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Reversal of Docetaxel Resistance With Bevacizumab and Thalidomide

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Abstract

Taxane resistance is a common clinical problem in the treatment of many metastatic malignancies. Observational clues or evidence of overcoming such resistance is important for developing treatments that can extend taxane activity. We report a case of the reversal of docetaxel resistance with the addition of antiangiogenic agents bevacizumab and thalidomide to docetaxel and prednisone in a patient with metastatic castration-resistant prostate cancer after PSAWG progression on docetaxel and prednisone. The patient then responded for an additional 7 months. The addition of bevacizumab and thalidomide after progression on docetaxel/prednisone might reverse docetaxel resistance. These or other antiangiogenic agents for overcoming clinical taxane resistance are candidates for further study.

Keywords

Antiangiogenesis; Castration-resistant prostate cancer; Reversal of taxane resistance

Introduction

Taxane resistance represents a significant challenge in the treatment of many metastatic malignancies. In metastatic castration-resistant prostate cancer (mCRPC), docetaxel plus prednisone is the only FDA-approved regimen that has been shown to improve survival. However, the survival advantage is only approximately 2 months with a median time to disease progression of about 6–8 months. Development of docetaxel resistance during treatment appears to be inevitable, and is responsible for most treatment failures.[1] There are no proven effective therapies for docetaxel-resistant mCRPC or any convincing reports showing whether the resistance can be reversed quickly after the resistance is detected. Herein, we report our observation of a patient with mCRPC whose disease progressed after 5.0 months of treatment with the standard docetaxel/prednisone regimen, but responded to the continued treatment with docetaxel/prednisone after the addition of bevacizumab and thalidomide. This led to an additional 5.5 months of a prostate-specific antigen (PSA) decline of < 50% and extended the treatment with docetaxel for an additional 7.3 months before disease progression by radiographic imaging.

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Case Report

The patient was a 69-year-old man with mCRPC to his bones and lymph nodes who was enrolled on a clinical trial combining docetaxel/prednisone, bevacizumab, and thalidomide.[2] He was treated with external-beam therapy 9 years earlier upon diagnosis of locally advanced prostate cancer with a Gleason's score of 4 + 4. Metastasis was detected 7 years after the radiation. The disease became castration resistant after androgen blockade. His prestudy PSA dynamics are shown in Figure 1, with a PSA doubling time of 0.7 months. He received an investigational combination treatment regimen including docetaxel 75 mg/m^2 and bevacizumab 15 mg/kg on day 1, and thalidomide 200 mg and prednisone 10 mg daily in a 21-day cycle. His mCRPC responded well to the study regimen; however, both bevacizumab and thalidomide were discontinued after 2 cycles of treatment per protocol guidelines because of an asymptomatic pulmonary thrombosis detected on staging computed tomography (CT) scan. He remained in the trial and received only docetaxel/prednisone (and therapeutic anticoagulation) for an additional 5 months until disease progression by the PSA Working Group (PSAWG) criteria, as shown in Figure 1, suggesting that his disease was developing docetaxel resistance.[3]

With the confirmed resolution of the thrombosis after 6 months of enoxaparin, the patient signed onto a standard care protocol to assess if he could benefit further from the combined antiangiogenesis therapy. Bevacizumab and thalidomide were reintroduced along with docetaxel/prednisone 4 weeks after the last dose of docetaxel/prednisone. PSA declines to the retreatment are shown in Figure 1, associated with 5.5 months of > 50% PSA declines. His staging scans remained stable for a total of 7.3 months until the detection of new bone lesions in the bone scan. He tolerated the retreatment well, with no recurrence of thrombosis or other significant adverse reactions.

These observations suggest that docetaxel resistance might be overcome by antiangiogenic agents such as bevacizumab and thalidomide. Recent reports have recently shown that a small percentage of patients with docetaxel-resistant mCRPC might respond to docetaxel rechallenge as second-line therapy[4–6]; however, it is not clear if the responses in those patients were due to partially resumed sensitivity after a prolonged docetaxel-free interval before the rechallenge or due to other agents (ie, carboplatin), which may have also exerted their antitumor activity against the disease. Unlike some of these reports, our case demonstrated the reversal of docetaxel resistance only 4 weeks after PSAWG progression. The single-agent activity of bevacizumab and thalidomide are both very modest in this disease and thus a response of this magnitude and duration would have been unlikely to these agents alone.

As antiangiogenic agents, both bevacizumab and thalidomide have been shown to alter tumor vasculature, eg, decreasing tumor vessel permeability and increasing intratumoral perfusion,[7,8] which might turn into an improved tumor delivery of a cytotoxic agent, thus enhancing its antitumor activity. This might stand as a possible explanation for the observed reversal of docetaxel resistance in this case. Indeed, the recent preclinical evidence obtained in tumor xenografts showed that limited tissue penetration is an important mechanism of tumor resistance to taxanes.[9]

Conclusion

In summary, the combination of bevacizumab and thalidomide with docetaxel might be able to reverse docetaxel resistance developed during the standard care of mCRPC with docetaxel/prednisone. Further examination of the role of these or other antiangiogenic

agents in overcoming docetaxel resistance may be important for enhancing or optimizing docetaxel efficacy and clinical benefit.

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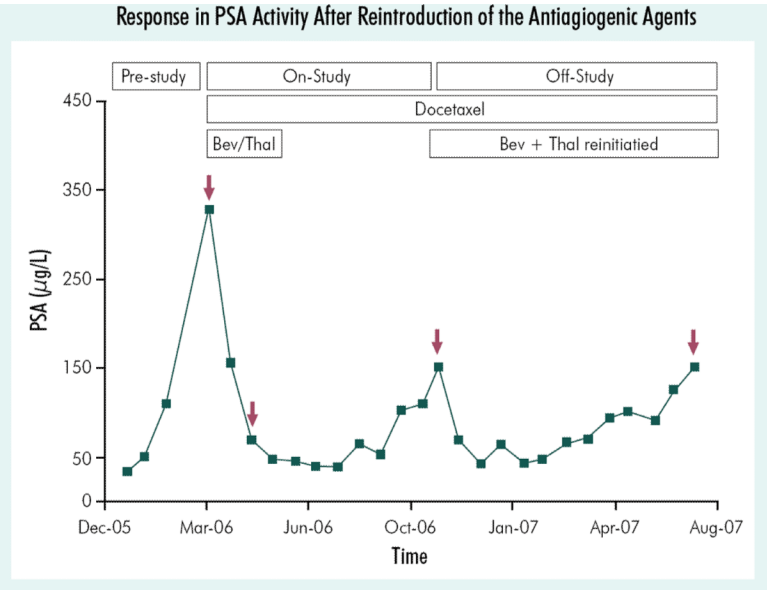

Figure 1. Changes in Prostate-Specific Antigen With Docetaxel-Based Treatments in the Patient With Metastatic Castration-Resistant Prostate Cancer

The bars above the curve specify treatment phases, duration of docetaxel treatment, and periods of treatment with bevacizumab (Bev) and thalidomide (Thal). The four arrows denote the important time points in treatment initiation, change, and termination, corresponding to the bars above and the relevant descriptions in the text.

Abbreviation: PSA = prostate-specific antigen