J Gynecol Oncol. 2017 Jul;28(4):e38
https://doi.org/10.3802/jgo.2017.28.e38
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Check for updates

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

Kathryn Maurer, Chad Michener, Haider Mahdi, Peter G. Rose

Division of Gynecologic Oncology, OB/GYN and Women's Health Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

OPEN ACCESS

Received: Aug 8, 2016
Revised: Feb 9, 2017
Accepted: Feb 15, 2017

Correspondence to
Kathryn Maurer
Division of Gynecologic Oncology, OB/GYN and Women's Health Institute, 9500 Euclid Avenue, Cleveland, OH 44195, USA.
E-mail: maurerk@ccf.org

Copyright © 2017. Asian Society of Gynecologic Oncology, Korean Society of Gynecologic Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs
Kathryn Maurer
https://orcid.org/0000-0002-5917-0173
Chad Michener
https://orcid.org/0000-0001-5170-6626
Haider Mahdi
https://orcid.org/0000-0002-6343-5314
Peter G. Rose
https://orcid.org/0000-0001-7705-3432

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

Author Contributions
Conceptualization: M.K., R.P.G.; Data curation: M.K., M.C., M.H., R.P.G.; Formal analysis: M.K.; Investigation: M.K.; Methodology: M.K., R.P.G.;

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/m^2. The remainder of patients received 135 mg/m^2 (n=13), 175 mg/m^2 (n=9), or 225 mg/m^2 (n=3). Thirty four patients (91.9%) received 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

Generated by xmlinkpress

Project administration: R.P.G.; Resources: R.P.G.; Software: M.K.; Supervision: M.C., M.H., R.P.; Validation: M.C., M.H., R.P.G.; Writing - original draft: M.K.; Writing - review & editing: M.K., M.C., M.H., R.P.G.

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/m^2 (n=2), 80 mg/m^2 (n=5), or 100 mg/m^2 (n=5). The remainder of patients received 135 mg/m^2 (n= 13), 175 mg/m^2 (n=9), or 225 mg/m^2 (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.

https://doi.org/10.3802/jgo.2017.28.e38

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 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.

https://doi.org/10.3802/jgo.2017.28.e38

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.

REFERENCES

1. Hájek R, Vorlicek J, Slavik M. Paclitaxel (Taxol): a review of its antitumor activity in clinical studies minireview. Neoplasma 1996;43:141-54.
PUBMED
2. Markman M, Kennedy A, Webster K, Kulp B, Peterson G, Belinson J. Paclitaxel-associated hypersensitivity reactions: experience of the gynecologic oncology program of the Cleveland Clinic Cancer Center. J Clin Oncol 2000;18:102-5.
PUBMED
3. Nyman DW, Campbell KJ, Hersh E, Long K, Richardson K, Trieu V, et al. Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies. J Clin Oncol 2005;23:7785-93.
PUBMED | CROSSREF
4. Gradishar WJ. Albumin-bound paclitaxel: a next-generation taxane. Expert Opin Pharmacother 2006;7:1041-53.
PUBMED | CROSSREF
5. Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 2005;23:7794-803.
PUBMED | CROSSREF

6. Micha JP, Goldstein BH, Birk CL, Rettenmaier MA, Brown JV 3rd. Abraxane in the treatment of ovarian cancer: the absence of hypersensitivity reactions. Gynecol Oncol 2006;100:437-8.
PUBMED | CROSSREF
7. Fader AN, Rose PG. Abraxane for the treatment of gynecologic cancer patients with severe hypersensitivity reactions to paclitaxel. Int J Gynecol Cancer 2009;19:1281-3.
PUBMED | CROSSREF
8. de Leon MC, Bolla S, Greene B, Hutchinson L, Del Priore G. Successful treatment with nab-paclitaxel after hypersensitivity reaction to paclitaxel and docetaxel. Gynecol Oncol Case Rep 2013;5:70-1.
PUBMED | CROSSREF
9. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common terminology criteria for adverse events (CTCAE): version 4.0. Washington, D.C.: U.S. Department of Health and Human Services; 2009 May 28. (v4.03: June 14, 2010).
10. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
PUBMED | CROSSREF
11. Bookman MA, Kloth DD, Kover PE, Smolinski S, Ozols RF. Short-course intravenous prophylaxis for paclitaxel-related hypersensitivity reactions. Ann Oncol 1997;8:611-4.
PUBMED | CROSSREF
12. Markman M, Kennedy A, Webster K, Peterson G, Kulp B, Belinson J. An effective and more convenient drug regimen for prophylaxis against paclitaxel-associated hypersensitivity reactions. J Cancer Res Clin Oncol 1999;125:427-9.
PUBMED | CROSSREF
13. Feldweg AM, Lee CW, Matulonis UA, Castells M. Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments. Gynecol Oncol 2005;96:824-9.
PUBMED | CROSSREF
14. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-80.
PUBMED | CROSSREF
15. Boulanger J, Boursiquot JN, Cournoyer G, Lemieux J, Masse MS, Almanric K, et al. Management of hypersensitivity to platinum- and taxane-based chemotherapy: cepo review and clinical recommendations. Curr Oncol 2014;21:e630-41.
PUBMED | CROSSREF
16. Teneriello MG, Tseng PC, Crozier M, Encarnacion C, Hancock K, Messing MJ, et al. Phase II evaluation of nanoparticle albumin-bound paclitaxel in platinum-sensitive patients with recurrent ovarian, peritoneal, or fallopian tube cancer. J Clin Oncol 2009;27:1426-31.
PUBMED | CROSSREF
17. Coleman RL, Brady WE, McMeekin DS, Rose PG, Soper JT, Lentz SS, et al. A phase II evaluation of nanoparticle, albumin-bound (nab) paclitaxel in the treatment of recurrent or persistent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer: a Gynecologic Oncology Group study. Gynecol Oncol 2011;122:111-5.
PUBMED | CROSSREF
18. Alberts DS, Blessing JA, Landrum LM, Warshal DP, Martin LP, Rose SL, et al. Phase II trial of nab-paclitaxel in the treatment of recurrent or persistent advanced cervix cancer: a gynecologic oncology group study. Gynecol Oncol 2012;127:451-5.
PUBMED | CROSSREF