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Docetaxel and nab-paclitaxel are safe alternative options for patients with gynecologic malignancies following hypersensitivity reaction to paclitaxel

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Summary

Docetaxel and nab-paclitaxel are safe alternatives to paclitaxel after hypersensitivity reaction occurs. There was no significant difference in overall survival between those that had paclitaxel, docetaxel, and nab-paclitaxel.

Key words: Hypersensitivity; Reaction; Paclitaxel; Docetaxel; Nab-paclitaxel.

Introduction

As the second most common gynecologic malignancy and the fifth leading cause of female's cancer-related deaths in the United States, epithelial ovarian cancer and the treatment thereof has lagged behind advances in treatment of other cancers. This is partly due to the "silent" nature of the disease and the average late stage that patients tend to present with. Traditional first-line chemotherapy of ovarian cancer is with carboplatin and paclitaxel. Paclitaxel is a toxin derived from the yew tree that promotes assembly and stabilization of microtubules, which arrests replication of rapidly dividing cells. It is poorly water soluble and is suspended in Cremophor. Cremophor is a heterogeneous, non-ionic surfactant used to dissolve poorly water-soluble compounds in a variety of applications including anesthetics, immunosuppressive agents, and sedatives. Paclitaxel is different than most of these applications in that the amount of cremophor solvent is roughly five times that used in these other applications. The use of this delivery vehicle has been associated with severe anaphylactoid hypersensitivity reactions and peripheral neuropathy [1]. Docetaxel is prepared by a semisynthesis beginning with the precursor extract from the yew plant and is dissolved in a solution of polysorbate and dehydrated alcohol [2]. The combination of docetaxel and carboplatin was found to have similar survival to that of paclitaxel with carboplatin with less toxicity in first line treatment of ovarian cancer in a phase III study published from SCOTROC 1 (Scottish Randomised Trial in Ovarian Cancer 1) in 2004 [3]. The study arms here were randomized to receive either docetaxel or paclitaxel in combination with carboplatin from the outset of first-line treatment of ovarian cancer. Less neurotoxicity and more myelosuppression were noted in the docetaxel arm [4]. Grade 3 or 4 neutropenia was noted in 94% of the docetaxel arm versus 82% of the paclitaxel arm. However this myelosuppression did not have significant effects on mortality and no patients stopped treatment early because of this side effect. However patients did stop their treatment with paclitaxel secondary to poor tolerance of associated neurotoxicity. However the most recent data from GOG 218, provided no evidence that neurotoxicity was improved in patients with advanced ovarian cancer that received docetaxel [5]. Up to 23% of patients that completed the traditional six-cycle regimen of paclitaxel and a platin-containing agent still have residual neuropathic symptoms 48 months after treatment with significant impairment in activities of daily living [6]. No studies to date have specifically evaluated outcomes in patients that were switched from paclitaxel to another taxane due to toxicity and or hypersensitivity reactions. Furthermore, the most recent formulation of taxanes for use in gynecologic malignancies, nab-paclitaxel, also needs further studies on efficacy and survival. Nab-paclitaxel is a nanoparticle of albumin-bound and stabilized paclitaxel, which has shown promising efficacy and toxicity profiles relative to other taxanes, such as paclitaxel and docetaxel. Nab-paclitaxel has been associated with higher intra-tumoral concentrations of paclitaxel relative to traditional formulation of Cremophor-based paclitaxel [7].

The objective of this study was to determine if there is a difference in tolerance and survival for patients who have paclitaxel reactions and are switched to docetaxel or other taxane agents for first-line chemotherapy in gynecologic malignancies.

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Table 1. — *Demographic data.*

	A Paclitaxel and docetaxel reaction	B Paclitaxel < 3	C Paclitaxel + 3	*p*-value
n	12	34	13	
Taxol cycles	1.1	1.6	4.2	
Total cycles of taxanes	2.6	6.6	7.2	
Baseline CA125	1165.6	809.8	2130.9	0.3142
Debulking				
Optimal	10	27	10	0.9945
Sub-optimal	2	5	2	
Histology				
Other	0	10	6	0.04298
Mixed	4	3	2	
Serous	8	15	4	
Endometriod	0	6	1	
Age mean	*	62.7	61.9	0.8039
Primary				
Ovary/primary Peritoneal/fallopian	8	22	11	0.4035
Uterine	4	12	2	
Stage				
I/II	5	10	4	0.7313
III/IV	7	24	9	
Grade				
1/2	0	6	6	0.01504
3	12	27	7	
Platin status				
Ref/res	2	14	5	0.3508
Sens	7	15	5	
OS months**				
Deaths	4	12	4	
Median	30.5 (25.8-NA)	51.9 (24.0-NA)	NA (21.4-NA)	0.259
PFS months**				
Death/progression/ recurrence	5	19	7	
Median	25.3 (14.1-NA)	13.0 (10.1-NA)	74.6 (9.4-NA)	0.241
Follow up				
Median months	21.1	18.3	24.5	0.1821

NA: No median estimate. * No data. ** Not statistically significant .
A: Patients that had a reaction to taxol and taxotere.
B: Patients with a reaction to taxol in the first or second cycle.
C: Patients with a reaction to taxol on cycle 3 or later.

Materials and Methods

After IRB approval was obtained, a search of the gynecologic malignancy chemotherapy database at Roswell Park Cancer Institute was performed, specifically looking for all patients whom had reactions to paclitaxel and were subsequently given docetaxel for their subsequent cycles of chemotherapy. Data was collected that included variables from number of cycles of paclitaxel/docetaxel, if they had further reaction to docetaxel and went on to receive nab-paclitaxel, CA125 at baseline, basic demographics, type of reaction, cancer histology and grade, cancer stage, debulking status, clinical response, primary site, and BMI. An exploratory analysis of these data was performed and Kaplan Meier curves were generated.

Table 2. — *Common complications for patients receiving taxanes, broken into groups of less than three and three or more cycles of paclitaxel.*

Symptom	Total observations	Paclitaxel/ docetaxel RXN	Paclitaxel < 3	Paclitaxel 3 +	*p*-value
Back pain	20	33%	35%	31%	0.95903246
Neuropathy	19	17%	29%	54%	0.12409234
Flushing	18	8%	41%	23%	0.08611511
Short of breath	10	8%	24%	8%	0.301957
Chest pain	6	8%	15%	0%	0.33139956
Anaphylaxis	5	25%	6%	0%	0.05743787
Rash	3	17%	0%	8%	0.07020789
Hives	1	8%	0%	0%	0.14118638
Rigors	1	0%	3%	0%	0.69960539

Results

At the time of the present study analysis, there were eight (13.5%) patients without evidence of disease, 31 (52.5%) patients with evidence of disease, and 20 (33.9%) that have died of disease. Forty-six (78%) of patients with paclitaxel reactions had a reaction before the third cycle of chemotherapy while 13 (22%) had reactions in the third or subsequent cycles. Patients with serous histology were also associated with more early paclitaxel reactions (23/59, 40%) and also had the highest proportion of patients that reacted to both paclitaxel and docetaxel (8/59, 13.5%) (p = 0.04298) (Table 1). Patients with grade 1 or 2 disease had equal numbers of patients in the less than three cycles of taxol and three or more cycles group, and none of these patients had reactions to taxol and taxotere. However in grade 3 disease, 12 patients (20.3%) had both paclitaxel and docetaxel reactions and went on to receive nab-paclitaxel (p = 0.01504) (Table 1). Early paclitaxel reactions (before the third cycle) are associated with a trend toward poorer patient outcomes with four times as many deaths noted in the less than three cycles of paclitaxel group. Median progression-free survival (PFS) was 13.1 months in those patients that reacted to paclitaxel in less than three cycles, versus 74.6 months in those that had three or more cycles and 25.3 months for those that reacted to both paclitaxel and docetaxel and received nab-paclitaxel (p = 0.241).

The most common reactions leading to a switch in taxane were back pain, neuropathy, flushing, and shortness of breath (Table 2). Anaphylactic reactions occurred in only five (8.5%) of patients that were transitioned to docetaxel. However 25% of patients that had double reactions had anaphylaxis (p = 0.05)

Discussion

It is not surprising, based on the present authors' knowledge of SCOTROC, that this single-institution experience did not show a significant difference in progression-free or

overall survival of patients switched from paclitaxel to docetaxel. Furthermore, a phase II study by the NSGO (Nordic Society of Gynecologic Oncology) of carboplatin plus docetaxel for second-line therapy of first platinum sensitive relapse showed similar overall response and survival to other studies using carboplatin in combination with either liposomal doxorubicin or paclitaxel for second line chemotherapy. However, the trend of the progression free survival analysis was more interesting. Intuitively, the present authors would expect that if those that are switched from paclitaxel to docetaxel may have worse survival (though not statistically significant with the present study numbers), then those with "double reactions" that then are given nab-paclitaxel would be even worse. This however was not how the numbers trended. It was seen that patients that had a significant paclitaxel reaction in their first two treatments had a median PFS of 13.1 months versus 74.6 months in those that were switched after three or more cycles of paclitaxel. More interestingly, however, is that those patients that had a "double reaction" in which they reacted to both paclitaxel and docetaxel and switched to nab-paclitaxel actually had longer progression-free survival (25.3 months) than those that only had a single reaction. GOG126-R, a phase II study by Coleman *et al.*, demonstrated significant clinical activity with nab-paclitaxel with an objective response of 23% and a progression-free survival of 4.5 months with overall survival at 17.4 months in patients that were platinum and taxane refractory [7]. Wang *et al.* showed an overall response rate of 70% with 28% complete response rate and 12.4 month median progression free survival in another phase II multicenter study of carboplatin and docetaxel as second-line treatment of platinum sensitive ovarian cancer [8].

Overall, patients that have to be switched from paclitaxel to taxotere tend to tolerate it well. The most common events leading to a switch were back pain, neuropathy, flushing, and shortness of breath. Twenty percent of the patients in the present study had to be switched to nab paclitaxel after further reaction was noted on docetaxel. These patients were switched after an average of 1.1 cycles of paclitaxel and docetaxel, implying that the patients that will not tolerate paclitaxel and docetaxel are more likely to react earlier rather than later.

Conclusion

Use of docetaxel did not show significant difference in outcomes of patients with gynecologic malignancies when evaluating for number of cycles of paclitaxel before switching to taxotere. Though this study is underpowered as a single-institution experience, it does have some interesting trends to consider for future trials. The finding that women who ultimately went on to be switched to nab-paclitaxel did better than those that remained on taxotere, though not statistically significant, is clinically intriguing. Nab-paclitaxel should be investigated in a multi-institutional and/or non-inferiority, toxicity profile setting to evaluate both tolerability and survival in comparison to docetaxel and paclitaxel for first line treatment of gynecologic cancers. This may enable sufficient numbers to power a study and better conclude if nab-paclitaxel affords better survival in gynecologic cancer patients.

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