RESEARCH ARTICLE

Treatment Outcomes of Paclitaxel for Refractory or Recurrent Epithelial Ovarian Cancer Patients in Thailand

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Abstract

Background: To study the response rate, toxicity profiles, and survival of refractory or recurrent epithelial ovarian cancer (EOC) patients treated with paclitaxel. Materials and Methods: Patients with refractory or recurrent EOC who were treated with paclitaxel between January 2002 and December 2011 at the Department of Obstetrics and Gynecology, Faculty of Medicine, Vajira Hospital were identified. Clinicopathological features of the patients including detailed data of paclitaxel treatment were collected. Results: During the study period, a total of 44 patients were identified, with a mean age of 52.9±8.2 years. Some 13.6% (six patients) had refractory cancer to first-line chemotherapy while 86.4% (38 patients) had recurrent cancer. Among these, 35 (79.6%) and 9 (20.4%) patients were considered as platinum-sensitive and platinum-resistant, respectively. Three patients (6.8%) received fewer than 2 cycles of paclitaxel due to loss to follow-up, leaving 41 patients evaluable for response. The overall response rate observed in all 41 patients was 41.5% (17 patients; 12 complete and five partial responses): 12.5% or 1/8 patients with refractory or platinum-resistant cancer and 48.5% or 16/33 patients with platinum-sensitive disease. Stable disease was demonstrated in 17.0% (seven patients) while progressive disease was apparent in 41.5% (17 patients). Median time to progress was 4.5 months (range, 0.67-58.6 months). Median progression-free survival was not reached while median overall survival was 16.3 months (95% confidence interval, 11.0 months -21.6 months). Common toxicities were neutropenia, neuropathy, and alopecia. Conclusions: Paclitaxel is an active agent for refractory or recurrent EOC. Neutropenia, neuropathy and alopecia are common side effects.

Keywords: Recurrent epithelial ovarian carcinoma - paclitaxel - response rate - Thailand

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Introduction

Ovarian cancer is the third most common gynecologic cancer worldwide (Ferlay et al., 2010). The global incidence of ovarian cancers is 224,747 new cases and 140,163 deaths per year (Ferlay et al., 2010). A standard treatment for epithelial ovarian cancer (EOC) is cytoreductive surgery. A goal is to remove tumor masses as much as possible (Elattar et al., 2011). Adjuvant chemotherapy, usually platinum-based, is given for patients with early stage with high risk features or advanced stage diseases. The recommended chemotherapy after primary cytoreductive surgery is paclitaxel and carboplatin (du Bois et al., 2003). As an adjuvant chemotherapy for advance stage with suboptimal disease, paclitaxel/ platinum yielded response rates of 70-80% (Muggia et al., 2000). This drug combination has survival advantage over cisplatin/ cyclophosphamide which had been commonly used prior to a discovery of paclitaxel. Nevertheless, single platinum drug or platinum combined with cyclophosphamide can be used in selected patients with a non-optimal performance status or in limited resource settings (Piccart et al., 2000; Tangjitgamol et al., 2005; Stuart et al., 2011).

After a completion of primary treatment, the patients who have recurrence at any time after 6 months are called platinum-sensitive (Thigpen et al., 1993). They are generally re-treated with platinum-based chemotherapy. A few randomized trials demonstrated higher response rate and longer survival of the patients who were treated with a combination regimen, such as platinum plus paclitaxel or pegylated liposomal doxorubicin or gemcitabine than single platinum agent (Parmar et al., 2003; Pfisterer et al., 2006; Pujade-Lauraine et al., 2010). On the other hand, the patients who do not response to primary platinum-based chemotherapy or relapse within 6 months after the end of

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treatment are known as platinum-refractory or platinum-resistant EOC respectively (Thigpen et al., 1993). These patients generally have poor prognosis and any further chemotherapy, usually single agent, is aimed to palliate the symptoms only (Cannistra, 2004). Since paclitaxel is most commonly used with platinum as adjuvant chemotherapy, these patients are also considered paclitaxel-resistant. Salvage therapy in these settings is non-platinum and non-taxane drug. The responses of refractory or platinum-resistant EOC to salvage chemotherapy are generally low and range from 10-20% (Lund et al., 1994; Rose et al., 1998; Gordon et al., 2001; Markman et al., 2002). Although the combined chemotherapy can yield higher responses, a survival improvement cannot be demonstrated (Bookman et al., 2009). Rarely and experimentally are that combined drugs will be used (Havrilesky et al., 2003).

Focusing on the role of paclitaxel given beyond a primary setting, the drug can be used in conjunction with carboplatin in platinum-sensitive patients (who may have or have not taxane) (Parmar et al., 2003) or it can be used in refractory or platinum-resistant patients who have not had paclitaxel as a primary treatment (taxane-naïve) (Rosenberg et al., 2002). The response rate of diseases to paclitaxel varied from 13-45% (Trimble et al., 1993; ten Bokkel Huinink et al., 1997; Piccart et al., 2000; Cantu et al., 2002; Rosenberg et al., 2002; Buda et al., 2004; Markman et al., 2006). This wide range of response depends mainly on the sensitivity to previous therapy or the setting when the drug is used. Other factors influencing the response rates are the extent of recurrent disease, type and number of previous chemotherapy regimen(s), etc. (Ushijima, 2010). One factor which is rarely mentioned is the circumstance which the study is conducted. We do not know whether the response rate from paclitaxel would be the same in the service settings outside clinical research when the condition of treatment is usually optimal.

The objective of this study was to evaluate the response rate, progression-free survival, overall survival and toxicity of the patients with recurrent or refractory EOC patients who were treated with paclitaxel in our institution.

Materials and Methods

The study was conducted after an approval from the Ethics Committee for Research involving Human Subjects of the institution. Patients with refractory or recurrent EOC who were treated at Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, University of Bangkok Metropolis between January 2002 and December 2011 were identified. Eligibility criteria included: patients with histopathologic diagnosis of EOC, had not responded or had disease recurrence after primary treatment and received paclitaxel. Paclitaxel may be used as single agent or combined with other chemotherapeutic agent. Patients who had low malignant potential tumors and had incomplete data of treatment were excluded.

Demographic, clinical, surgical, pathologic, and follow-up data were obtained from the patients' medical records. Data collected were: age, the International Federation of Gynecology and Obstetrics (FIGO) stage, tumor histopathology and grade, outcome of primary surgery, type of first-line chemotherapy and response of disease, status of platinum-sensitivity, number of cycles of paclitaxel, response rate and side effects of paclitaxel, and time to progression (TTP) which was obtained from the time from starting paclitaxel to the time of progressive or recurrent diseases.

The clinical response was determined from physical examinations, radiologic imaging, or CA125 according to the Gynecologic Oncology Group response criteria (Swenerton et al., 1998). Complete response (CR) was defined when there was no clinical evidence of tumor after chemotherapy treatment while partial response (PR) was defined when tumor reduction was ≥50%. Stable disease (SD) was defined as a tumor that was unchanged in size, had decreased <50% or increased <25%. Progressive disease (PD) was defined as an increase in tumor size >25% or development of new lesion.

Platinum-sensitive disease was defined when a response to initial platinum-base chemotherapy had lasted more than 6 months after treatment ended. Platinum-resistant disease was defined when disease did not response (with stable or progressive diseases) to primary platinum treatment or recurred within 6 months after the end of therapy. Progression-free survival (PFS) was calculated from the TTP after receiving paclitaxel. For patients who were lost to follow-up, PFS data were right-censored at the time of the last evaluation or contact when the patient was known to be progression-free. Overall survival (OS) was obtained from the date of paclitaxel started to the date of death or last follow-up visit. For patients who were alive at the end of the study, overall survival data were right-censored at the time of the last evaluation or contact.

As a general practice in our institution, chemotherapy regimen in the primary of recurrent settings was selected by the gynecologic oncologists who discussed in a tumor board of the department. Many factors were all taken into account for the decision making. Aside from the platinum-sensitivity status and performance status of the patients, reimbursement policy was also considered. Nevertheless, general principle of chemotherapy treatment for EOC was applied. Primary chemotherapy may be single platinum drug, platinum with cyclophosphamide or with paclitaxel as appropriate for the patient. Paclitaxel given in the non-primary settings may be single agent or combined with platinum. The dose of paclitaxel was 175 mg/m^2 every 3-4 weeks or 80 mg/m^2 every week. Pre-treatment evaluation prior to each cycle of chemotherapy included a detailed history taking including the patient's well-being, symptoms of diseases and side effects of previous treatment, physical examination, complete blood count (CBC), and blood chemistry including CA 125 level. Chest radiography, optional pelvic or abdominal ultrasonography or computerized tomography are performed at an interval of every 2-3 cycles or earlier if indicated. Interval CBC was performed at 7-14 days after first day of each cycle. Hematologic and other toxicities are graded to 0-4 according to WHO criteria (WHO, 2005). The toxicities in each cycle were recorded. The most severe toxicity in each patient was used in this study. Dose reduction was allowed

based on the patient's performance status and toxicities. All patients were to receive a minimum of two cycles of paclitaxel (or 6 times of weekly paclitaxel) before the first evaluation for clinical response, unless progression of diseases was clearly evidenced or unacceptable toxicity was experienced. The therapy was continued until the disease completely responded. In the circumstances of partial response or stable disease, the drug was continued or changed to other drug upon decision of the physician, patients' tolerability to side effects, and their preference.

Data were analyzed using SPSS statistical software version 11.5 (SPSS, Chicago, IL). Descriptive statistics were used for demographic data. PFS and OS were analyzed with the Kaplan-Meier method. Survival data between groups were compared with the Log-rank test. The outcomes were significant only if $p < 0.05$.

Results

Between January 2002 and December 2011, 61 patients were treated for progressive, persistent or recurrent ovarian cancer after primary chemotherapy. Out of the 61 patients, 44 patients had ever received paclitaxel in the non-primary settings. Mean age of the patients was 52.9±8.2 years. Approximately 70% of the patients (31 patients) were postmenopausal. Nearly two thirds of the patients (28 patients or 63.6%) had advanced stages III-IV while 16 (36.4%) had early stages I-II. The primary operative procedures were performed in our institution in 25 patients (56.8%) while the remaining had their primary surgery elsewhere and were referred for further treatment. Out of 44 patients, optimal surgery (residual diseases ≤1 cm) was achieved in 33 patients (75%). The most common histopathology was serous carcinoma (20 patients or 45.5%). Forty-one patients (93.2%) had moderate or poorly differentiated tumors. The characteristic features of diseases, the type and result of primary surgery are shown in Table 1.

Out of 44 patients who were included in the study, 43 patients who had advanced disease or early stage with high risk features received adjuvant chemotherapy after primary surgery. One patient who had stage IA with grade 1 tumor had no further treatment. The first-line chemotherapy was paclitaxel and carboplatin in 24 patients (55.8%). The other 19 patients (44.2%) had cisplatin or carboplatin with cyclophosphamide (18 patients) or only carboplatin (one patient). These patients were considered as taxane-naïve. The adjuvant chemotherapy was given ranging from 1-12 cycles (median, 6 cycles). The overall response rate to first-line chemotherapy was 79.1% (34 patients). The detail of primary chemotherapy treatment and their responses are shown in Table 2.

Among 44 patients who failed primary treatment, 13.6% (six patients) had refractory cancer to first-line chemotherapy, 6.8% (three patients) recurred within 6 months (platinum-resistant), and 79.6% (35 patients) recurred later than 6 months (platinum-sensitive in 34 patients and chemotherapy-naïve in one patient). Median

Table 1. Characteristic Features of Diseases and Primary Surgery (N=44)

Tumor characteristics and details of surgery			No.	%
Stage:	I		8	18.2
	II		8	18.2
	III		25	56.8
	IV		3	6.8
Histology:	Serous adenocarcinoma		20	45.5
	Mucinous adenocarcinoma		6	13.6
	Clear cell carcinoma		9	20.4
	Endometrioid adenocarcinoma		7	15.9
	Transitional cell carcinoma		1	2.3
	Mixed epithelial tumor		1	2.3
Tumor grade:	I		3	6.8
	II		10	22.7
	III		31	70.5
Result of primary surgery:		Optimal surgery	33	75.0
		Suboptimal surgery	11	25.0

Table 2. Details of Adjuvant Chemotherapy after Primary Surgery and Details of Paclitaxel Treatment of Recurrent or Refractory Epithelial Ovarian Cancer

	No.	%
First line chemotherapy:		
Type of chemotherapeutic drugs (N = 43*)		
Cisplatin or carboplatin plus cyclophosphamide	18	41.9
Paclitaxel plus carboplatin	24	55.8
Single carboplatin	1	2.3
Platinum sensitivity (N = 44*)		
Platinum-sensitive*	35	79.6
Platinum-resistant	9	20.4
Paclitaxel treatment in non-primary settings (N = 41**)		
Setting of paclitaxel treatment		
Second-line (including re-induction treatment)	32	78.1
Beyond second-line***	9	21.9
Previous taxane exposure		
Taxane-naïve	17	41.5
Previously treated with taxane	24	58.5
Paclitaxel use according to primary platinum-sensitivity		
Platinum-sensitive	33	80.5
Paclitaxel and carboplatin	27	65.9
Single paclitaxel	6	14.6
Platinum-resistant	8	19.5
Paclitaxel and carboplatin	1	2.4
Single paclitaxel	7	17.1
Response to paclitaxel		
Complete response	12	29.3
Partial response	5	12.2
Stable diseases	7	17.0
Progress diseases	17	41.5

*One patient had no adjuvant chemotherapy, and was included in the platinum-sensitive group; **Detail of paclitaxel treatment was described only in 41 patients with evaluable response; ***Paclitaxel in nine patients was given as third-line (six patients), fourth-line (two), seventh-line (one)

Table 3. Adverse Events of Paclitaxel Treatment (N=44)

Events	Grade (number of patients)				Percent
	1	2	3	4	
Hematologic side effects					
Neutropenia	1	6	7	13	61.4
Thrombocytopenia	2	3	1	1	15.9
Anemia	11	6	1	0	40.9
Peripheral neuropathy	22	4	1	0	61.4
Alopecia	4	19	2	0	56.8
Gastrointestinal symptom	4	0	0	0	9.1
Allergic reaction	0	1	0	0	2.3

TTP of nine patients with refractory or platinum-resistant patients was 1.9 months (range, 0.7-4.9 months) while a TTP among 35 platinum-sensitive or chemotherapy naïve was 23.5 months (range, 8.0-57.3 months). Of note, 22 patients (50.0% of all patients or 62.9% of platinum-sensitive patients) recurred after 12 months of primary treatment. Treatment for all refractory or resistant cancer was second-line chemotherapy: paclitaxel (four patients), oral etoposide (three patients), and gemcitabine or liposomal doxorubicin (one patient each). These drugs were also alternatively used in the subsequent settings after failed preceding treatment. Among 35 patients who were primary platinum-sensitive or chemotherapy-naïve, nine underwent secondary cytoreduction and all had optimal surgery while the remaining had only chemotherapy. Almost all of these platinum-sensitive patients had platinum-reinduction chemotherapy (paclitaxel/ carboplatin in 27 patients and cisplatin or carboplatin with cyclophosphamide in six). Only two patients had either single paclitaxel or oral etoposide (one patient each).

Focusing to the patients who had paclitaxel in non-primary settings, the drug was given to all 44 patients as second-, third-, or further-lines chemotherapy. Almost all (42/44 patients) had paclitaxel 175 mg/m^2 every 3-4 weeks either with (29 patients) or without carboplatin (13 patients). The other two patients received 80 mg/m^2 of paclitaxel every week (as the second-line or seventh-line). Median number of paclitaxel treatment was 5 cycles (range, 1-10 cycles). Three patients (two had platinum-sensitive and one had platinum-resistant diseases) received only one cycle of paclitaxel and carboplatin and were lost follow-up before a response evaluation. The overall response rate of paclitaxel was 41.5% (17/41 patients): 29.3% CR (twelve patients) and 12.2% PR (five patients). Stable disease was additionally achieved in 17.0% (seven patients), giving the overall control rate of 58.5%. The other 41.5% (17 patients) had disease progression. Details of paclitaxel treatment of 41 patients with evaluable response are shown in Table 2. In relation to the sensitivity status to primary platinum treatment, 33 patients with platinum-sensitive diseases had 48.5% response rate to paclitaxel (16/33 patients). The response in these platinum-sensitive patients was higher in the patients who received combined paclitaxel/ carboplatin than those who had single paclitaxel: 51.9% (14/27 patients) and 33.3% (2/6 patients), respectively. In contrast to the patients who had platinum-resistant diseases, the response was seen only in 1/8 patient (12.5%). She had combined paclitaxel/ carboplatin as the fourth-line drug (after failed primary cisplatin/ cyclophosphamide, oral etoposide, gemcitabine).

We then considered the response by the patient's prior use of paclitaxel. The response rate among the patients who had never had paclitaxel (taxane-naïve) was 35.3% (6/17 patients: five platinum-sensitive and one platinum-resistant). Of note, the response among the patients who had previous taxane treatment (paclitaxel re-induction) was 45.8% or 11/24 patients (all were platinum-sensitive). We re-categorized the patients by their primary chemotherapy into 4 groups and found different responses. The response was best at 50.0% in platinum- and taxane-sensitive patients (11/22 patients). The responses in other groups were as follow: 45.5% in platinum-sensitive and taxane-naïve (5/11 patients), 16.7% in platinum-resistant but taxane-naïve (1/6 patients), and no response in two patients with both platinum- and taxane-resistant.

Median TTP of diseases after paclitaxel treatment was 4.5 months (range, 0.67-58.6 months). Although the median TTP in platinum-sensitive group of 5.1 months (range, 0.67-58.6 months) was longer than 2.5 months (range, 1.7-23.3 months) in the platinum-resistant group, the difference was not statistically significant (p=0.106). The median PFSs of all 44 patients and 35 platinum-sensitive patients were not reached while that of the platinum-resistant patients was 2.5 months (95%CI, 1.4-3.5 months) (p=0.021).

By the time of this study, 34 of the 44 patients (77.3%) were dead. Median overall survival (OS) was 16.3 months (95%CI, 11.0-21.6 months). The median OS of the platinum-sensitive patients was significantly longer than those who were platinum-resistant, 19.8 months (95% CI, 14.8-24.7 months) compared to 8.7 months (95% CI, 7.2-10.3 months) (p=0.005).

Regarding the side effects of paclitaxel, among 44 patients who were treated with paclitaxel, hypersensitivity reaction developed during the second cycle of treatment in one patient. She refused further treatment with any chemotherapeutic drug. No paclitaxel-related deaths were encountered in our study. Hematologic toxicity was the most common side effect. Neutropenia was found in 61.4% (27 patients), being ≥grade 3 in 45.5%. Anemia and thrombocytopenia were encountered in 40.9% (18 patients) and 15.9% (seven patients), being ≥grade 3 in 2.3% and 4.5%, respectively. Of note, most neutropenic events (85.2%) occurred in patients who had paclitaxel in combination with carboplatin. Only one patient (platinum-sensitive) developed febrile neutropenia after receiving paclitaxel/carboplatin. She was treated with broad spectrum antibiotics and G-CSF support. Among 13 patients who received only single paclitaxel (not combined with platinum), ≥grade 3 neutropenia was experienced in 11.1%. Other side effects associated with paclitaxel (non-adjuvant setting) were: neuropathy in 61.4% (27 patients), being ≥grade 2 in 11.4% and alopecia in 56.8% (25 patients), being ≥grade 2 in 47.7%. The alopecia was reversible in all patients after the end of paclitaxel treatment. The adverse events of paclitaxel treatment are shown in Table 3.

Discussion

Disease recurrence is one of the most important adverse events after primary treatment for EOC. This is especially true for refractory or platinum-resistant cancer when the chance of cure is minimal and the aim of treatment is only to delay progression of disease. Balancing drug toxicity and a quality of life is a more important concern in this circumstance. This is in contrast to the patients with platinum-sensitive recurrent diseases which can be cured when the aim of treatment is to prolong survival. Despite having different courses of disease as

well as the aims of treatment, the chemotherapy being used for refractory or recurrent diseases are about the same with only few exceptions. Refractory disease and platinum-resistant EOC are treated with single agent chemotherapy while platinum-sensitive cancer is usually treated with platinum-based chemotherapy combination.

Paclitaxel is a chemotherapeutic agent derived from bark of the Pacific yew, *Taxus brevifolia*, which shows excellent activity for many cancers including EOC (Alberts et al., 2009). For over two decades when taxanes, particularly paclitaxel, has become a standard front-line chemotherapy along with carboplatin. The drug also has definite activity in treatment of recurrent ovarian cancer either in platinum-sensitive or –resistant patients.

Paclitaxel has also been used in our institution for many years as primary adjuvant chemotherapy or in a recurrent setting. As an adjuvant chemotherapy after primary surgery, nearly half of our EOC patients (19/44 patients) did not have paclitaxel together with platinum drug or were taxane-naïve. This was because of limited financial resource in some of our patients especially in early years when the cost of paclitaxel was still very high. Our study demonstrated a modest overall response rate of 41.5% (17/41) in recurrent or refractory EOC treated by paclitaxel. When stable diseases were included, the disease control rate was 58.5%.

As expected, the response rates varied according to the platinum- or taxane-sensitivity status. Taking only platinum-sensitivity status into consideration, paclitaxel in platinum-sensitive patients yielded 48.5% response rate (51.9% from paclitaxel/ carboplatin and 33.3% from paclitaxel alone). Our 51.9% response rate from paclitaxel/ carboplatin in platinum-sensitive patients was lower than the results in one large randomized trial involving 802 platinum-sensitive EOC patients (Parmar et al., 2003). The authors from that trial reported 66% response rate from paclitaxel/carboplatin compared to 54% in those who had single carboplatin or other platinum-based chemotherapy. The difference might be because our study had lower number of taxane-naïve patients (44.2% in our study vs 69% in their trial) and lower number of the highly platinum-sensitive patients or platinum-free period >12 months (62.9% vs 77%, respectively).

When we considered taxane or taxane/platinum sensitivity status, we found 35.3% response rate among 17 taxane-naïve patients (who had either platinum-sensitive or -resistant) which was lower than 45.8% in 24 patients who had received previous paclitaxel (and carboplatin). This was most likely because of all of the 24 patients had platinum-sensitive diseases. The response was highest in the platinum- and taxane-sensitive patients (50.0%), lower in taxane- naïve with either platinum-sensitive or –resistant (45.5% or 16.7%), and worst in those who were both platinum- and taxane-resistant (0%). These results emphasized the important activity of platinum regardless of prior paclitaxel exposure. On the other hand, it may reflect the aggressiveness of cancer itself that the less aggressive cancer will respond to primary drug and subsequent drugs while the aggressive cancer will resist to any treatment. The response rate of 33.3% from single paclitaxel in our platinum-sensitive patients was in the range of 20-56% as had been reported in other studies focusing on platinum-sensitive disease (McGuire et al., 1989; Thigpen et al., 1994; Piccart et al., 2000; Kita et al., 2004).

The activity of paclitaxel in platinum-resistant patients in our study was disappointing. We could demonstrate the response of 12.5% in eight evaluable patients of this group. Previous studies showed 16-62% response rate of platinum-resistant disease having paclitaxel (McGuire et al., 1989; Trimble et al., 1993; Thigpen et al., 1994; Piccart et al., 2000; Thirapakawong et al., 2001; Markman et al., 2002; Ghamande et al., 2003; Kita et al., 2004; Linch et al., 2008). The difference of treatment outcome may be due to the limited number of patients in this particular group of patient. Furthermore, paclitaxel was given as third line setting or beyond wherein the prognosis was poor and any treatment would be unsatisfactory. One observation was our study used paclitaxel in a tri-weekly schedule in most patients (95%). The response rate of this monthly schedule of administration was reported to be lower than that obtained for the weekly administration: 17-37% (McGuire et al., 1989; Trimble et al., 1993; Thigpen et al., 1994; Piccart et al., 2000) compared to 46-62% (Thirapakawong et al., 2001; Ghamande et al., 2003; Kita et al., 2004), respectively. Some authors proposed that weekly paclitaxel may take advantage of cell cycle specificity of paclitaxel-cytotoxicity as well as tumor anti-angiogenesis leading to better outcomes (Browder et al., 2000; Miller et al., 2001). Aside from this mechanism, the weekly paclitaxel given 80 mg/m^2 should be considered as dose dense therapy (higher total dose per time period) which was reported to yield better treatment outcome than a conventional drug dosages (Katsumata et al., 2009). Few recent studies demonstrated activity of weekly paclitaxel given in combination with carboplatin in platinum-resistant ovarian cancer patients (Sharma et al., 2009; Cadron et al., 2013). The response rates were as high as 35-60%.

Our study showed the median TTP of 4.5 months and median OS of 16.3 months in 44 patients who had paclitaxel. Particularly to the platinum-sensitive patients, the median TTP and OS were 5.1 months and 19.8 months respectively. The figures from our study were worse than the ones demonstrated in the ICON 4 trial (Parmar et al., 2003) which used paclitaxel/ carboplatin (median PFS of 12 months and OS of 29 months) and in the study of Cantu et al. (2002) who used tri-weekly paclitaxel in the platinum-sensitive patients (median TTP of 9 months and OS of 26 months) (Cantu et al., 2002). Again the lesser number of very highly sensitive patients (disease-free interval >12 months) in our study (62.9%) was found compared to those found in their studies (77% and 100%) (Cantu et al., 2002; Parmar et al., 2003). The median TTP and OS in our platinum-resistant patients were only 3 months and 9 months respectively. These were slightly lower than 4-6 months for TTP and 8-14 months for OS found in other studies which used either weekly (Thirapakawong et al., 2001; Markman et al., 2002; Ghamande et al., 2003) and were comparable to the corresponding figures of 4 months and 9 months from the studies which used the tri-weekly schedule (Trimble

et al., 1993; Thigpen et al., 1994).

The major adverse effect of hematologic toxicity from paclitaxel demonstrated in our study was neutropenia. We found neutropenic events in 61.4% in our study. However, most neutropenic events occurred in patients who received combined paclitaxel-platinum. A subgroup of patients who received only single tri-weekly paclitaxel, neutropenic events in our study were less than other studies giving the same dosage, 11.1% of grade 3-4 compared to 13-23% (Piccart et al., 2000; Cantu et al., 2002; ten Bokkel Huinink et al., 2004). The weekly schedule of administration may have lower toxicity than the conventional tri-weekly. Few studies reported only 4-8% of grade 3-4 neutropenia in their patients who had weekly paclitaxel (Markman et al., 2006; Linch et al., 2008). One randomized phase III trial by Rosenberg et al. compared the toxicity of tri-weekly versus weekly paclitaxel in 208 patients (Rosenberg et al., 2002). Grade 3-4 neutropenia were lower in those who had the weekly regimen, 18% vs 45%. The rates of anemia and thrombocytopenia in our study were low and comparable to other studies (<5% of grade 3-4) (Cantu et al., 2002; Rosenberg et al., 2002; Markman et al., 2006; Linch et al., 2008). Some authors proposed the low rate of thrombocytopenia may be due to platelet-sparing effect of paclitaxel (Guminski et al., 2001).

Our study found only 11% of ≥grade 2 peripheral neuropathy. This was lower compared to other previous studies, 11-28% in weekly and 11-29% in tri-weekly regimen (Cantu et al., 2002; Rosenberg et al., 2002; Markman et al., 2006; Linch et al., 2008). We do not know this low rate of neuropathy was due to a suboptimal record of this toxicity outside a clinical research setting or a less concern of this particular symptom in our patients (and physicians) in comparison to the Westerns.

In conclusion, our study also shows that paclitaxel is an active agent for refractory or recurrent EOC. The response was modest and the toxicity was tolerable. Weekly paclitaxel is in the interesting area for further research to evaluate the activity and toxicity in the recurrent settings than the exist regimens that have only modest rate and short period of responses.

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