Abraxane for the Treatment of Gynecologic Cancer Patients With Severe Hypersensitivity Reactions to Paclitaxel

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Background: Paclitaxel is used in the treatment of most gynecologic malignancies. It is solubilized in Cremophor EL, a polyoxyethylated castor oil agent responsible for the high rate of paclitaxel-associated hypersensitivity reactions. Abraxane, a newer, Cremophor–free form of albumin bound paclitaxel has demonstrated an activity and an improved toxicity profile in breast and lung cancers.

Case Reports: Five patients with gynecologic cancers (2 ovarian, 2 endometrial, and 1 cervical malignancy) received Abraxane after having a hypersensitivity reaction to paclitaxel. All five patients tolerated Abraxane well, experiencing no reactions or major side effects to the drug.

Discussion: Abraxane is well tolerated in women with gynecologic cancer who have experienced a paclitaxel-associated hypersensitivity reaction. Further studies are ongoing to determine the clinical activity of Abraxane in the treatment of these malignancies.

Key Words: Paclitaxel, Hypersensitivity reaction, Abraxane, Chemotherapy

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proximal ileal transverse enterocolostomy, and creation of an ileal mucous fistula; however, the SBO recurred 1 month later secondary to diffusely metastatic abdominal disease. After management of the SBO with conservative measures, she was initiated on weekly 80-mg/m² Abraxane and has tolerated her first 4 doses well without HSRs or neutropenia and evidence of recurrent intestinal obstruction.

Case 2
A 50-year-old woman with uterine fibroids underwent a laparotomy by a general gynecologist but was found to have carcinomatosis with enlarged, bilateral ovarian masses and a serum cancer antigen 125 (CA-125) level of 3713 U/mL. The disease was deemed unresectable by a general surgeon who was consulted intraoperatively. She was referred to a gynecologic oncologist 14 days postoperatively who recommended adjuvant chemotherapy with possible interval debulking. After premedication with dexamethasone and antihistamines and receiving 3 mL of her first dose of paclitaxel (175 mg/m²), she experienced intense flushing, chest pain, bronchospasm, hypotension, and dyspnea with an oxygen saturation of 79%. Her paclitaxel infusion was discontinued, and she was successfully resuscitated. The patient then received 4 cycles of carboplatin (AUC, 6) and gemcitabine (400 mg/m²) and underwent an optimal debulking procedure followed by 4 more cycles of the same regimen with normalization of her serum CA-125 level. Four months later, her CA-125 levels rose precipitously, and she received several different single-agent regimens sequentially but did not respond. The patient developed shortness of breath from diffuse pulmonary interstitial metastases and was given 100-mg/m² Abraxane. She tolerated her first course well, but in view of her progressive disease and symptoms, she did not receive further therapy and died of her disease 1 month later.

Case 3
A 60-year-old woman with postmenopausal bleeding and a history of idiopathic thrombocytopenic purpura had an endometrial biopsy revealing a poorly differentiated endometrial cancer. A preoperative CA-125 level was 418 U/mL. Stage IV papillary serous endometrial cancer was diagnosed at the time of a staging procedure. After premedication with steroids and antihistamines, she was initiated on carboplatin (AUC, 4) and paclitaxel (135 mg/m²), empirically reduced dosing secondary to her idiopathic thrombocytopenic purpura and a baseline platelet count of 73,000/mcL but experienced reactions (severe flushing, dyspnea with hypoxia, and hives) soon after her paclitaxel infusion was started. Her symptoms resolved upon discontinuation of the drug and with fluids and additional antihistamines. She was treated with single-agent carboplatin for an additional cycle, but her CA-125 level and ascites increased. She was treated with gemcitabine (400 mg/m²) and carboplatin (AUC, 4) for 6 cycles, after which her serum CA-125 levels increased for 3 months. The patient’s regimen was changed to weekly 100-mg/m² Abraxane therapy. She received 9 weeks of therapy without neutropenia or thrombocytopenia and did not have a recurrence of her paclitaxel-associated HSR. Although her CA-125 level did decrease, she developed progressive ascites and died 1 month after her last dose of Abraxane.

Case 4
An 80-year-old woman with multiple comorbidities had a diagnosis of metastatic papillary serous endometrial cancer by endometrial biopsy and abdominopelvic computed tomography (CT). In view of extensive pelvic disease with a 5-cm tumor involving the vagina and left parametria, a plan for neoadjuvant chemotherapy with carboplatin and paclitaxel was made. She received standard premedication with steroids and antihistamines; however, as her paclitaxel infusion was started, she experienced severe pain between her shoulder blades, hypotension, nausea, and intense flushing. The infusion was immediately discontinued, and her symptoms resolved. She was switched to weekly 80-mg/m² Abraxane therapy and carboplatin (AUC, 2). She has successfully completed 6 weeks of therapy at this time without further HSRs or myelosuppression. Her vaginal disease has resolved, and the parametrial disease is responding; therefore, further therapy with Abraxane is planned.

Case 5
A 58-year-old woman with a remote history of right-breast cancer was referred to a gynecologic oncologist for a poorly differentiated adenocarcinoma. She reported a history of irregular, copious vaginal bleeding and on presentation, was noted to have a large endocervical mass and a hemoglobin level of 5 U/dL. The patient received a blood transfusion and imaging, and biopsy studies demonstrated a large cervical adenosquamous carcinoma extending through the rectal wall. The patient was initiated on neoadjuvant chemotherapy with carboplatin (AUC, 6) and 175-mg/m² paclitaxel. After experiencing severe reactions (hypotension, respiratory compromise, and flushing) within minutes of receiving the first drops of IV paclitaxel, the patient was treated with 5 cycles of neoadjuvant chemotherapy with gemcitabine (400 mg/m²) and carboplatin (AUC, 6). She subsequently underwent an exploratory laparotomy, which revealed a normal-appearing, small uterus and evidence that the tumor originated from the cervix. A partial omentectomy was performed to resect metastatic nodular disease.

Since then, she received an additional 16 cycles of gemcitabine and carboplatin complicated by neutropenic fever on 3 occasions. Because of the progression of the disease, she was then treated with radiation therapy (external beam radiation therapy totaling 45 Gy and additional brachytherapy totaling 20.2 Gy). A posttreatment CT demonstrated a stationary mass in the right part of the pelvis, and a subsequent positron emission tomography demonstrated an uptake consistent with persistent disease. After unsuccessful treatment with 6 cycles of Almita (Eli Lilly and Co), the patient developed symptoms of a rectovaginal fistula, which was confirmed by barium enema. After a diverting colostomy, she was initiated on weekly Abraxane therapy (80 mg/m²). She received 24 weeks of therapy and experienced no episodes of neutropenia or neuropathy and stabilization of her disease. However, after her last dose, she had evidence of progression on a CT scan, and the treatment was changed to Cetuximab (Bristol-Meyers Squib, New York, NY).

DISCUSSION
Paclitaxel (Taxol) is one of the most widely used chemotherapeutic agents for the treatment of solid tumors, including ovarian, endometrial, cervical, breast, non–small-cell lung, and gastric cancers. Although active in most of these malignancies, some patients will not tolerate the drug secondary to HSRs of varying degrees of severity. Because this reaction occurs with the first exposure to paclitaxel, it is not a true anaphylactoid reaction, which requires prior exposure and sensitization. Severe HSRs (severe hypotension and respiratory compromise) occurring with initial exposure are best referred to as pseudoanaphylactoid reactions. In a retrospective report of more than 450 patients receiving paclitaxel for treatment of a female pelvic malignancy, Markman and colleagues reported an incidence of 9% of significant paclitaxel HSRs. In this same report, they describe successfully rechallenging 93% of patients who experienced HSRs with paclitaxel within 30 minutes after the occurrence of the reaction. However, in 1 patient described as having a poor performance status and a pseudoanaphylactoid-type reaction (severe hypotension and respiratory
compromise), the authors chose not to readminister paclitaxel. Therefore, in gynecologic oncology patients who have mild to severe, nonanaphylactoid reactions to paclitaxel, it is reasonable to offer them a rechallenge of the drug. However, it is less clear whether patients with pseudo–anaphylactoid-type reactions to paclitaxel or those who experience a second HSR should be reexposed to this agent.

Abraxane, an albumin-bound, Cremophor EL–free formulation of paclitaxel, represents an innovation in chemotherapy that may allow patients who experience severe or anaphylactoid HSRs the opportunity to continue on a taxane-based regimen. Abraxane not only appears to be well tolerated in patients with cancer who have HSRs to paclitaxel, but also has less overall myelosuppression. Noteworthily, Abraxane has been shown to be more neurotoxic than standard paclitaxel, although a more rapid improvement of peripheral neuropathy has been reported. For these reasons, Abraxane may be administered using higher doses than that of standard paclitaxel, with shorter infusion duration and without the requirement for corticosteroid and antihistamine premedication.

In the cases presented in this institutional review board–approved, retrospective case series, all 5 women with gynecologic malignancies experienced significant paclitaxel-associated HSRs during their first exposure to the drug (Table 1). All experienced severe acute reactions characterized by dyspnea, hypotension, and flushing (with varying degrees of bronchospasm and respiratory compromise), within minutes of receiving IV Taxol. Although HSRs to paclitaxel usually occur with the first dose, delayed HSRs less commonly occur with later infusions.

It is possible that some of the patients presented in this series might have tolerated a paclitaxel rechallenge. However, the drug was not offered secondary to the severity of their respective reactions. All of the patients tolerated Abraxane therapy well and experienced no recurrence in their HSRs or any grades 3 to 4 neutropenia or peripheral neuropathy. Noteworthily, although the solvent Cremophor EL is thought to be the cause of most paclitaxel-associated HSRs, paclitaxel itself is capable of initiating HSRs independent of the effects of its vehicle. This is evidenced by an in vitro study of histamine release from the leukocytes of patients who had a documented HSR to paclitaxel in which paclitaxel stimulated histamine release, whereas the Cremophor EL did not. Therefore, Abraxane should still be used with caution in patients with HSRs to paclitaxel.

Currently, there are no published trials demonstrating the clinical activity of Abraxane for the treatment of gynecologic malignancies. Two recent prospective trials have demonstrated that Abraxane has a significant activity in the treatment of metastatic breast (overall response rate, 16%) and non–small-cell lung cancers (overall response rate, 16%). Furthermore, in the phase 3 metastatic breast cancer trial, Abraxane demonstrated superior disease-free and overall survival rates when compared with standard paclitaxel. No conclusions can be drawn on the objective response rates of Abraxane in this series, as the patients represented had different gynecologic malignancies with varying stages of disease, and Abraxane was introduced at different time points in their respective treatment cycles. However, of the 5 patients experienced a partial response or stabilization of their disease while on Abraxane therapy. Clinical trials are underway, including a Gynecologic Oncology Group study of Abraxane therapy in cervical cancer, to determine the activity and toxicity of this taxane in the treatment of women with both primary and recurrent gynecologic malignancies.

### REFERENCES


### TABLE 1. Patient characteristics and Abraxane profiles

<table>
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