

## CASE REPORT

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# Hemorrhagic Cystitis in a Patient Receiving Docetaxel for Prostate Cancer

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**Abstract:** A case is reported in which docetaxel was used to treat a patient with hormone refractory metastatic prostate cancer. The treatment was terminated at the third course of docetaxel following the development of hemorrhagic cystitis. This reaction was unexpected, as it is not a known reaction to docetaxel. Hemorrhagic cystitis has been associated with cyclophosphamide, where the metabolite acrolein has been implicated. The mechanism of this reaction from docetaxel is not yet known.

**Keywords:** cystitis, docetaxel, prostate, cancer

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## Introduction

Hemorrhagic cystitis is a serious complication which can occur in patients undergoing treatment for cancer. It is commonly known to be associated with oxazaphosphorine alkylating agents such as cyclophosphamide and ifosfamide, where the metabolite acrolein is implicated.<sup>1</sup> It has also been reported following dacarbazine and temozolamide administrations.<sup>2</sup> This adverse effect has also been observed in about 5% of patients who received radiotherapy to the pelvis.<sup>3</sup>

Docetaxel is a semi-synthetic taxol derived from the needles of the yew tree. It has been used in the treatment of several malignancies like breast cancer, lung cancer, gastric cancer, head and neck cancers, and prostate cancer.<sup>4</sup> Docetaxel acts by inhibiting microtubule formation and as a poison to the mitotic spindle. The drug is metabolized in the liver to its hydroxylated metabolite—cyclized oxalozolidinedione (M4)<sup>5</sup>—and about 75% of the metabolites are excreted via bile or the faecal route while less than 10% clearance is via the kidneys. Less than 10% of the drug is eliminated as the parent compound.<sup>6</sup> The common side-effects following docetaxel administration include neutropenia, anaemia, thrombocytopenia, hypersensitivity reactions, fluid retention and changes to the nails.<sup>7</sup>

Hemorrhagic cystitis is a potentially life-threatening side-effect seen in about 6% of patients on alkylating agents like cyclophosphamide and ifosfamide, where it is linked to the metabolite acrolein. It has also been associated with non-steroidal anti-inflammatory drugs (NSAIDs),<sup>8</sup> penicillin and methicillin.<sup>9</sup> Hemorrhagic cystitis is not a known reaction to docetaxel.

## Case Report

A 73-year-old patient had radical prostatectomy and bilateral orchidectomy for prostate cancer. Three years later, he developed bony metastasis within the pelvic bones. The patient was prepared for chemotherapy. Full blood count, liver function tests, serum electrolytes, urea creatinine and calcium were within normal limits. His prostate specific antigen was 20 ng/ul. The chest x-ray was not remarkable and the abdominopelvic ultrasound revealed a normal bladder. The involvement of the pelvic bones was confirmed by a plain x-ray of the pelvis and by a Technisium99 bone scan.

The patient was started on docetaxel 75 mg/m<sup>2</sup> with oral prednisolone 5 mg twice daily continuously according to protocol and was on a three-week cycle. Premedication was with oral dexamethazone, with 8 mg taken 12 h, 3 h and 1 h before the docetaxel infusion which was given over 70 minutes. Antacids (polycrol gel) were given with the prednisolone and the patient also received intravenous ondansetron (8 mg) before the docetaxel infusion. A day after the third cycle, the patient developed gross haematuria with mild dysuria. Urinalysis confirmed the haematuria, but urine microscopy and culture did not yield any growth. The full blood count was within normal limits. An ultrasound of the abdomen and pelvis revealed slight mucosal thickening within the bladder with no definite mass.

The patient was managed conservatively with continuous bladder drainage and increased fluid intake. The haematuria reduced in intensity and finally stopped after two weeks. The packed cell volume reduced from 34% to 28% while other blood cells were still within normal limits. No blood transfusion was required. Docetaxel was discontinued and palliative radiotherapy treatment was given to the pelvic bones with a dose of 25Gray in 10 fractions within 2 weeks. He was also placed on zedronic acid 4 mg every four weeks. The patient was still alive six months after treatment.

## Discussion

Docetaxel is used either singly or in combination with other agents in the treatment of various malignancies. In combination with prednisolone, it has been shown to prolong survival in hormone refractory metastatic prostate cancer better than mitozanthrone and prednisolone therapy, hence its choice in this condition. The recommended dose in the treatment of prostate cancer is 75 mg/m<sup>2</sup> every three weeks for four courses with oral prednisolone 5 mg twice daily continuously. The recommended premedication is 8 mg oral dexamethazone taken 12 h, 3 h and 1 h before docetaxel infusion.<sup>10</sup> Acrolein, which is associated with hemorrhagic cystitis from alkylating agents like cyclophosphamide, is not a known metabolite of docetaxel and our patient was not on any other agent known to produce a predisposition to hemorrhagic cystitis immediately before or during docetaxel therapy.



The Naranjo Adverse Drug Reaction Probability scale<sup>11</sup> was used to score this drug reaction. Based on the objective assessment using the scale, the resultant score classifies docetaxel as a 'probable' cause of hemorrhagic cystitis in this patient. Hemorrhagic cystitis is an inflammatory reaction caused by a complex process which involves kinins, cyclooxygenases, interleukins, free radicals and other intracellular reactive oxygen species. Acrolein, the metabolite of oxazaphosphorins, can initiate this inflammatory process.<sup>12</sup> Docetaxel may have a yet-to-be-identified metabolite that triggered off this reaction in our patient. An allergic or immunological mechanism has also been suggested as being responsible for the development of hemorrhagic cystitis.<sup>13</sup>

Another explanation for the occurrence of this phenomenon in this patient is that there could have been gradual build-up of immunological response against the previous two doses of the agent, which became more serious with the third dose, resulting in hemorrhagic cystitis.

## Conclusion

This is the first report which shows that docetaxel at conventional doses for hormone refractory metastatic prostate cancer is associated with hemorrhagic cystitis. Clinicians should be alert to the possibility of this side-effect in some patients and further studies are needed to identify the mechanism of this association.

## Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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