcomes of dural metastases in men with metastatic castrate-resistant prostate cancer: a case series. *J Palliat Med* 2010; 13:1125-9.
9. Tremont-Lukats IW, Bobustuc G, Lagos GK, et al. Brain metastasis from prostate carcinoma. The M. D. Anderson Cancer Center experience. *Cancer* 2003; 98: 363-8.
10. Straub PW. Chronic intravascular coagulation. Clinical spectrum and diagnostic criteria, with special emphasis on metabolism, distribution and localization of I 131-fibrinogen. *Acta Med Scand Suppl* 1971; 526:1-95.
11. Tu SM, Kim J, Pagliaro LC, et al. Therapy tolerance in selected patients with androgen-independent prostate cancer following strontium-89 combined with chemotherapy. *J Clin Oncol* 2005; 23:7904-10.
12. Lowe FC, Somers WJ. The use of ketoconazole in the emergency management of disseminated intravascular coagulation due to metastatic prostatic cancer. *J Urol* 1987; 137:1000-2.
13. Talebi TN, Manoharan M, Singal R. Resolution of thrombocytopenia secondary to disseminated intravascular coagulation with docetaxel chemotherapy in prostate cancer. *Am J Ther* 2010 Jun 9. [Epub ahead of print].
14. Goldenberg SL, Fenster HN, Perler Z, et al. Disseminated intravascular coagulation in carcinoma of prostate: role of estrogen therapy. *Urology* 1983; 22:130-2.
15. Leibovici D, Spiess PE, Agarwal PK, et al. Prostate cancer progression in the presence of undetectable or low serum prostate-specific antigen level. *Cancer* 2007; 109:198-204.
16. Lujan M, Paez A, Miravalles E, et al. Prostate cancer detection is also relevant in low prostate specific antigen ranges. *Eur Urol* 2004; 45:155-9.
17. Meeks JJ, Loeb S, Helfand BT, et al. Characteristics of prostate cancers detected at prostate specific antigen levels less than 2.5 g/ml. *J Urol* 2009; 181:2515-9.
18. Bonet M, Merglen A, Fioretta G, et al. Characteristics and outcome of prostate cancer with PSA <4 g/ml at diagnosis: a population-based study. *Clin Transl Oncol* 2009; 11:312-7.
19. Saxman S, Ansari R, Drasga R, et al. Phase III trial of cyclophosphamide versus cyclophosphamide, doxorubicin, and methotrexate in hormone-refractory prostatic cancer. A Hoosier Oncology Group study. *Cancer* 1992; 70:2488-92.
20. Schmidt JD, Scott WW, Gibbons R, et al. Chemotherapy programs of the National Prostatic Cancer Project (NPCP). *Cancer* 1980; 45:1937-46.
21. Saika T, Kusaka N, Tsushima T, et al; Okayama Urological Cancer Collaborating Group (OUCCG). Treatment of androgen-independent prostate cancer with dexamethasone: a prospective study in stage D2 patients. *Int J Urol* 2001; 8:290-4.
22. Gittes RF. Carcinoma of the prostate. *N Engl J Med* 1991; 324:236-45.
23. Kassi E, Moutsatsou P. Glucocorticoid receptor signaling and prostate cancer. *Cancer Lett* 2011; 302:1-10.
24. Aggarwal R, Weinberg V, Small EJ, et al. The mechanism of action of estrogen in castration-resistant prostate cancer: clues from hormone levels. *Clin Genitourin Cancer* 2009; 7:E71-76.
25. Robertson CN, Roberson KM, Padilla GM, et al. Induction of apoptosis by diethystilbestrol in hormone-insensitive prostate cancer cells. *J atl Cancer Inst* 1996; 88: 908-17.