

# Hemorrhagic Cystitis With Low-Dose Cyclophosphamide Therapy for Breast Cancer: A Rare Occurrence

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## Abstract

Cyclophosphamide (CP) is known to cause hemorrhagic cystitis (HC), and this adverse effect is more commonly seen in patients receiving high individual doses used in the treatment of sarcomas and conditioning regimens during hematopoietic cell transplant. There are a few reported cases of HC in doses used for breast cancer. We report the case of a 63-year-old lady with stage IIA breast cancer who was started on adjuvant CP and docetaxel therapy at a dose of 600 mg/m<sup>2</sup> and 75 mg/m<sup>2</sup> respectively. She developed gross hematuria in less than 24 h after her first cycle and was found to have evidence suggestive of HC on cystoscopy done subsequently. She went on to complete three more cycles of adjuvant chemotherapy with CP and docetaxel with concurrent mesna and hydration. She did not develop any further episodes of hematuria. We review the literature pertaining to our case, and also compare the characteristics of the patient in our case with previously described cases of breast cancer who developed HC with low-dose CP.

**Keywords:** Breast cancer; Hemorrhagic cystitis; Low-dose cyclophosphamide; Mesna

## Introduction

Cyclophosphamide (CP) is a DNA alkylating agent, and is an important agent in the management of several pediatric and adult malignancies, rheumatological conditions and vasculitis [1]. With regard to breast cancer, it is one of the most widely used chemotherapeutic agents, and is a part of several combination chemotherapeutic regimens [2, 3]. Hemorrhagic cystitis (HC) can be caused by several chemotherapeutic agents, but common clinical encounters have been reported with CP and ifosfamide [4]. HC with CP is usually noted either with high individual doses as used for myeloablative stem cell transplant

conditioning or large cumulative doses over a prolonged duration as in rheumatological disorders like lupus nephritis and granulomatosis with polyangiitis [5, 6]. Rare cases of HC following smaller doses as used in breast cancer have also been reported [7]. We report a rare case of HC following a single dose of CP used for adjuvant therapy of breast cancer and its successful management and prevention with mesna and hydration.

## Case Report

A 63-year-old woman presented to the hospital with gross hematuria. She had a past medical history of prediabetes, a hysterectomy secondary to an endometrial infection and recently diagnosed breast cancer. A hypoechoic lesion was identified on routine mammogram in the left upper outer quadrant of her breast. Thereafter, she underwent a left breast ultrasound-guided biopsy of this hypoechoic lesion, which was located at the 2 o'clock position, 5 cm from the nipple. It was around 11 mm in size at that time. Pathology was positive for invasive ductal carcinoma, grade 2, estrogen receptor (ER) and progesterone receptor (PR) positive. She then underwent an magnetic resonance imaging (MRI) of the bilateral breasts which revealed a 2.5 cm left breast mass at the 2 o'clock position with no lymphadenopathy. Scattered T2 hyperintensities were seen, which were compatible with cysts. One month later she underwent a left breast lumpectomy with a left axillary sentinel lymph node biopsy. Pathology revealed a 1.7 × 1.3 × 1.1 cm invasive ductal carcinoma with focal ductal carcinoma *in situ* (DCIS) findings and focal ductal hyperplasia. Tumor was grade 2 with presumed lymphovascular invasion. ER positive 100%, PR positive 100%, human epidermal growth factor receptor 2 (HER2) equivocal. Fluorescence *in situ* hybridization (FISH) came back negative. The left axillary sentinel lymph node was positive for a 3.5 mm focus of adenocarcinoma.

The decision was made to initiate her on adjuvant CP and docetaxel therapy. She received her first dose of CP regimen at a dose of 600 mg/m<sup>2</sup> in 250 mL normal saline (NS) along with docetaxel at 75 mg/m<sup>2</sup> in 250 mL NS. She then developed gross hematuria in less than 24 h after her first cycle. She presented to the emergency department (ED) with complaints of gross hematuria, increased urinary frequency and urgency with micturition. It was associated with difficulty in passing urine, abdominal cramps and suprapubic pain. She did not have any other constitutional symptoms. She was not on any antiplatelets or anticoagulants. Initial laboratory workup in the ED showed no markers for a coagulopathy, and urinalysis was not sugges-

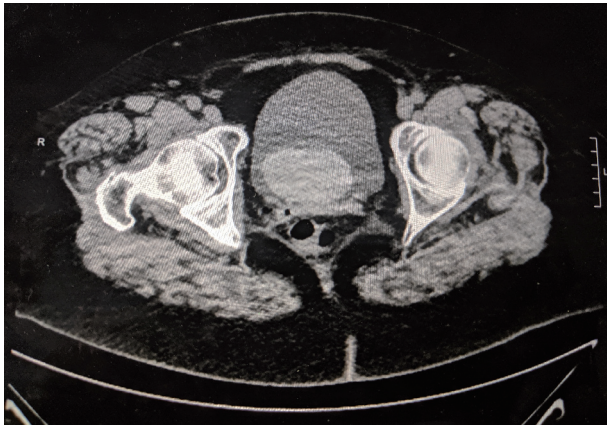
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**Figure 1.** CT abdomen and pelvis demonstrating a possible hematoma in the bladder.

tive of a urinary tract infection (UTI). As the patient continued to complain of a feeling of urinary retention, she had a bladder scan done with a volume of 650 mL in her bladder. A Foley catheter was placed in the ED with some relief in her discomfort. She had a non-contrast computed tomography (CT) scan which revealed a mass in the urinary bladder likely a hematoma versus a bladder mass (Fig. 1). Irrigation was attempted without much success and Foley was upsized with evacuation of several clots after bladder infusions. The patient's oncologist was consulted and suspicion for HC was low at this point. A repeat ultrasound was done which did not show the echogenic mass.

Patient was then given a voiding trial and she voided without any difficulty. She was scheduled for a follow-up with urology for a cystoscopy after discharge. The cystoscopy revealed an erythematous inflammatory lesion of 6 mm on the left ureteral orifice over the posterior wall. No calculi were visualized. Part of the flat erythematous patch was biopsied and the entire area was treated with fulguration. Pathology of the biopsied tissue showed some disorganization and a rare papillary fragment, suggestive of HC.

For the subsequent cycle, the patient received her infusion with mesna 120 mg/m<sup>2</sup> before CP, 4 h and 8 h after. She was also given continuous intravenous (IV) NS at the rate of 125 mL/h for a total of 3.5 L to flush the acrolein from her system. She was given additional oral mesna 200 mg on an outpatient basis. She did not have a recurrence of HC after cycle two. She subsequently received two further cycles of CP with docetaxel with a similar regimen of mesna. She has had no further episodes of hematuria since then. She subsequently received adjuvant radiation therapy for her breast cancer as well.

## Discussion

We report a case of HC in a patient with breast cancer on low-dose CP therapy. It is a very uncommon occurrence with only three cases reported in literature so far. HC is a potentially morbid inflammatory bleeding of the bladder mucosa that can occur due to various etiologies like bacterial infection, viruses like polyomavirus, toxins like aniline dyes, radiation and ex-

posure to drugs like CP, ifosfamide, danazol, busulphan and allopurinol [8]. The incidence of HC following high-dose CP is around 30%, with literature showing a range of 12-41% [8, 9]. CP is used in the treatment of various rheumatological conditions like granulomatosis with polyangiitis, microscopic polyangiitis, lupus nephritis and rheumatoid arthritis. Although the dose used in these conditions are much smaller (1.5 to 2 mg/kg/day orally or 500 - 1,000 mg/m<sup>2</sup> as monthly or biweekly pulsed regime) than that used in the treatment of malignancies (600 - 1,000 mg/m<sup>2</sup> as weekly or biweekly regimes), the drug is given over a prolonged period of time resulting in larger cumulative doses [7, 8]. Among patients with confirmed HC, the mean dosage of CP was 100 g over a period of 30 months [8].

Although rare, a few cases of HC in cancer patients have been described. Marshall et al, describes a patient who experienced HC following a single 600 mg/m<sup>2</sup> dose of CP along with docetaxel used for breast cancer. It was subsequently prevented with mesna and hydration (Table 1, case 2) [7]. This was very similar in presentation to our case. Wong et al illustrates a case of severe HC in ovarian cancer after a single 600 mg/m<sup>2</sup> dose [10]. Tanaka et al reported two cases of HC in breast cancer patients following cumulative dosage of 60.8 and 74.8 g of CP (Table 1, cases 3 and 4) [11].

CP undergoes hepatic microsomal breakdown to hydroxycyclophosphamide, then to aldophosphamide which is eventually broken down into phosphoramidate mustard and acrolein. While phosphoramidate mustard is the active antineoplastic metabolite, acrolein has no particular therapeutic activity [12]. Acrolein is toxic to the entire urinary tract, but the bladder is the most effected as it is exposed to the metabolite the longest [13]. Acrolein acts as a proinflammatory irritant that activates tumor necrosis factor alpha, interleukin 1 beta and endogenous nitric oxide (NO) [14]. All of this in a dose and time dependent manner causes necrosis, sloughing, ulceration, leucocytic infiltration and eventually hemorrhage of the bladder wall mucosa. It also causes increase in plasma protein extravasation and wet weight of the bladder [15]. CP is a drug that undergoes complex metabolic changes in the body involving cytochrome P450, glutathione S transferase and aldehyde dehydrogenase enzymes. Polymorphisms in these enzymes may affect toxicity and clinical outcomes [16]. CP is also associated with bladder wall fibrosis and an increased risk of urothelial cancer. In a study done in Wegener's granulomatosis patients treated with CP, the incidence of bladder cancer was around 5% [13].

The drug sodium 2-mercaptoethanesulfonate, also known as mesna has been used in the prevention of HC caused by both ifosfamide and CP [17]. Mesna can be administered as both IV and oral forms. The sulfhydryl groups of mesna bind with the urotoxic elements of acrolein and prevent it from acting on the bladder wall [4, 18]. The efficacy of mesna, especially in CP patients is controversial and HC still occurs in 10-40% of mesna-treated patients [19]. Liberal hydration before and several hours after administration of CP is recommended to prevent HC [4]. In 1991, Shepard et al conducted a randomized control trial with 100 patients and showed that hyper-hydration is non-inferior to mesna in preventing HC. Some authors have also opined that hyper-hydration is more safe and cost effective than mesna [20, 21]. A single institutional study was done by Saito

**Table 1.** Comparison of Baseline Patient Characteristics in Reported Cases of Low-Dose CP and HC in Breast Cancer

	Case 1 (current case)	Case 2 [7]	Case 3 [11]	Case 4 [11]
Age in years	63	62	67	65
Treatment initiated	CP and docetaxel	CP and docetaxel	CP and adriamycin followed by CP and capecitabine	CP and capecitabine
Total dose received prior to symptoms	600 mg/m <sup>2</sup>	600 mg/m <sup>2</sup>	60.8 g (600 mg/m <sup>2</sup> for six cycles followed by 100 mg/day)	78.4 g (100 mg/day × 14 days every 3 weeks)
Time from initiation of CP therapy to duration of symptoms	Within 24 h	2 days	30 months	39 months
Treatment of HC	Continuous bladder irrigation and cystoscopic fulguration	Resolved spontaneously	Bladder irrigation with drainage, hyperbaric oxygen therapy and bilateral ureterostomy	Trans-urethral electric coagulation, continuous bladder irrigation, hyperbaric oxygen therapy
Subsequent CP use	Yes, three cycles with mesna infusion	Yes, three cycles with mesna infusion	No	No
Post treatment follow-up	No recurrence	No recurrence	No recurrence for 2 years	No recurrence for 6 months

Y et al who showed that patients receiving low and intermediate doses of CP (< 1,500 mg/m<sup>2</sup>/day) would benefit from > 125 mL/h of fluids to prevent HC, and those getting high dose CP (> 1,500 mg/m<sup>2</sup>/day) should receive both mesna and vigorous hydration to prevent HC [22]. Majority of the evidence on the role of mesna in preventing CP-induced HC has been in rheumatological disorders, and even in the same, most of the data have been extrapolated from ifosfamide in cancer patients and from animal models. Thus the role of mesna even in rheumatological conditions where it has been extensively studied is uncertain, which thus entails more research in this area [4]. The data are even scarce with regard to its use in cancer patients as only a few case reports have been published [7, 10, 11]. Regardless, our experience and that of Marshall et al [7] support the fact that the use of mesna has been effective. Recently, a number of reports have shown that hyperbaric oxygen therapy may be effective in treating HC, even in those patients who are refractory to other modalities [23, 24]. But large scale trials are lacking and are needed to establish the same results.

Our experience, similar to that of Marshall et al [7], has shown that in HC caused by CP used in doses to treat breast cancer, mesna and hydration have been effective to prevent recurrence. More case reports and clinical trials are needed to establish standard guidelines to treat HC especially in cancer patients.

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## Conflict of Interest

None to declare.

## Informed Consent

Not applicable.

## Author Contributions

Prashanth Ashok Kumar: preparation and writing of manuscript, editing of manuscript, case analysis; Shweta Paulraj: preparation and writing of manuscript, editing of manuscript; Abirami Sivapiragasam: guide and mentor, editing of manuscript, patient care and management.

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