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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Universal tolerance of nab-paclitaxel for gynecologic malignancies in patients with prior taxane hypersensitivity reactions

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ABSTRACT

Objective: To report on the incidence of nab-paclitaxel hypersensitivity reactions (HSRs) in patients with prior taxane HSR.

Methods: From 2005 to 2015, all patients who received nab-paclitaxel for a gynecologic malignancy were identified. Chart abstraction included pathology, prior therapy, indication for nab-paclitaxel, dosing, response, toxicities including any HSR, and reason for discontinuation of nab-paclitaxel therapy.

Results: We identified 37 patients with gynecologic malignancies with a history of paclitaxel HSR who received nab-paclitaxel. Six patients (16.2%) had a prior HSR to both paclitaxel and docetaxel while the other 31 patients had not received docetaxel. No patients experienced a HSR to nab-paclitaxel. Median number of cycles of nab-paclitaxel was 6 (range 2–20). Twelve patients received weekly dosing at 60 to 100 mg/m². The remainder of patients received 135 mg/m² (n=13), 175 mg/m² (n=9), or 225 mg/m² (n=3). Thirty four patients (91.9%) received nab-paclitaxel in combination with carboplatin (n=28, 75.7%), IP cisplatin (n=1, 2.7%), carboplatin and bevacizumab (n=3, 8.1%), or carboplatin and gemcitabine (n=2, 5.4%). Reasons for discontinuing nab-paclitaxel included completion of adjuvant therapy (n=16), progressive disease (n=18), toxicity (n=1), and death (n=1). There were no grade 4 complications identified during nab-paclitaxel administration. Grade 3 complications included: neutropenia (n=9), thrombocytopenia (n=4), anemia (n=1), and neurotoxicity (n=1).

Conclusion: Nab-paclitaxel is well-tolerated with no HSRs observed in this series of patients with prior taxane HSR. Given the important role of taxane therapy in nearly all gynecologic malignancies, administration of nab-paclitaxel should be considered prior to abandoning taxane therapy.

Keywords: Albumin-Bound Paclitaxel; Drug Hypersensitivity; Drug Therapy

INTRODUCTION

Paclitaxel is a key cytotoxic agent in the first line and recurrent setting for most gynecologic malignancies. Although active in these malignancies, some patients will not tolerate the drug secondary to hypersensitivity reactions (HSRs). While the exact etiology of the HSRs is not specifically known, the Cremophor solvent required for the hydrophobic paclitaxel

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is thought to play a role [1]. In a retrospective report of more than 450 patients receiving paclitaxel for treatment of a female pelvic malignancy, Markman and colleagues [2] reported a 9% incidence of significant paclitaxel HSRs. Nab-paclitaxel is a soluble form of paclitaxel that is linked to albumin nanoparticles. The use of nanotechnology as a delivery system for paclitaxel was designed in part to neutralize paclitaxel's hydrophobicity and thus eliminate the need for the Cremophor solvent [3,4]. The clinical activity of nab-paclitaxel has been compared to paclitaxel. In a phase III metastatic breast cancer trial, patients treated with nab-paclitaxel had a higher response rate, prolonged time to tumor progression, and an absence of HSRs [5]. This anti-tumor activity in combination with the lack of HSRs makes the drug an appealing option for patients with HSRs to paclitaxel. The first published case report of the use of nab-paclitaxel in the treatment of ovarian cancer described a patient with HSR to paclitaxel who tolerated nab-paclitaxel [6]. Subsequently, an additional case series reporting on a total of 5 patients with ovarian cancer who received nab-paclitaxel after HSR to paclitaxel with mixed responses but no HSRs [7]. Finally, a more recent case report describes a patient with ovarian cancer who had successful treatment with nab-paclitaxel after HSR to both paclitaxel and docetaxel [8]. These cases represent the entirety of the published literature on the use of nab-paclitaxel in patients with gynecologic malignancies and a prior taxane HSRs.

Given these promising case reports, several patients had been treated at our institution with nab-paclitaxel after a HSR to paclitaxel and docetaxel. Therefore, we sought to summarize our experience with nab-paclitaxel in these patients and report on the safety of this option in patients with prior taxane HSRs.

MATERIALS AND METHODS

We performed a retrospective chart review. Using International Classification of Diseases, Ninth Revision (ICD-9) codes for the gynecologic malignancies and pharmacy data to identify all administrations of nab-paclitaxel, we were able to identify all women over age 18 who had ovarian, primary peritoneal, fallopian tube, cervical, or uterine cancer who received at least one dose of nab-paclitaxel at our institution from 2005–2015. Chart review then identified all women who had a prior HSR to either paclitaxel and/or docetaxel as the indication for nab-paclitaxel use.

Medical record review included review of clinic notes, infusion center notes, pathology reports, surgical reports, imaging, and laboratory data. Serious grade 3 or 4 adverse effects were noted per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) [9]. The assessment of tumor response was based on radiologic evaluation according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [10] or decline in CA-125 in patients without measurable disease.

RESULTS

We identified 37 women with gynecologic malignancies and a history of paclitaxel HSR who received nab-paclitaxel. This included 22 women with ovarian cancer, 12 with endometrial cancer, 2 with uterine sarcoma, and 1 with cervical cancer. Six women (16.2%) had a prior HSR to both paclitaxel and docetaxel while the other 31 (83.8%) women had not received

docetaxel. None of the women experienced a HSR to nab-paclitaxel. Their demographic, clinical, and treatment data is summarized in **Table 1**.

Prior to paclitaxel administration, all patients had received premedication with dexamethasone (20 mg), diphenhydramine (50 mg), and famotidine (20 mg) IV 30 minutes before chemotherapy. Eighty-six percent of the patients experienced their HSR during their initial treatment with paclitaxel, whereas 3 individuals (8.1%) and 2 individuals (5.4%) had their first reactions during course 2 and 3, respectively. Prior to docetaxel administration, patients received premedication with dexamethasone (20 mg PO evening before and morning of treatment), diphenhydramine (50 mg) and famotidine (20 mg) IV 30 minutes before chemotherapy. All HSRs to docetaxel (n=6) occurred during their initial treatment. The signs and symptoms of HSR in these patients included at least one, but usually several, of the following: pruritus, chest tightness, severe back pain, dyspnea, extreme anxiety, tachycardia, diffuse erythroderma, and hypotension or hypertension. None of the patients included in this series required intubation for anaphylaxis however a few patients did require hospital admission and monitoring.

For nab-paclitaxel administration, patients received premedication with dexamethasone (10 mg IV) alone for the first 3 cycles after which this was discontinued unless they were also receiving a moderate to high emetogenic drug in combination. Patients were closely observed in the outpatient chemotherapy suite during their first and second infusion to monitor for HSR. The median number of cycles of nab-paclitaxel was 6 (range 2–20). Twelve patients received weekly dosing at 60 mg/m² (n=2), 80 mg/m² (n=5), or 100 mg/m² (n=5). The remainder of patients received 135 mg/m² (n= 13), 175 mg/m² (n=9), or 225 mg/m² (n=3) every 21 days. Three patients received single agent nab-paclitaxel. The remainder of the patients (n=34, 91.9%) received nab-paclitaxel in combination regimens. Agents received in combination were: carboplatin (n=28, 75.7%), intraperitoneal cisplatin (n=1, 2.7%),

Table 1. Demographic, clinical, treatment characteristics of patients with taxane HSR receiving nab-paclitaxel

Variable	No. (%)
No. of patients	37
Age (median, range)	63 (34–79)
Race	
White	35 (94.6)
African American	2 (5.4)
Malignancy	
Ovarian	22 (59.4)
Endometrial	12 (32.4)
Uterine sarcoma	2 (5.4)
Cervical	1 (2.8)
HSR to taxane	
Paclitaxel only	31 (83.8)
Paclitaxel and docetaxel	6 (16.2)
Cycle of paclitaxel HSR	
1	32 (86.0)
2	3 (8.1)
3	2 (5.4)
Cycle of docetaxel HSR (n=6)	
1	6 (100.0)
Cycle of nab-paclitaxel (median, range)	6 (2–20)
Indication for taxane therapy	
Adjuvant	20 (54.0)
Recurrent/Measurable disease	17 (46.0)

HSR, hypersensitivity reaction.

carboplatin and bevacizumab (n=3, 8.1%), or carboplatin and gemcitabine (n=2, 5.4%). While 20 patients received nab-paclitaxel in the adjuvant setting, 17 patients had either measurable disease evaluable for response or elevated CA-125. The best overall response was complete response for 4 patients, partial response for 6 patients, stable disease for 1 patient, and progression for 6 patients. The overall response rate was 58.8%. Reasons for discontinuing nab-paclitaxel included completion of adjuvant therapy (n=17, 45.9%), progressive disease (n=18, 48.6%), toxicity (n=1, 2.6%), and death (n=1, 2.6%). The one death of a patient undergoing nab-paclitaxel therapy occurred during adjuvant treatment of a suboptimally debulked ovarian cancer patient receiving carboplatin and nab-paclitaxel. She died of pulseless electrical activity cardiac arrest 9 days after receiving nab-paclitaxel while admitted to the intensive care unit (ICU) with *Clostridium Difficile* colitis. She was not neutropenic at that time. There were no other possible treatment-related grade 4 complications noted. Grade 3 complications included: neutropenia (n=9), thrombocytopenia (n=4), anemia (n=1), and neurotoxicity (n=1). The rates of alopecia were not able to reliably be ascertained from this retrospective chart review.

DISCUSSION

Nab-paclitaxel is well-tolerated with no HSRs observed in this cohort of several patients with a prior taxane HSR. While premedications have reduced the incidence of taxane related HSR to around 4%–6% [11,12], given the common use of taxanes in the adjuvant and recurrent setting in nearly all gynecologic malignancies, it is important to address options for those patients who develop HSR after appropriate premedication.

Both retreatment and desensitization protocols have been described for these patients [2,13-15]. Markman and colleagues [2] described a retreatment strategy for patients experiencing a paclitaxel associated HSR as well as a desensitization protocol. Using their algorithm, nearly all of the patients with initial HSRs to paclitaxel were eventually able to tolerate the medication. While this remains an option for some patients and retreatment is a strategy used at our institution in select patients with mild to moderate reactions, the patients included in this study represent patients who were not re-challenged after their HSR due to clinician judgment, patient preference, or overall clinical picture. Furthermore, desensitization programs are lengthy, require multiple drug formulations, and often require inpatient hospital admission. Importantly, severe reactions have been reported in the setting of taxane desensitization.

The retrospective cohort described in this series included a variety of histologies and stages who received treatment in both the adjuvant and recurrent setting. Therefore, we are unable to draw conclusions about the efficacy of nab-paclitaxel. There are, however, 2 prospective phase II studies of nab-paclitaxel in recurrent ovarian, fallopian tube, and primary peritoneal cancer [16,17] and one phase II trial of nab-paclitaxel in recurrent or persistent cervix cancer [18]. The ovarian cancer trials showed activity of the drug with overall response rates of 64% (platinum sensitive) and 23% (platinum resistant).

In recurrent and persistent cervical cancer, 10 (28.6%) of the 35 patients had a partial response and another 15 patients (42.9%) had stable disease. While there are no trials of nab-paclitaxel in the adjuvant setting, which is where the majority of patients with HSRs to taxanes will occur, we find the activity seen in these phase II trials as well as studies in breast cancer and other solid tumors reassuring.

No hypersensitivity reactions with nab-paclitaxel

Table 2. Summary of prior reports of nab-paclitaxel use after taxane HSR

Publication	No. of patients	Age range	Taxane with HSR	No. of cycles of taxane prior to HSR	No. of cycles of nab-paclitaxel received	Dose of nab-paclitaxel (mg/m ²)
Micha et al. [6]	1	60	Paclitaxel	1	3	30
Fader et al. [7]	5	47–80	Paclitaxel	1–1	1–24	80, 100
de Leon et al. [8]	1	60	Paclitaxel and docetaxel	1	3	100

HSR, hypersensitivity reaction.

In this case series, nab-paclitaxel was well-tolerated with only one patient stopping therapy due to toxicity. Hematologic toxicities made up 14 of the 15 grade 3 complications. Previous work has compared the toxicity profiles of nab-paclitaxel and paclitaxel. The largest phase III trial of these 2 drugs in metastatic breast cancer showed the incidence of grade 4 neutropenia lower for nab-paclitaxel compared with paclitaxel (9% vs. 22%) [5]. However, grade 3 sensory neuropathy was more common in the nab-paclitaxel arm than in the paclitaxel arm (10% vs. 2%). Febrile neutropenia was rare (<2%), and no different between the 2 drugs. Importantly, this study also demonstrated no HSRs in the nab-paclitaxel arm.

While isolated case reports exist suggest the safety of the use of nab-paclitaxel inpatients with taxane HSRs, these reports encompassed a total of seven patients (**Table 2**) [6–8]. We now present data from an entire series of patients with significant HSRs to taxanes who were treated with nab-paclitaxel. Nab-paclitaxel was universally tolerated in this cohort of patients with no HSRs reported. While the overall number of patients treated thus far is still small and does not completely rule out the risk of a significant reaction occurring in the future, we are reassured by the safety profile described here. While we acknowledge that the drug cost of nab-paclitaxel is higher than either other taxane, when compared to desensitization protocols, its administration would result in shorter chemotherapy chair time and nursing administration costs. At the very least, it could be used for patients who fail retreatment or desensitization protocols.

Given the important role of taxane therapy in gynecologic malignancies, nab-paclitaxel administration should be considered prior to moving to other treatment options for patients with taxane HSRs.

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