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# Successful desensitization to docetaxel after severe hypersensitivity reactions in two patients

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## Abstract

**Purpose** Two cases of successful desensitization to docetaxel after severe hypersensitivity reactions are reported.

**Summary** Two patients with gynecological malignancies (uterine leiomyosarcoma and ovarian adenocarcinoma) experienced severe hypersensitivity reactions with docetaxel, including flushing, numbness, sharp radiating pain, severe nausea and vomiting, apnea, and unresponsiveness. Both patients received ondansetron before docetaxel. One patient received dexamethasone, diphenhydramine, and famotidine premedication before docetaxel, as she had previously reacted to paclitaxel. Docetaxel infusions were stopped, and the reactions were treated with diphenhydramine and dexamethasone (one patient also received famotidine). After resolution of symptoms, the docetaxel was not reinitiated due to the nature of the reactions. For the next cycle, both patients received a graded drug challenge or desensitization. Both were pre-medicated with dexamethasone, diphenhydramine, and famotidine. The docetaxel was given as infusions of 0.1%, 1%, and 10% of the dose, with each infusion given over one hour. After this, the remainder of the dose was infused over one hour. Both patients tolerated this desensitization well and completed a total of three and four cycles each. The first patient to receive the desensitization did complain of chest pain during the first desensitization, and the infusion rate was decreased to administer the drug over two hours. After she tolerated two cycles of two-hour infusions, the infusion rate was increased to administer each docetaxel infusion over one hour.

**Conclusion** Two patients who had severe hypersensitivity reactions to docetaxel successfully received further docetaxel doses via a desensitization procedure that involved the sequential administration of solutions containing increasing concentrations of the drug.

The semisynthetic taxane derivative docetaxel has become vital to the treatment of many malignancies and has received approval from the Food and Drug Administration for the treatment of early and advanced breast cancer, advanced non-small cell lung cancer, hormone refractory prostate cancer, advanced gastric/gastroesophageal junction cancer, and locally advanced head and neck cancer.<sup>1</sup> Its use is also recommended by the National Comprehensive Cancer Network for use in the treatment of various gynecological malignancies, including ovarian cancer and uterine sarcomas.<sup>2,3</sup>

Docetaxel therapy can be complicated by hypersensitivity reactions. Common symptoms of docetaxel hypersensitivity include chest tightness, back pain, dyspnea, rash, flushing, bronchospasm, and occasionally hypotension. Patients should be premedicated with corticosteroids before initiation of the docetaxel infusion. The prescribing information for docetaxel recommends dexamethasone 8 mg orally twice daily for three days starting one day before the infusion, except in patients with hormone-refractory prostate cancer already receiving daily prednisone.<sup>1</sup> For those patients, premedication with dexamethasone 8 mg orally at 12, 3, and 1 hour before docetaxel infusion is recommended.<sup>1</sup> An alternative to this protracted premedication is to administer i.v. dexamethasone 20 mg 30–60 minutes before the docetaxel infusion.<sup>4</sup> Despite this pre-medication, patients may still have a hypersensitivity reaction to the drug. According to the package labeling, 25–30% of patients receiving docetaxel had hypersensitivity reactions regardless of premedication, while 17–33% of patients receiving premedication with dexamethasone for three days had a reaction to docetaxel.<sup>1</sup>

It is unclear whether patients' reactions to docetaxel are due to the docetaxel molecule or to the polysorbate 80 included in the injectable formulation. Multiple studies have attempted to elucidate the mechanism of docetaxel hypersensitivity reactions and have questioned whether they are truly allergic in nature.<sup>5,6</sup> A study measuring histamine and tryptase levels in patients before, during, and after docetaxel administration found no increase in either marker of mast-cell-mediated histamine release.<sup>6</sup> In addition, patients generally experience hypersensitivity reactions to taxane medications during the first infusion, which argues against an immunologically driven reaction. In a study of hypersensitivity reactions to paclitaxel, 56% of patients reacted with the first dose, 41% with the second, and 3% with subsequent doses.<sup>7</sup> Moreover, patients with mild reactions often tolerate reinitiation of the infusion at a slower rate.<sup>5</sup> Nevertheless, it is standard to treat reactions to docetaxel similarly to histamine-mediated allergic reactions, and permanent discontinuation is recommended in patients who develop severe reactions.<sup>2,5,6</sup>

An option for patients for whom docetaxel discontinuation would seem warranted because of hypersensitivity reactions is graded drug challenge or desensitization. Many successful desensitization protocols for paclitaxel and platinum agents have been published; however, limited data are available describing successful docetaxel desensitization.<sup>8,9</sup> We report two cases of docetaxel desensitization after severe hypersensitivity reactions.

### **Case report 1**

A 50-year-old white woman had a history of iron-deficiency anemia, hypertension, and melanoma (with a lesion excised 6 years ago). She denied tobacco use and occasionally drank alcohol. She

had been pregnant twice, had given birth twice at full term, had used hormonal contraceptives for approximately three months in her lifetime, and was diagnosed with a uterine fibroid 4 years ago.

The fibroid was monitored yearly by ultrasound until it was noticed to be increasing in size. A biopsy was negative for malignancy; however, she began to bleed, and the mass continued to grow. With these new symptoms, the patient underwent a surgical exploration and was found on pathology review to have leiomyosarcoma. The tumor was limited to the uterine corpus without involvement of the lower uterine segment or cervix. The patient had no evidence of cancer in her lymph nodes (15 sampled), omentectomy samples, and samples from peritoneal washings obtained during surgery. Lymphovascular space invasion was suspected. The patient did well postoperatively and was to receive i.v. chemotherapy with gemcitabine 900 mg/m<sup>2</sup> on days 1 and 8 and docetaxel 75 mg/m<sup>2</sup> on day 8 of every 21-day cycle.

On the first cycle, the patient tolerated the gemcitabine given on day 1. On day 8, she received ondansetron 8 mg orally (but no corticosteroids) in preparation for the chemotherapy infusions. Within five minutes of the start of the docetaxel infusion—the gemcitabine had not yet been given—the patient became flushed and complained of facial numbness, with sharp pain in her back that radiated down her leg. She also had severe nausea and vomiting. At the onset of symptoms, the docetaxel infusion was discontinued and the patient received diphenhydramine hydrochloride 50 mg i.v. and dexamethasone 20 mg i.v. The patient's symptoms subsided, but given the nature of her reaction, the decision was made not to attempt reinitiation of the docetaxel infusion. After approximately one hour, gemcitabine was administered and well tolerated.

For cycle 2, desensitization was attempted on day 8 to allow docetaxel administration. The procedure was based on published reports involving paclitaxel and platinum-based agents and modified on the basis of the authors' experience with desensitization.<sup>8,9</sup> The procedure called for four infusion bags of 0.9% sodium chloride injection with increasing concentrations of docetaxel. Bag 1 contained 0.1% of the total docetaxel dose in 100 mL, bag 2 contained 1% of the total docetaxel dose in 100 mL, bag 3 contained 10% of the total docetaxel dose in 100 mL, and bag 4 contained the remainder of the docetaxel dose in 250 mL. The 100-mL volume chosen for the first three infusions was consistent with previous procedures for paclitaxel desensitization.<sup>8</sup> Ideally, the concentration of docetaxel should be maintained between 0.3 and 0.74 mg/mL,<sup>1</sup> but, with such low doses, this was not possible. (The prescribed docetaxel dose was 150 mg.) The last infusion volume was increased to 250 mL to keep the concentration of docetaxel below 0.74 mg/mL. The desensitization doses were administered within four hours of preparation, and there was no visual evidence of docetaxel instability.

Although desensitizations have been completed in the outpatient setting,<sup>8</sup> the patient was admitted to the general oncology unit for observation during desensitization and for approximately 12 hours after chemotherapy administration. Premedications given there included dexamethasone 20 mg, diphenhydramine hydrochloride 50 mg, and famotidine 20 mg i.v. The patient had also taken dexamethasone 20 mg and famotidine 20 mg orally before appearing for cycle 2.

Bag 1 of the desensitization solution was started at an infusion rate of 100 mL/min. Within 30 minutes, the patient complained of back pain similar to that experienced during cycle 1. The

infusion was stopped, and diphenhydramine hydrochloride 50 mg i.v. and famotidine 20 mg i.v. were administered. After 30 minutes, the infusion was restarted at 50 mL/hr. The patient tolerated the remainder of bag 1 and went on to receive the contents of each remaining bag over 2 hours without incident.

During cycle 3, the patient was again admitted to the general oncology unit and premedicated as in cycle 2. She tolerated all four desensitization bags of docetaxel, each administered over 2 hours. During cycle 4, the infusion rate of the desensitization bags was increased to be administered over 1 hour, and the patient tolerated the doses well.

## **Case report 2**

A 43-year-old white woman had complaints of abdominal pain, bloating, weight loss, decreased appetite, and shortness of breath. She had a history of sleep apnea and psoriasis, as well as a cesarean section and cholecystectomy. She had been pregnant once and given birth once and had a history of tobacco use. She denied any allergies and was not taking any medications before being seen for her current symptoms. She was found to have ascites, and malignant cells were found in the ascitic fluid upon paracentesis. At this time, the patient had a cancer antigen 125 concentration of 924 units/mL (normal, <35 units/mL), which suggested the presence of ovarian cancer.

The patient had a total abdominal hysterectomy and bilateral salpingo-oophorectomy with debulking omentectomy. Her postoperative diagnosis was suboptimally resected, stage IIIC adenocarcinoma of the ovary. At this time, chemotherapy was commenced with paclitaxel, intraperitoneal carboplatin, and bevacizumab. During her first treatment with i.v. paclitaxel at 80 mg/m<sup>2</sup>, the patient began to feel lightheaded approximately 10 minutes into her one-hour infusion despite premedication with ondansetron 8 mg, dexamethasone 20 mg, diphenhydramine hydrochloride 50 mg, and famotidine 20 mg i.v. She experienced flushing and severe chest pain and then became unresponsive and apneic for approximately 20 seconds, during which time she was incontinent of her urine. The infusion was stopped, and the patient regained consciousness after approximately 30 seconds. The reaction was further treated with i.v. dexamethasone 20 mg, diphenhydramine hydrochloride 50 mg, and famotidine 20 mg. Despite these, the patient experienced pain and severe nausea and had one episode of emesis, which may have been related to the morphine that was administered for pain. Her symptoms resolved, and all additional chemotherapy was discontinued due to the severity of the reaction.

The decision was made to replace paclitaxel with docetaxel. Though not extensively evaluated, some patients are able to tolerate docetaxel despite reactions to paclitaxel; however, the frequency of cross-sensitivity may be as high as 90%.<sup>10</sup> Seven days after her initial reaction, the patient was to receive i.v. docetaxel 75 mg/m<sup>2</sup> (a total dose of 123 mg) and carboplatin intraperitoneally. Despite premedication with dexamethasone 20 mg orally the night before chemotherapy and 20 mg i.v. on the day of chemotherapy, along with ondansetron 24 mg orally, diphenhydramine hydrochloride 50 mg i.v., and famotidine 20 mg i.v., the patient again reacted within five minutes of starting the docetaxel infusion. She complained of nausea and flushing, after which her eyes rolled back and she was unable to speak. She also was observed to be having mild tonic jerking

movements. The infusion was stopped, and the aforementioned reaction ceased after approximately one minute.

It was decided to continue cycle 1 with the same docetaxel desensitization protocol used in the previous case (i.e., 0.1%, 1%, 10%, and 88.9% of the total docetaxel dose in 100, 100, 100, and 250 mL of 0.9% sodium chloride injection in bags 1–4, respectively). The patient received oral dexamethasone 20 mg every 6 hours, diphenhydramine hydrochloride 50 mg every 6 hours, and famotidine 20 mg during the 24 hours before admission to the general oncology inpatient unit. Before initiation of the desensitization procedure, the patient received another dose of dexamethasone 20 mg orally, ondansetron 8 mg i.v., diphenhydramine hydrochloride 50 mg i.v., and famotidine 20 mg i.v. Each of the four bags of the desensitization protocol was administered over 1 hour without any problems, and the patient was able to receive the intraperitoneal carboplatin. For cycles 2 and 3, the patient received the same premedications and tolerated desensitization without any signs or symptoms of hypersensitivity.

## Discussion

Whether reactions to taxanes are truly allergic in nature is debatable; however, the majority of patients who react severely can tolerate these medications if administered via a graded drug challenge or desensitization. In a large series of patients ( $n = 57$ ) who underwent rapid desensitization after a hypersensitivity reaction to chemotherapy (carboplatin, paclitaxel, docetaxel, trastuzumab, doxorubicin, or uromitexan), 88% of the 255 courses of therapy were completed without any evidence of a hypersensitivity reaction.<sup>8</sup> Of the 57 patients in that report, only 1 patient received two courses of docetaxel with the desensitization protocol; both courses were tolerated. The desensitization protocol included three solutions (1% of the dose in 100 mL of infusion fluid, 10% of the dose in 100 mL, and 100% of the dose in 100 mL, with the last solution not being completely administered) that were administered in a stepwise fashion, with 12 increases in rate every 15 minutes (4 increases per solution). All solutions were prepared with 5% dextrose injection. Overall, the patients received the entire desensitization protocol over an average of 5.8 hours in the inpatient setting and 3.8 hours in the outpatient setting.

Another report described the use of a rapid desensitization protocol in patients receiving taxanes.<sup>9</sup> In this report, 72 (94%) of the 77 courses of therapy in 17 patients were tolerated without additional hypersensitivity reactions. Of the 17 patients, only 3 received docetaxel (all after reacting to paclitaxel). It is unclear from the report, however, whether the patients received paclitaxel desensitization or docetaxel desensitization. The protocol used in that study was similar to the one described above,<sup>8</sup> except the volume of 5% dextrose injection was 250 rather than 100 mL. The every-15-minute increase in infusion rate was the same in both regimens. The latter report described a premedication scheme including dexamethasone 20 mg orally 12 and 6 hours before the infusion and diphenhydramine hydrochloride 50 mg i.v. and ranitidine 50 mg i.v. 30 minutes before the infusion.

An additional series of 18 patients receiving 60 desensitizations (carboplatin, cisplatin, docetaxel, oxaliplatin, paclitaxel, rituximab) using the protocol described above<sup>9</sup> (three increases in

concentration every 15 minutes) has been described.<sup>11</sup> Of the 60 desensitizations, 58 (97%) allowed administration of the full dose of chemotherapy.

Lastly, 33 women received desensitization to carboplatin, cisplatin, docetaxel, and oxaliplatin with a protocol of increasing infusion rate and drug concentration over 4–6 hours.<sup>12</sup> Of the 307 desensitizations, 268 (87%) were tolerated without any adverse reaction. All patients who experienced a reaction during the desensitization reacted to carboplatin.

In addition to the above patient series, one case report described the use of a desensitization protocol in a 35-year-old man with lung cancer.<sup>13</sup> The patient developed a severe anaphylactic reaction (urticaria and bronchospasm) within 5 minutes of starting the docetaxel infusion. The reaction was treated with dexchlorpheniramine and dexamethasone. To facilitate further administration of the docetaxel, the patient received 13 increasing doses (0.0001%, 0.0003%, 0.001%, 0.003%, 0.01%, 0.03%, 0.1%, 0.3%, 1%, 3%, 10%, 30%, and 50% of the total dose) injected every 30 minutes. The complete dose took 6.5 hours to administer, and the patient tolerated it without any evidence of hypersensitivity.

The two cases we reported, along with the published series and case report, support the feasibility of desensitization via graded docetaxel dose escalations in patients with a history of docetaxel hypersensitivity reactions. The hypersensitivity reactions described are typical of taxane reactions. They occurred at the beginning of the infusions, and both patients experienced symptoms commonly observed in these reactions. The desensitization protocol we used differed from previously published protocols with taxanes in that the doses were given over one to two hours without a rate increase. The absence of rate changes decreases the nursing workload and may decrease the likelihood of errors, given the simplified administration regimen. Premedication before desensitization in our patients was similar to that described in the medical literature.<sup>9</sup> Based on these case reports and published regimens, patients receiving a docetaxel desensitization should, at a minimum, be premedicated with dexamethasone 20 mg orally for two doses before the infusion along with a histamine H<sub>1</sub>-receptor blocker and a histamine H<sub>2</sub>-receptor blocker 30 minutes before the infusion.

Further study regarding the mechanistic causes of taxane hypersensitivity and infusion reactions is necessary. With a clear understanding of this mechanism, adjustments and standardization of premedication and patient selection may reduce the rates of taxane hypersensitivity. Until then, desensitization represents a feasible and effective method to continue the use of docetaxel in patients who would otherwise require termination of the medication.

## **Conclusion**

Two patients who had severe hypersensitivity reactions to docetaxel successfully received further docetaxel doses via a desensitization procedure that involved the sequential administration of solutions containing increasing concentrations of the drug.

## **Footnotes**

The authors have declared no potential conflicts of interest.

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