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Prolonged remission of fulminant castrate-resistant prostate cancer: a case report

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Abstract

Castrate-resistant prostate cancer (CRPC) is the main cause of prostate cancer (PC) morbidity and mortality. Newer therapies have only modestly improved survival. CRPC patients' various comorbidities mean one must treat them cautiously. Cyclophosphamide, vincristine, and dexamethasone (CVD) therapy has a favorable risk-benefit profile, and diethylstilbestrol (DES) was used widely in PC. The patient we describe responded remarkably to combination treatment with CVD plus DES. The 77-year-old man had fulminant CRPC with multiple comorbidities and bony metastases in March 2008. In May 2008, his prognosis was dismal: performance status score, 4; pancytopenia; $51 \times 10^9/l$ platelets; abnormal coagulation profile consistent with disseminated intravascular coagulopathy; and cranial images consistent with dural metastases. We administered one dose of CVD (cyclophosphamide [300 mg/m² IV], vincristine [1 mg IV], and dexamethasone [0.75 mg PO b.i.d.]) plus DES (1 mg PO b.i.d.). He responded quickly with no clinically significant toxicity. His performance status improved and platelet count increased to $89,000 \times 10^9/l$. We administered maintenance CVD (cyclophosphamide, 150 mg/day PO for 21 days every 28 days; vincristine, 1 mg IV weekly; dexamethasone, 0.5 mg PO b.i.d.) plus DES (1 mg PO b.i.d.) for 5 months. In January 2011, nearly 3 years after his initial treatment, he remained alive and well. CVD plus DES may help selected patients with advanced CRPC who are too ill to tolerate or benefit from other therapies.

Keywords

Prostate cancer; Low prostate-specific antigen level; Cyclophosphamide; vincristine; dexamethasone chemotherapy; Diethylstilbestrol; Dural metastasis; Disseminated intravascular coagulation

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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 the deaths from PC (~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 (i.e., several months) in randomized trials.^{3–5} Most men with CRPC are elderly and have clinically significant comorbidities (e.g., 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 been also used successfully for treating patients with CRPC.⁷

This report 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, 7,540 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 workup identified multiple bony lesions involving the calvarium, spine, ribs, hemipelvis, and scapula. His PSA concentration was 0.8 µg/l and testosterone, 23 nmol/l.

In May 2008, the patient was hospitalized with symptoms of clinically significant fatigue, worsening memory, and altered mental status. Cranial computed tomography (CT) revealed contrast-enhanced extra-axial 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 cells, $2.9 \times 10^9/l$; hemoglobin, 6.5 mmol/l; and platelets, $51 \times 10^9/l$. His fibrinogen concentration was $>20.5 \mu\text{mol/l}$ owing to acute-phase response, and D-dimer was elevated, at 27.4 nmol/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 one dose of CVD (cyclophosphamide [300 mg/m^2 IV],

vincristine [1 mg IV], and dexamethasone [0.75 mg PO b.i.d.] plus DES (1 mg PO b.i.d.). He was discharged and was 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 platelets increased to $89,000 \times 10^9/l$, D-dimer decreased to 5 nmol/l, and fibrinogen decreased to 6.2 $\mu\text{mol/l}$. Maintenance CVD (cyclophosphamide, 150 mg/day PO for 21 days every 28 days; vincristine, 1 mg IV weekly; dexamethasone, 0.5 mg PO b.i.d.) plus DES, 1 mg PO 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 performance status score had improved, he was given two doses of docetaxel (35 mg/m² IV 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 versus 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 report 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, ketaconazole, and docetaxel, are reportedly effective in PC-associated DIC¹²⁻¹⁴, but the essence of its management is treatment of the underlying condition.

Even though the use of PSA as a surrogate marker for PC detection and follow-up is not satisfactorily sensitive or specific, 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 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 regimens¹⁹, and vincristine has modest single-agent activity against it.²⁰ Dexamethasone has significantly reduced PSA levels, and a substantial percentage of patients whose PSA decreased also had radiographic evidence of disease regression²¹, as did our patient. Additionally, glucocorticoids (e.g., 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 (e.g., NF- κ B, 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.

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Figure 1.

(a) Cranial computed tomographic image obtained before treatment illustrates one of the contrast-enhanced extra-axial 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

Figure 2. Graph depicts the changes in the 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