

Weekly Paclitaxel Versus Three-Weekly Paclitaxel in Recurrent Platinum-Resistant Epithelial Ovarian and Peritoneal Cancers: A Phase III Study

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ABSTRACT

INTRODUCTION: Treatment of recurrent platinum-resistant ovarian and peritoneal cancers represents a therapeutic challenge. The aim of this Phase III prospective study was to compare the survival benefits, objective response rate, and toxicities among patients treated by weekly paclitaxel with those who underwent three-weekly paclitaxel in recurrent platinum-resistant ovarian and peritoneal cancers.

METHOD: Patients with recurrent platinum-resistant ovarian and peritoneal cancer were allocated to receive either weekly paclitaxel (arm 1) at 80 m/m² or three-weekly paclitaxel (arm 2) at 175 mg/m².

RESULTS: Fifty-five patients were enrolled (30 arm 1, 25 arm 2). The mean age was 56.7 years, and the median performance status was 0 (Eastern Cooperative Oncology Group [ECOG]). For arms 1 and 2, the objective response rates were 27% and 16%, the median progression-free survival were 7 and 4.5 months, and the median overall survival were 15.5 and 12.5 months, respectively. Treatments also significantly improved the quality of life. Treatment was associated with mild toxicities, and while neuropathy was slightly higher for weekly paclitaxel over three-weekly paclitaxel, hematological toxicities were significantly lower for the former than the latter.

CONCLUSION: Paclitaxel rechallenge showed antitumor activity in recurrent platinum-resistant ovarian and peritoneal cancers. Weekly paclitaxel achieved better results than three-weekly paclitaxel in terms of survival benefits, quality of life, and toxicities.

KEYWORDS: weekly, paclitaxel, platinum-resistant, ovary, ORR, PFS, QOL

CITATION: Osman et al. Weekly Paclitaxel Versus Three-Weekly Paclitaxel in Recurrent Platinum-Resistant Epithelial Ovarian and Peritoneal Cancers: A Phase III Study. *Clinical Medicine Insights: Oncology* 2016;10:35–41 doi: 10.4137/CMO.S38204.

TYPE: Original Research

RECEIVED: January 20, 2016. **RESUBMITTED:** March 13, 2016. **ACCEPTED FOR PUBLICATION:** March 15, 2016.

ACADEMIC EDITOR: William Chi-shing Cho, Editor in Chief

PEER REVIEW: Six peer reviewers contributed to the peer review report. Reviewers' reports totaled 1149 words, excluding any confidential comments to the academic editor.

FUNDING: Authors disclose no external funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

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Introduction

Ovarian cancer is the most common cause of death among women with gynecological malignancies. Nearly 70% of ovarian cancers recur by time, and approximately 13,850 women in the USA die each year from ovarian cancer.¹

Patients with recurrent disease are categorized as *platinum-sensitive*, *partly sensitive*, or *platinum-resistant*. Platinum-resistant disease defines patients who have progressed within six months of completing the initial platinum-based chemotherapy.²

Treatment of recurrent platinum-resistant ovarian and peritoneal cancers represents a therapeutic challenge. Patients with resistant disease have a worse prognosis when compared with those who have a treatment-free interval of more than six months.³

Commonly used chemotherapy agents in the treatment of recurrent platinum-resistant ovarian and peritoneal cancers are listed in Table 1.

Recently, the *AURELIA trial* by Pujade-Lauraine et al. showed that addition of bevacizumab to chemotherapy

(paclitaxel, Pegylated liposomal doxorubicin (PLD), or topotecan) in recurrent platinum-resistant ovarian and peritoneal cancers resulted in an improvement in *progression-free survival* (PFS) by 3.3 months and in *overall survival* (OS) by 3.3 months. In addition, the objective response rate (ORR) was improved from 11.8% to 27.3% with the addition of bevacizumab.⁴

Study Objectives

The objective of this study was to compare the survival benefits, ORR, and toxicities among patients treated with weekly paclitaxel with those who underwent three-weekly paclitaxel in patients with recurrent platinum-resistant ovarian and peritoneal cancers. The primary end points were ORR and PFS. The secondary end points were OS, quality of life (QOL), and toxicities.

Patients and Methods

Inclusion criteria. Patients were eligible for inclusion in the current Phase III prospective study if they met the following criteria:

**Table 1.** Chemotherapy regimens in recurrent platinum-resistant ovarian and peritoneal cancers.

STUDY	CHEMOTHERAPY	RESPONSE RATE	PROGRESSION FREE SURVIVAL (PFS)	TOXICITIES GRADE 3, 4
Abushahin et al., 2008 (19)	Topotecan weekly, every 4 weeks	15–20%	5.7 months	7% hematological
Gordon et al., 2000 (20)	Pegylated liposomal doxorubicin (PLD) every 4 wk	20–26%	7 months	Hand-foot syndrome 10%
Ferrandina et al., 2008 (21)	Gemcitabine on d 1, 8 every 3 weeks OR d 1, 8, 15 every 4 weeks	25%	7.2 months	5% haematological
GOG et al., 2006 (15)	Paclitaxel weekly on d 1, 8, 15 every 4 weeks	20.9%	7 months	8% fatigue, 6% hematological 4% neuropathy
Rose et al., 2003 (22)	Docetaxel every 3 weeks	22.4%	4 months	25% hematological
Piccart et al., 2000 (16)	3 Weekly paclitaxel	17%	4 months	22% hematological

Histologically proven *high-grade* epithelial ovarian cancer or primary peritoneal cancer, which progressed or relapsed after *first-line chemotherapy*. Most recent carboplatin-based regimen should be less than six months earlier. Additionally, patients should have received only one line of chemotherapy, which should include paclitaxel as part of their first-line treatment. Furthermore, the progression or relapse must have been radiologically documented. Finally, patients should be between the ages of 18 and 70 years and had a performance status of ≤ 2 (ECOG). Patients should have adequate hematological, liver, and renal functions with baseline laboratory criteria that included neutrophils $\geq 1.5 \times 10^3/\text{mL}$; platelet count $\geq 15 \times 10^3/\text{mL}$; creatinine $\leq 1.6 \text{ mg/dL}$; total bilirubin level ≤ 1.25 , the upper limit of normal; and ALT, AST ≤ 3 , the upper limit of normal (< 5 in the case of liver metastasis). Histologies included different subtypes of epithelial ovarian and peritoneal cancers, including serous, endometrioid, clear cell, mucinous, Brenner, undifferentiated, and others.

Patients were excluded from the trial if they did not meet the above criteria. Additionally, patients who received more than one line of chemotherapy and patients with significant comorbidities, including peripheral neuropathy Grade 4, were further excluded. The current research complied with the principles of the Declaration of Helsinki. The research was approved by the Ethical Committee of Ain Shams University, and patients gave their written, informed consent to participate.

Settings. Ain Shams University Hospital, Ain Shams University Specialized Hospital, and Ismailia Oncology Teaching Hospital, Egypt.

Study design. Arm 1 patients were enrolled to receive weekly paclitaxel at 80 mg/m^2 on days 1, 8, and 15, every 28 days for a total of 6 cycles. Arm 2 patients were treated with paclitaxel at 175 mg/m^2 on day 1, every 21 days for a total of 6 cycles. Prior to chemotherapy administration, CBC, renal function, liver function tests, and bilirubin were checked at

days 1, 8, and 15 of each cycle. Dose modification was based on Table 2.^{5,6}

Evaluation. Baseline CT thoracic–abdominal–pelvic (TAP) was performed before treatment protocol and serum level of CA 125 was checked at baseline. CA 125 was repeated every other cycle from Cycle 3. After completion of chemotherapy, patients underwent CT TAP and CA 125 to evaluate chemotherapy response. CT TAP was requested at any point where disease progression (DP) was suspected.

Response definitions were based on “racist 1.0,” where *complete response* (CR) was defined as complete disappearance of the tumors, *partial response* (PR) included at least a 30% decrease in the sum of the longest diameters, *disease progression* (DP) meant at least a 20% increase in the sum of the longest diameters, and *stable disease* (SD) was defined as all other situations.⁷

ORR was defined as CR plus PR.^{7,8}

Follow-up. After the treatment protocol, patients were followed up according to the NCCN guideline – every three months in the first two years, every six months for the following three years, and then annually thereafter.

At each clinic interview, patients underwent history, physical examination, and laboratory investigations in the form of CA 125. CT TAP was undertaken as clinically indicated.⁸

QOL evaluation. We applied The Functional Assessment of Cancer Therapy-General (FACT-G) questionnaires (Arabic translation version) to assess the “quality of life.” The questionnaires were put to our patients on the following four occasions: at the start of treatment (baseline), after the end of the treatment protocol, eight weeks after treatment, and eight weeks thereafter.⁹

Toxicity. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria – version 2.0.¹⁰

Early toxicity was defined as that occurring during chemotherapy up to eight weeks “post chemotherapy.” Late toxicity referred to that occurring more than eight weeks after treatment.



Table 2. Dose modification.^{5,6}

NEUTROPHILS (10 ³ /ml)	PLATELETS (10 ³ /ml)		DOSE
1-Hematology			
<i>For day 1 of each cycle: (for both weekly, 3 weekly paclitaxel)</i>			
≥1	and	>100	100%
<1	or	<100	For 3 weekly, Delay until recovery, and resume in the same dose level. For weekly, if the first occurrence: As 3 weekly. If second occurrence: Delay, reduce to 60 mg/m ²
Febrile neutropenia	For 3 weekly, Reduce dose to 155 mg/m ² after first occurrence. In case of second occurrence, use G-CSF together with the same dose of paclitaxel. For weekly: Reduce dose by 1 dose level* after first occurrence. If second occurrence, as for 3 weekly.		
<i>For day 8, 15 weekly paclitaxel</i>			
≥0.5	and	≥50	100%
<0.5	or	<50	Omit & reduce subsequent treatments by 1 dose level*
ALT	TOTAL BILIRUBIN (mg/dl)		PACLITAXEL DOSE (mg/m ²) WEEKLY
2-Hepatic function tests: weekly paclitaxel			
<2 × ULN	≤1.4		80
>2 × ULN Or >5 × ULN If liver metastases	≤1.4		65
<10 × ULN	>1.4–2.9		40
≥10 × ULN	>2.9		25
ALT	TOTAL BILIRUBIN		PACLITAXEL DOSE (mg/m ²) 3 WEEKLY
3-Hepatic function tests: 3 weekly paclitaxel			
<10 × ULN	≤1.25 × ULN		175
<10 × ULN	1.26–2 × ULN		135
<10 × ULN	2.01–5 × ULN		90
≥10 × ULN	>5 × ULN		Not recommended
Dose modification for paclitaxel by other toxicities			
Grade	Paclitaxel dose		
Grade 2 motor or sensory neuropathy	Decrease paclitaxel dose by 1 dose level***		
All other Grade 2 non-hematologic toxicities	Hold treatment until toxicity resolved to less than or equal to Grade 1 and Decrease subsequent paclitaxel doses by 1 dose level***		
Greater than or equal to Grade 3 non-hematologic toxicities	Hold treatment. Re-evaluate treatment plan. Consider discontinuing treatment with this protocol		

Notes: *Dose levels for weekly paclitaxel: 70 then 60 then 50 mg/m². **Dose levels for 3 weekly paclitaxel: 175 then 135 then 90 mg/m².

Statistical analysis. All calculations were carried out using Prism 6 software. Analyses were carried with the intention to treat. The mean and median were used for the description of data. *t*-test and *P* value were used to compare between the two group characters. OS and PFS for each arm were analyzed using Kaplan–Meier method. PFS were checked from the time of randomization until relapse or last follow-up visit, while the OS was defined from the time of randomization until death or the last follow-up visit. *P* value was statistically significant at ≤0.05.

Results

Between September 2010 and September 2014, 55 patients were enrolled: 30 patients were assigned to treatment arm 1, and 25 patients were assigned to arm 2. All our patients fulfilled the eligibility criteria of the current study. The mean age was 56.7 years (Table 3).

Treatment protocol. All the 55 included patients had been treated according to our protocol. The median number of therapy was 6 cycles in both arms (range 4–8). Six patients from arm 1, and four patients from arm 2 received beyond six

**Table 3.** Patient characteristics of each treatment arm.

CHARACTERISTICS	ARM 1		ARM 2		P VALUE
	NUMBER	%	NUMBER	%	
Age					
Mean	56.5	–	57	–	0.4
Median	56	–	57	–	
Range	17–70	–	17–70	–	
Performance status: (ECOG)					
0	20	67%	18	72%	–
1	6	20%	4	16%	–
2	4	13%	3	12%	–
Performance status (median)	0	–	0	–	0.5
Pathological classification					
Serous endometrioid clear cell	25	83%	22	88%	0.3
	2	7%	1	4%	0.4
	3	10%	2	8%	0.4
Origin					
Ovarian	28	93%	23	92%	0.1
peritoneal	2	7%	2	8%	0.3
Time interval from last chemotherapy					
0–2 months	4	13%	3	12%	0.3
>2–4 months	16	54%	12	48%	0.2
>4–6 months	10	33%	10	40%	0.5
Recurrence					
Locoregional	14	46%	10	40%	0.4
Distant	8	27%	7	28%	0.2
Both	8	27%	8	32%	0.7

cycles. A total of 327 chemotherapy cycles were given to both arms (182 arm 1, 145 arm 2).

Response data. All patients underwent response assessment: 2 patients achieved CR (arm 1), 10 patients achieved PR (6 arm 1, 4 arm 2), and 17 patients had SD (10 arm 1, 7 arm 2). The remaining 26 patients had DP (12 arm 1, 14 arm 2). The ORRs in the current study were 27% and 16%, for arms 1 and 2, respectively (Tables 4 and 5).

Patients who had DP were reassessed for their fitness to further treatment. Of those, 8 were lost follow-up, 5 received further treatment (third line; 3 from arm 1

and 2 from arm 2), and the remaining 13 did not receive additional therapy.

Survival data. After a *follow-up* period of 24 months, the median PFS for arms 1 and 2 were 7 and 4.5 months, respectively, and the mean PFS for arms 1 and 2 were 6.9 and 5 months, respectively. The median OS for arms 1 and 2 were 15.5 and 12.5 months, respectively, and the mean OS for arms 1 and 2 were 16 and 11.9 months, respectively. The six-month PFS were 60% and 40%, while the six-month OS were 82% and 65%, respectively (Figs. 1 and 2).

QOL assessment. At baseline, 44 patients (80% of total) underwent QOL assessment (24 patients from arm 1 and 20 patients from arm 2). At baseline, the mean score was 40/108 (range 34/108 to 48/108). Just after treatment, 37 patients underwent assessment (those who achieved ORR, SD, and a further 8 patients who had DP), the mean score was 42/108 (range 30/108 to 50/108). At 8 weeks after treatment, 35 patients underwent assessment. These were the same patients who underwent previous assessment with the exception of two DP patients who refused participation. The mean score was 48/108 (range 36/108 to 54/108).

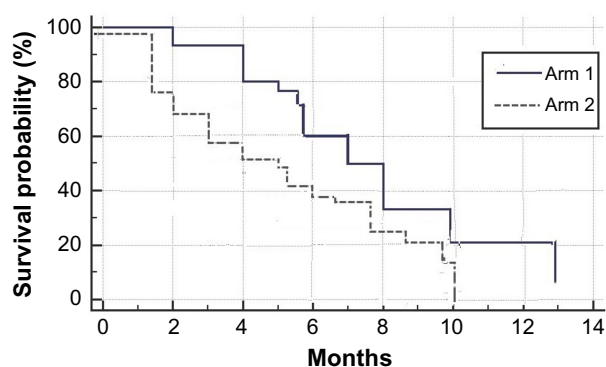
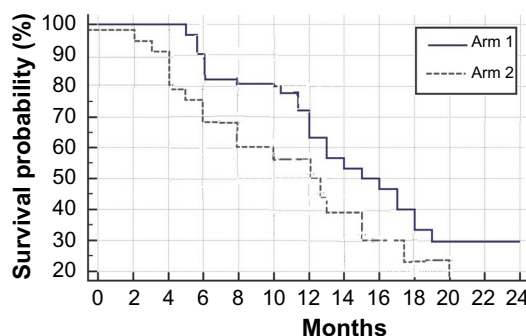
Table 4. Response evaluation for the treatment arms.

	ARM 1 (WEEKLY)		ARM 2 (THRICE WEEKLY)	
	NUMBER	%	NUMBER	%
CR	2	7%	0	0%
PR	6	20%	4	16%
SD	10	33%	7	28%
DP	12	40%	14	56%

Table 5. Characteristics of the 12 patients who achieved objective responses.

PATIENT NUMBER	RESPONSE	AGE	PS	PATHOLOGY	ORIGIN	TIME INTERVAL* MONTHS	RECURRENCE
1 arm 1 (Weekly)	CR	48	0	Serous	Ovarian	5	Both
2 arm 1 (Weekly)	CR	36	1	Endometrioid	Ovarian	5.5	Locoregional
3 arm 1 (Weekly)	PR	50	0	Serous	Peritoneal	5	Both
4 arm 1 (Weekly)	PR	19	0	Serous	Ovarian	3	Locoregional
5 arm 1 (Weekly)	PR	51	0	Endometrioid	Ovarian	4.5	Distant
6 arm 1 (Weekly)	PR	55	0	Serous	Ovarian	4	Distant
7 arm 1 (Weekly)	PR	57	1	Serous	Ovarian	5	Locoregional
8 arm 1 (Weekly)	PR	58	1	Serous	Peritoneal	5.5	Distant
9 arm 2 (Thrice weekly)	PR	59	0	Serous	Ovarian	5.5	Distant
10 arm 2 (Thrice weekly)	PR	53	0	Endometrioid	Ovarian	5	Locoregional
11 arm 2 (Thrice weekly)	PR	56	0	Serous	Ovarian	5	Locoregional
12 arm 2 (Thrice weekly)	PR	54	1	Serous	Ovarian	4.5	Distant

Note: *Time interval: The time from adjuvant chemotherapy completion to the first relapse.


Figure 1. PFS for the study groups – *P* value: 0.02.

Figure 2. OS for the study groups – *P* value: 0.03.

At eight weeks thereafter, 30 patients underwent assessment. These were the same patients who underwent assessment at 4 weeks posttreatment, with the exception of 2 DP and 3 SD patients who refused participation. The mean score was 50/108 (range 42/108 to 62/108; Fig. 3).

Toxicities. *Early toxicities.* A total of 327 chemotherapy cycles were given to both arms (182 to arm 1 and 145 to arm 2). Generally, for both arms, treatment protocols were tolerated well. No deaths have been reported in relation to treatment protocols. Dose reductions happened in 25% and 34% of cycles in arms 1 and 2, respectively. Treatment was discontinued in 4 patients from arm 1 (at cycle 6, 2 patients for grade 3 and 4 neuropathy and 2 for grade 4 neutropenia) and in 5 patients from arm 2 (4 at cycle 6, 1 at cycle 4). Of those, 4 patients for grade 3 and 4 neutropenia, and 1 for grade 4 neuropathy. Grades >2 toxicities for both arms are summarized in Table 6.

Late toxicities. There was no grade 3 or 4 late morbidity related to treatment in the follow-up period.

Discussion

Despite several advances in the understanding of its pathobiology, ovarian cancer remains an incurable disease with frequent relapses. The survival rate of ovarian cancer is still disappointingly low when compared with that of breast or prostate cancer. One of the factors contributing to the poor survival rate in ovarian cancer is the development of chemotherapy resistance following several rounds of chemotherapy. Furthermore, there is not yet any standard chemotherapy for platinum-resistant recurrence.^{11,12}

The aim of chemotherapy in recurrent platinum-resistant ovarian cancer is palliative with improvement of QOL being the major goal.¹³

The primary objectives of the current Phase III prospective study were to compare between weekly paclitaxel and three-weekly paclitaxel as salvage treatment for recurrent platinum-resistant ovarian and peritoneal cancers in terms of ORR and PFS. Both of these represented the main objective for treatment of such an incurable disease. Toxicities were the other important factor taken into account, especially as paclitaxel was previously administered to all patients.^{13,14}

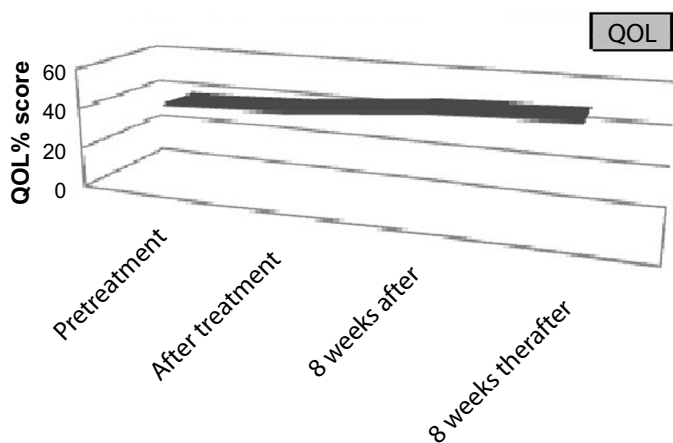


Figure 3. QOL assessment for the study group.

Confirmatory data for paclitaxel rechallenge came from metastatic breast cancer studies, where several trials confirmed its effectiveness and mild toxicity profile. Additionally, in recurrent platinum-resistant ovarian cancer, there is not yet any standard treatment protocol, although previous Phase II studies confirmed the effectiveness and low toxicity profile of paclitaxel in recurrent ovarian cancer.^{12,15-18}

We applied simple randomization to select patients of each treatment arm¹³ with an initial randomization plan of 1:1. However, this was added to be as follows. For the first 24 patients, the selection criterion was 2:1 in favor of arm 1, and for the remaining 31 patients, the selection criterion was 1:1. This was because the study was run in three institutes with different patient loads and the investigators' preferences of initially recruiting more arm 1 patients based on preliminary results. The power of the current study was 70%. Furthermore, the two groups were matched with no statistically significant differences in their characteristics. Additionally, our patient groups showed no ethnic or geographical variations.

Table 6. Grade >2 early toxicities for arms 1 and 2.

TOXICITY	ARM 1 (WEEKLY) 172 CYCLES		ARM 2 (THRICE WEEKLY) 138 CYCLES	
	GRADE 3 (%)	GRADE 4 (%)	GRADE 3 (%)	GRADE 4 (%)
Leuconeutropenia	18	1	20	2
Anemia	0	0	1	1
Thrombocytopenia	0	0	1	0
Febrile neutropneia	3	0	5	0
Nausea, Vomiting, GIT Upset	1	0	2	0
Mucositis	0	0	3	0
Neuropathy	11	1	11	1
Fatigue	3	0	5	0

Limited data are available to compare between chemotherapy agents in recurrent platinum-resistant ovarian and peritoneal cancers. The majority of studies in recurrent platinum-resistant disease were Phase II rather than Phase III studies.

The current trial aims to answer important research questions in recurrent platinum-resistant ovarian and peritoneal cancers, including the possibility for a first-line regimen upon recurrence and the feasibility of paclitaxel rechallenge. We selected to run a Phase III trial to compare different dose schedules of paclitaxel, looking for the best dose schedule with the fewest and least impacting side effects. Most likely, our trial is one of the few that compared chemotherapeutic agents in such a disease. Furthermore, to the best of our knowledge up to the date of publication, there was no Phase III trial to compare taxane agents and taxane schedules.

In the current study, weekly paclitaxel achieved better ORR and PFS results than three-weekly paclitaxel. The difference in ORR between the two regimens may be attributed to relative cancer resistance to three-weekly paclitaxel that was given as first-line therapy. Confirmatory evidence of the effectiveness of weekly paclitaxel over three-weekly regimen came from the trial of Katsumata et al. They observed a better OS and PFS with *dose-dense* paclitaxel regimen in comparison with the conventional dose in the adjuvant setting.¹⁸

The authors did not perform further multivariate analysis for confounders because of the small number of patients, the aim of the current study being to look for a *new hope* treatment and the nature of the disease with frequent and short interval relapses.

Furthermore, although both regimens were associated with a mild toxicity profile, the toxicity profile for weekly paclitaxel was significantly lower than three-weekly paclitaxel. Hematological toxicities and neuropathy were the most commonly encountered side effects, specifically 19% for grade 3 and 12% for grade 4.

When comparing our results with those of Gynecologic Oncology Group (GOG) et al.¹⁵, the current study achieved better ORR with more grade 3 and 4 neuropathy. This difference may be explained in part by the relatively small sample size of both trials and in part to our guidelines for *treatment delay*. Our guideline stated that treatment delay applies only for grade 3 and 4 neuropathy. This might explain the relatively higher neuropathy numbers in our trial.

In the current study, the QOL data were analyzed as they were considered key indicators as to the response to treatment. A subjective response is considered an important factor for response assessment in such palliative disease. There was no previous guideline to follow in evaluating QOL in participating patients. Therefore, the authors selected to evaluate QOL mainly on patients who achieved ORR and/or SD rather than those who achieved DP. This was to show the changes in QOL just in responders rather than through the whole group, although some data were also included from those. Including more patients with DP would flaw the QOL results.



Furthermore, willingness of patients was another important factor to consider in such assessment, and the authors observed that patients with DP participated less in QOL assessment. The authors calculated the QOL changes for the group as a whole, due to the small number of patients in addition to the authors planned to check the subjective changes in patients treated with paclitaxel rechallenge either weekly or thrice weekly.

Paclitaxel significantly improved the QOL in patients with recurrent *platinum-resistant* ovarian and peritoneal cancers. Importantly, when we assessed the QOL at the end of the treatment, there were no significant changes or treatment-related side effects.

Further studies are required to confirm our results, ideally with a relatively larger number of patients and more research expenditures.

Conclusion

Paclitaxel rechallenge still showed antitumor activity in recurrent *platinum-resistant* ovarian and peritoneal cancers. Weekly paclitaxel achieved significant better survival results and lower toxicities than three-weekly paclitaxel. Weekly paclitaxel represented a good treatment hope for such patients.

Author Contributions

Conceived and designed the experiments: MO, ME, KN. Analyzed the data: MO, ME, KN. Wrote the first draft of the manuscript: MO, ME, KN. Contributed to the writing of the manuscript: MO, ME, KN. Agree with manuscript results and conclusions: MO, ME, KN. Jointly developed the structure and arguments for the paper: MO, ME, KN. Made critical revisions and approved final version: MO, ME, KN. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer WE: statistics, 2010. *CA Cancer J Clin*. 2010;60:277–300.
2. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. *CA Cancer J Clin*. 2011;61:183–203.
3. Pujade-Lauraine E, Paraiso D, Cure H, et al. Predicting the effectiveness of chemotherapy (Cx) in patients with recurrent ovarian cancer (ROC): a GINECO study. *Proc Am Soc Clin Oncol*. 2002;21:Abstract829.
4. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;32(13):1302–8.
5. BCCA Protocol Summary. Available at: <http://www.bccancer.bc.ca/HPI/Drug-Database/DrugIndexPro/Paclitaxel.htm>. 2010.
6. Bristol-Myers Squibb. TAXOL® product monograph; 22 February 2010. www.bms.com
7. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92(3):205–16.
8. NCCN Clinical Practice Guidelines in Oncology, Ovarian Cancer, Version 1, 2013, Available at http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
9. Cella D, Tulsky D, Gray G, et al. The functional assessment of cancer therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11:570–9.
10. Common Toxicity Criteria (CTC) Version 2.0, Available at http://www.eortc.be/services/doc/ctc/ctcv20_4-30-992.pdf. Published April 30, 1999.
11. Chien J, Kuang R, Landen C, Shridhar V. Platinum-sensitive recurrence in ovarian cancer: the role of tumor microenvironment. *Front Oncol*. 2013;3:251.
12. Perez EA, Vogel CL, Irwin DH, Kirshner JJ, Patel R. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol*. 2001;19:4216–23.
13. Taguchi T, Aihara T, Takatsuka Y, et al. Phase II study of weekly paclitaxel for docetaxel-resistant metastatic breast cancer in Japan. *Breast J*. 2004;10:509–13.
14. Yonemori K, Katsumata N, Uno H, et al. Efficacy of weekly paclitaxel for docetaxel-resistant metastatic breast cancer. *Breast Cancer Res Treat*. 2005;89:237–41.
15. Gynecologic Oncology Group (GOG), Markman M, Blessing J, et al. Phase II trial of weekly paclitaxel (80 mg/m²) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2006;101:436–40.
16. Piccart MJ, Green JA, Lacave AJ, et al. Oxaliplatin or paclitaxel. in patients with platinum-pretreated advanced ovarian cancer: a randomized phase II study of the European Organization for Research and Treatment of Cancer Gynecology Group. *J Clin Oncol*. 2000;18:1193–202.
17. Suresh KP. An overview of randomization techniques: an unbiased assessment of outcome in clinical research. *J Hum Reprod Sci*. 2011;4(1):8–11.
18. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet*. 2009;374(9698):1331–8.
19. Abushahin F, Singh DK, Lurain JR, Grendys EC, Rademaker AW, Schink JC. Weekly topotecan for recurrent platinum resistant ovarian cancer. *Gynecol Oncol*. 2008;108:53–7.
20. Gordon AN, Granai CO, Rose PG, et al. Phase II study of liposomal doxorubicin in platinum- and paclitaxel-refractory epithelial ovarian cancer. *J Clin Oncol*. 2000;18:3093–100.
21. Ferrandina G, Ludovisi M, Lorusso D, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. *J Clin Oncol*. 2008;26:890–6.
22. Rose PG, Blessing JA, Ball HG, et al. A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2003;88:130–135. *J Clin Oncol*. 1997 Jun;15(6):2183–93.