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Original Article

Randomized phase III trial comparing pegylated liposomal doxorubicin (PLD) at 50 mg/m² versus 40 mg/m² in patients with platinum-refractory and -resistant ovarian carcinoma: the JGOG 3018 Trial

Takashi Motohashi[1], **Akira Yabuno**[2], **Hiroshi Michimae**[3], **Tetsuro Ohishi**[4], **Miwa Nonaka**[5], **Masashi Takano**[6], **Shin Nishio**[7], **Hiroyuki Fujiwara**[8], **Keiichi Fujiwara**[2], **Eiji Kondo**[9], **Toru Sugiyama**[10], **Tsutomu Tabata**[1]

[1]Department of Obstetrics and Gynecology, Tokyo Women's Medical University, Tokyo, Japan
[2]Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Tokyo, Japan
[3]Kitasato University School of Pharmacy, Tokyo, Japan
[4]Department of Obstetrics and Gynecology, Tottori University School of Medicine, Yonago, Japan
[5]Global Clinical Research Coordinating Center Division of Clinical Research Kitasato University Hospital, Tokyo, Japan
[6]Department of Clinical Oncology, National Defense Medical College Hospital, Tokorozawa, Japan
[7]Department of Obstetrics and Gynecology, Kurume University School of Medicine, Kurume, Japan
[8]Department of Obstetrics and Gynecology, Jichi Medical University, Tochigi, Japan
[9]Department of Obstetrics and Gynecology, Mie University School of Medicine, Mie, Japan
[10]Department of Obstetrics and Gynecology, St. Mary's Hospital, Kurume, Japan

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Correspondence to
Tsutomu Tabata
Department of Obstetrics and Gynecology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan.
E-mail: tabata.tsutomu@twmu.ac.jp

ORCID iDs
Takashi Motohashi
https://orcid.org/0000-0003-3459-7485
Akira Yabuno
https://orcid.org/0000-0002-1221-0609
Hiroshi Michimae
https://orcid.org/0000-0003-4494-2529
Tetsuro Ohishi
https://orcid.org/0000-0001-9374-0101
Miwa Nonaka
https://orcid.org/0000-0001-5050-2664
Masashi Takano
https://orcid.org/0000-0001-6916-9398
Shin Nishio
https://orcid.org/0000-0003-2526-630X
Hiroyuki Fujiwara
https://orcid.org/0000-0002-8888-9937

ABSTRACT

Objective: The standard dose for pegylated liposomal doxorubicin (PLD) is 50 mg/m² every 4 weeks. While 40 mg/m² has recently been used in clinical practice, evidence supporting this use remains lacking.
Methods: This phase III randomized, non-inferiority study compared progression-free survival (PFS) for patients with platinum-resistant ovarian carcinoma between an experimental arm (40 mg/m² PLD) and a standard arm (50 mg/m² PLD) until 10 courses, disease progression or unacceptable toxicity. Eligible patients had received ≤2 prior lines. Stratification was by performance status and PFS of prior chemotherapy (<3 months versus ≥3 months). The primary endpoint was PFS and secondary endpoints were overall survival (OS), toxicity profile, clinical response and tolerability. The total number of patients was 470.
Results: The trial was prematurely closed due to slow recruitment, with 272 patients randomized to the experimental arm (n=137) and standard arm (n=135). Final analysis was performed with 234 deaths and 269 events for PFS. In the experimental arm vs. standard arm, median PFS was 4.0 months vs. 4.0 months (hazard ratio [HR]=1.065; 95% confidence interval [CI]=0.830–1.366) and median OS was 14.0 months vs. 14.0 months (HR=1.078; 95% CI=0.831–1.397). Hematologic toxicity and oral cavity mucositis (≥grade 2) were more frequent in the standard arm than in the experimental arm, but no difference was seen in ≥grade 2 hand-foot skin reaction.
Conclusion: Non-inferiority of 2 PLD dosing schedule was not confirmed because the trial was closed prematurely. However, recommendation of dose reduction of PLD should be based both on efficacy and safety.

Keiichi Fujiwara
https://orcid.org/0000-0002-7388-0243
Eiji Kondo
https://orcid.org/0000-0001-9773-2520
Toru Sugiyama
https://orcid.org/0000-0002-2385-9040
Tsutomu Tabata
https://orcid.org/0000-0003-0243-8180

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Presentation
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Conflict of Interest
Dr. Fujiwara reports personal fees from Jannsenn during the conduct of the study. Also he reports grants from Kaken, Shionogi, GSK, Lilly, Immunogen, and Oncotherapy; personal fees from Nihon Kayaku, Novartis, Kyowahakko Kirin, Janssen, Daiichi Sankyo, and Mochida; grants and personal fees from Astra Zeneca, Pfizer, Eisai, MSD, Taiho, Zeria, and Chugai during relevant financial activities outside the submitted work.
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Keywords: Chemotherapy; Ovarian Neoplasms; Doxorubicin; Recurrence

INTRODUCTION

Several clinical trials have demonstrated the efficacy of pegylated liposomal doxorubicin (PLD) in patients with recurrent ovarian cancer. In particular, PLD has been the first choice for patients with platinum-refractory or -resistant ovarian cancer [1]. The United States Food and Drug Administration (FDA) has approved a PLD dose of 50 mg/m^2 delivered on a schedule of every 28 days. However, a dose of 40 mg/m^2 is widely used in patients with platinum-resistant ovarian cancer, because of the reported lower incidence of palmar-plantar erythrodysesthesia (PPE) [2]. Indeed, some retrospective studies have found lower incidences of hand-foot syndrome or mucositis with a dose of 40 mg/m^2 than with 50 mg/m^2, while both doses appear to offer similar efficacy. However, previous phase II and III studies using PLD for recurrent ovarian cancer concluded that the 50-mg/m^2 dose was tolerable and manageable [3,4]. Some recent phase III clinical trials have used PLD at 50 mg/m^2 as the standard chemotherapy for comparison with various targeted therapies, including lurbinectedin (NCT02421588), trabectedin [5], olaparib [6] and vintafolide (NCT01170650) [7]. Unfortunately, no phase III trials have compared PLD doses of 50 and 40 mg/m^2.

The PLD schedule of 50 mg/m^2 has been approved worldwide, and is used as the standard dose. If the PLD schedule of 40 mg/m^2 is to become a standard dose in clinical trials, we think that a non-inferiority study comparing PLD 50- and 40-mg/m^2 doses in patients with recurrent ovarian cancer is needed. Of course, we expect advances in antineoplastic strategies that are effective and relatively safe, and that improve survival and quality of life (QOL) for patients with cancer. However, evidence-based medicine aims to apply the best available evidence gained using the scientific method to clinical decision-making [8]. We should seek to assess the strength of evidence for the risks and benefits of different treatments, including lack of treatment [9].

MATERIALS AND METHODS

1. Study design

We conducted a Phase III randomized, multicenter, non-inferiority study comparing progression-free survival (PFS) for patients with platinum-resistant Müllerian carcinoma (epithelial ovarian, fallopian tube, or primary peritoneal carcinoma) treated with an experimental arm (40 mg/m^2 PLD) versus a standard arm (50 mg/m^2 PLD) until 10 courses, disease progression or unacceptable toxicity. The dosing interval was increased by an additional 2 weeks if the patient experienced neutrophil count ≤1,500/μL, platelet count ≤100,000/μL, bilirubin ≥1.2 mg/dL, grade 1/2 hand-foot skin reaction, or grade 1/2 mucositis. Treatment dose was reduced to <10 mg/m^2 from the previous dose if the patient experienced grade 3/4 hand-foot skin reaction or mucositis. The minimum treatment dose was 30 mg/m^2 in both arms.

The primary objective was to establish the non-inferiority of PFS for both arms (40 mg/m^2 vs. 50 mg/m^2 PLD), and secondary endpoints were adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0), best

response rate according to Response Evaluation Criteria in Solid Tumors (RECIST), overall survival (OS), and tolerability.

2. Patients

Patients were recruited at multiple institutions in Japan from February 2010. Eligible patients were those with Müllerian carcinoma who experienced disease recurrence or disease progression up to 6 months after the last chemotherapy, had received no more than two previous chemotherapy lines, and had a life expectancy >3 months, irrespective of whether measurable lesions were present. Patients were required to be 20–79 years old and to have an Eastern Cooperative Oncology Group performance status (PS) of 0–2. Adequate hematologic, renal, and hepatic functions were required, including absolute white blood cell count ≥3,000/μL, neutrophil count ≥1,500/μL, hemoglobin ≥9.0 g/dL, platelet count ≥100,000/μL, bilirubin ≤1.2 mg/dL, aspartate aminotransferase and alkaline phosphatase levels ≤100 IU/mL, and serum creatinine ≤1.5 g/dL. Chest radiography, electrocardiography, and echocardiography were performed at baseline. Patients who were considered eligible to undergo surgery by each institutional tumor board were excluded from this study. Patients who had synchronous primary carcinoma and had received chemotherapy or radiotherapy were also ineligible.

The ethics committees at each participating institution approved the study. All patients provided written informed consent. The protocol was coordinated by the Japanese Gynecologic Oncology Group (JGOG; protocol number 3018).

3. Randomization

All participating institutions or the coordinating center of the study group were required to complete the JGOG 3018 Institution Registration form to provide an institutional review board approval certificate for this trial, as well as institutional contact information. Eligible patients were randomly assigned 1:1 to one of two treatment regimens in equal proportions by the Clinical Trial Coordinating Center randomization system of the Kitasato University Research Center for Clinical Pharmacology Clinical Trial Coordinating Center randomization system.

Stratification was by PS (0 vs. 1 vs. 2) and PFS of prior chemotherapy (<3 months vs. ≥ 3 months).

4. Procedure

The investigator administered the assigned protocol treatment. Eligible patients were randomly assigned to receive PLD at 50 mg/m^2 on day 1 every 4 weeks for 10 cycles (standard arm) or PLD at 40 mg/m^2 on day 1 every 4 weeks for 10 cycles (experimental arm). No further anticancer therapy was to be administered after the completion of 10 cycles of the protocol therapy until progression or intolerable adverse event was documented. The follow-up period was 2 years after the end of registration. Dose modification rules were predefined. Antiemetic therapy was provided according to the standard procedure at each participating institution.

Disease assessment, which included clinical examination, abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI), and serum carbohydrate antigen (CA) 125 measurement, was performed at baseline, every two cycles, and every 3 months after the end of treatment. Safety assessment included physical examination, blood tests (hematology and biochemistry), and collection of the history of adverse events, and was performed at baseline and before each cycle.

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5. Outcomes

PFS was the primary endpoint and was defined as the duration from the date of random assignment to the date of progression. Disease progression was assessed by radiologic review or CA125 according to RECIST and Gynecological Cancer Intergroup (GCIG) criteria [10-12].

Secondary endpoints included OS, best response rate, adverse events, and tolerability. OS was defined as the duration from the date of randomization to the date of death. All adverse events were documented on the case report form according to Common Terminology Criteria for Adverse Events, version 3.0. Total toxicity was the worst grade suffered for each item by each patient at any time during the trial. The response rate was assessed by investigators according to RECIST and GCIG criteria. Patients not evaluated because of death, toxicity, or refusal were considered as non-responders.

6. Statistical analysis

The primary objective of this study was to determine whether PLD 40 mg/m^2 was noninferior to PLD 50 mg/m^2 in the treatment of patients with recurrent or persistent Müllerian carcinoma as assessed by PFS. On the basis of the results of a previous study [13], we assumed that median PFS for the PLD 50-mg/m^2 arm (standard arm) was 13.5 weeks, corresponding to 3 weeks in PFS. With an accrual time of 5.5 years and a minimum follow-up of 1 year, 461 patients were originally required for a one-sided α level of 0.05 and power ≥80%. After protocol modification due to the prolonged accrual period, 470 patients were finally required.

PFS and OS were estimated using the Kaplan-Meier method and Greenwood formula. PFS and OS analyses were conducted using a stratified Cox regression model. Efficacy analyses were performed under an intention-to-treat strategy. Safety analysis was conducted for all treated patients. A one-sided value of $p<0.05$ was considered indicative of statistical significance, and 95% confidence intervals (CI) were used unless otherwise stated. The proportion of adverse events ≥grade 2 was compared between treatment groups using Fisher's exact test.

Planned interim analysis was conducted, then half the planned sample size was reached. Multiplicity of the primary endpoint was adjusted using the O'Brien-Fleming-type alpha spending function. If the primary objective of the trial had been attained, the study would have been be closed, and the results presented and published immediately.

RESULTS

1. Analysis

The target total number of patients in this trial was 470, but from February 2010 to March 2017, only 271 patients were randomly assigned to the PLD 40-mg/m^2 arm (n=136) and PLD 50-mg/m^2 arm (n=135). Unfortunately, we were unable to obtain PLD from the company for half a year from July 2012 because of supplier problems. Furthermore, enrollment was closed in March 2017, because the accrual rate was considered too slow. After enrolment, 7 cases had not been treated with PLD due to poor condition, refusal, or other complications. All survival analyses were intention-to-treat, and adverse events analysis was performed except for these 7 patients who had not been administered treatment.

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Table 1. Patient characteristics

Characteristics	PLD 50 mg/m^2 (n=135)	PLD 40 mg/m^2 (n=136)
Median age (yr)	61 (30–79)	63 (31–79)
ECOG PS		
0	109 (80.7)	112 (82.4)
1	23 (17.0)	22 (16.2)
2	3 (2.2)	2 (1.5)
Histology		
Serous	89 (65.9)	93 (68.4)
Endometrioid	9 (6.7)	5 (3.7)
Clear cell	19 (14.1)	26 (19.1)
Other	18 (13.4)	12 (8.8)
FIGO stage		
I	14 (10.4)	11 (8.1)
II	2 (1.5)	6 (4.4)
III	85 (63.0)	93 (68.4)
IV	33 (24.4)	26 (19.1)
Unknown	1 (0.7)	0
Treatment-free interval		
<3 months	79 (58.5)	78 (57.4)
≥3 months, <6 months	54 (40.0)	54 (39.7)
≥7 months*	0	2 (1.5)
Recurrence during pretreatment	2 (1.5)	2 (1.5)
This chemotherapy is		
2nd-line chemotherapy	67 (49.6)	69 (50.7)
3rd-line chemotherapy	61 (45.2)	61 (44.9)
4th-line chemotherapy†	7 (5.2)	6 (4.4)
Primary surgery	135 (100)	133 (97.8)
No residual	54 (40.0)	57 (41.6)
Optimal (<1 cm)	20 (14.8)	16 (11.7)
Suboptimal (≥1 cm)	47 (34.8)	39 (28.5)

Values are presented as median (range) or number (%).
ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; PLD, pegylated liposomal doxorubicin; PS, performance status.
*Randomization factor deviation; †4th-line chemotherapy was ineligible.

2. Patients

Baseline patient characteristics were well balanced between the 2 arms (**Table 1**). Median age was 62 years. About 58% of patients had a treatment-free interval <3 months, and about 80% of patients had PS 0. Two patients who showed recurrence ≤7 months after last chemotherapy showed deviation from this protocol. Thirteen patients (7 patients in the PLD 50-mg/m^2 arm, 6 patients in the PLD 40-mg/m^2 arm) were ineligible because they had received chemotherapy as 4th-line treatment.

3. Tolerability

Table 2 shows the reason for delayed cycles. Seven patients who had not been administered treatment were excluded. The PLD 50-mg/m^2 arm included 57.3% of those patients who had been given reduced doses of chemotherapy, whereas the PLD 40-mg/m^2 arm had 48.1%, showing no difference in incidence between arms. The PLD 50-mg/m^2 arm included more cycle delays than the 40-mg/m^2 arm because of neutropenia, thrombocytopenia, or oral cavity mucositis. **Table 3** shows dose reductions for PLD because of grade 3/4 hand-foot skin reactions or oral cavity mucositis. In the PLD 50-mg/m^2 arm, 23.7% of patients needed dose reduction of treatment, compared to 9.6% in the PLD 40-mg/m^2 arm. **Table 4** shows primary reasons for study-off in this trial. Patients who completed protocol treatment (10 cycles) comprised 11.1% of the PLD 50-mg/m^2 arm and 12.5% of the PLD 40-mg/m^2 arm. The most primary reason for treatment study-off was disease progression in both arms, but no

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Table 2. Cycles delayed

Variables	PLD*		
	At 50 mg/m² (n=131)	At 40 mg/m² (n=133)	p-value
Patients with cycle delayed, No. (%)	75 (57.3)	64 (48.1)	0.137
Reason (multiple answers)			
Neutrophil count <1,500/μL	105	80	<0.001
Platelet count <100,000/μL	5	0	0.023
Bilirubin >1.2 mg/dL	1	1	0.991
Hand-foot skin reaction ≥grade 2	14	11	0.503
Mucositis-oral cavity ≥grade 2	13	3	0.009
Non-hematologic toxicities ≥grade 3	6	3	0.298
Other	13	14	0.872

*Except for 7 cases that had not been given treatment.

Table 3. Dose reduction of PLD

Variables	PLD 50 mg/m² (n=135)		PLD 40 mg/m² (n=136)	
	PLD (mg/m²)	No. (%)	PLD (mg/m²)	No. (%)
Level 0	50	99 (73.3)	40	120 (88.2)
Level 1	40	27 (20.0)	30	13 (9.6)
Level 2	30	5 (3.7)	-	-
Treatment not given	-	4 (3.0)	-	3 (2.2)

PLD, pegylated liposomal doxorubicin.

Table 4. Primary reason for study-off

Variables	PLD 50 mg/m² (n=135)	PLD 40 mg/m² (n=136)	p-value
Completed protocol treatment (10 cycles)	15 (11.1)	17 (12.5)	-
Study treatment off	120 (88.9)	119 (87.5)	-
Primary reason for study treatment off			
Disease progression	75 (62.5)	92 (77.3)	0.013
Adverse events	22 (18.3)	7 (5.9)	0.003
Patient withdrawal	9 (7.5)	12 (11.1)	0.481
Death	3 (2.5)	3 (2.5)	0.992
Other	11 (9.2)	5 (4.2)	0.125

difference in incidence was evident between arms. The PLD 40-mg/m² arm showed a greater incidence of disease progression as the primary reason for study-off, but a significantly lower frequency of adverse events than the 50-mg/m² arm.

4. Efficacy

The final analysis was performed for 234 deaths and 269 events for PFS in 271 patients. Median PFS was 4.0 months vs. 4.0 months in the 40-mg/m² arm vs. 50-mg/m² arm (hazard ratio [HR]=1.065; 95% confidence interval [CI]=0.830–1.366) (**Fig. 1A**). No significant difference in the two PFS curves was identified. Median OS was 14.0 months vs. 14.0 months in the 40-mg/m² arm vs. 50-mg/m² arm (HR=1.078; 95% CI=0.831–1.397) (**Fig. 1B**). No significant heterogeneity was identified between arms.

According to RECIST, 213 patients showed measurable disease (104 in the 50-mg/m² arm and 109 in the 40-mg/m² arm). Overall response rates for the two treatment regiments were 17.3% (2.9% complete response, 14.4% partial response) in the 50-mg/m² arm and 12.8% (0.9% complete response, 11.9% partial response) in the 40-mg/m² arm.

5. Adverse events

Adverse events are summarized in **Table 5** as the number of patients who exhibited events ≥grade 2. PLD 50 mg/m² was associated with an increase in hematologic toxicity (anemia,

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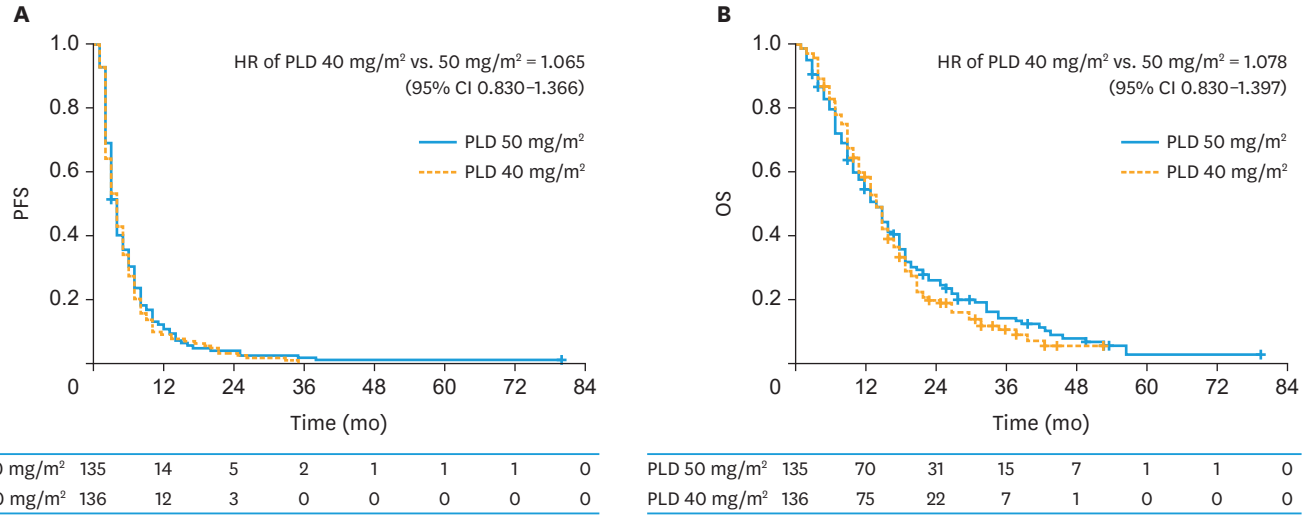

Fig. 1. Kaplan-Meier curves for PFS (A) and OS (B).
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin.

Table 5. Adverse events (≥grade 2)

Adverse events	PLD*						p-value†
	At 50 mg/m² (n=131)			At 40 mg/m² (n=133)			
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	
Hematologic							
Anemia	48 (79)	22 (17)	10 (8)	34 (26)	11 (8)	6 (5)	<0.001
Leukopenia	47 (36)	51 (39)	12 (9)	47 (35)	32 (24)	7 (5)	<0.001
Neutropenia	27 (21)	53 (40)	29 (22)	26 (20)	40 (30)	14 (11)	<0.001
Thrombocytopenia	20 (15)	10 (8)	3 (2)	6 (5)	3 (2)	1 (1)	<0.001
Febrile neutropenia	0	8 (6)	0	0	5 (4)	0	0.409
Cardiac general	0	0	0	0	0	0	-
General condition							
Fatigue	13 (10)	5 (4)	0	11 (8)	4 (3)	0	0.581
Fever	7 (5)	0	0	5 (4)	0	0	0.570
Weight loss	10 (8)	1 (1)	0	8 (6)	0	0	0.485
Skin							
Alopecia	2 (2)	0	0	0	0	0	0.282
Hand-foot skin reaction	15 (11)	11 (8)	0	16 (12)	4 (3)	0	0.333
Ulceration	2 (2)	0	0	0	0	0	0.245
Gastrointestinal							
Anorexia	15 (11)	8 (6)	0	11 (8)	5 (4)	0	0.228
Constipation	10 (8)	1 (1)	0	10 (8)	1 (1)	0	1.000
Diarrhea	3 (2)	0	0	7 (5)	0	0	0.334
Mucositis (oral cavity)	23 (18)	10 (8)	0	13 (10)	5 (4)	0	0.009
Nausea	10 (8)	8 (6)	0	12 (9)	3 (2)	0	0.581
Vomiting	6 (5)	6 (5)	0	5 (4)	3 (2)	0	0.362
Acute infusion reaction	1 (1)	0	0	3 (2)	1 (1)	0	0.370

Values are presented as number of patients (%).
PLD, pegylated liposomal doxorubicin.
*Except for the 7 cases that had not been given treatment; †Analysis of grade 2 of greater adverse events between treatment groups.

leukopenia, neutropenia or thrombocytopenia). For non-hematological toxicity, oral cavity mucositis (≥grade 2) was more frequent in the 50-mg/m² arm than in the 40-mg/m² arm, but no difference was evident in hand-foot skin reactions ≥grade 2 (≥grade 2, p=0.333 and ≥grade 3, p=0.067, respectively).

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DISCUSSION

In a phase I study of PLD in patients with recurrent ovarian cancer [14], the maximal tolerated dose of PLD was either 50 mg/m^2 every 3 weeks or 60 mg/m^2 every 4 weeks. After that, the recommended dose of PLD was decided as 50 mg/m^2 every 4 weeks. In general, the effect of chemotherapy is considered to correlate with the dose of chemotherapy. The phase II study concluded that 50 mg/m^2 PLD every 4 weeks showed a response rate of 16.7%–21.9% in recurrent ovarian cancer. Furthermore, PPE and stomatitis can usually be managed by dose adjustment [15,16]. On the other hand, a phase II study using PLD at 40 mg/m^2 every 4 weeks in patients with refractory ovarian cancer showed that this dose regimen resulted in less frequent toxicity (stomatitis, hand-foot syndrome) than PLD at 50 mg/m^2 [17]. However, the response rate for PLD at 40 mg/m^2 was 9%. A difference in response rate was apparent between the two dose arms, although eligibility criteria differed between each clinical trial.

Some randomized phase III studies have compared each single-agent chemotherapy for recurrent ovarian cancer [4-6,13,18]. In those studies, most studies used a PLD schedule of 50 mg/m^2 as the standard-dose chemotherapy [4,5,13], but the study by Ferrandina et al. [18] used a PLD schedule of 40 mg/m^2. No difference in PFS was found for platinum-resistant ovarian cancer patients treated with each single-agent chemotherapy. However, whether equivalence of PFS or time to progression (TTP) was achieved between the PLD schedules of 40 and 50 mg/m^2 remained unclear. Most phase III studies used PFS or TTP as an endpoint, but PFS or TTP could be influenced by some factors: patient eligibility criteria and plans for PFS assessment. As for patient eligibility criteria for a clinical trial in patients with recurrent ovarian cancer, the clinical trial arm that included more patients with platinum-resistant ovarian cancer clearly showed worse prognosis than the arm that included fewer patients with platinum-resistant ovarian cancer. Comparing prognosis between clinical trials is thus difficult, because rates for patients with platinum-resistant or partially platinum-sensitive pathologies differed between some clinical trials.

Various randomized phase III studies have compared PLD with other single-agent chemotherapies, with some yielding median PFS of 12.4–20.9 weeks, higher than our result. On the basis of the results from the study by Mutch et al. [13], which demonstrated a median PFS of 12.4 weeks, we assumed a median PFS of 13.5 weeks for the PLD 50 mg/m^2 arm (standard arm). In our study, median PFS was 12.0 weeks. Excluding the study by Mutch et al. [13], the remaining phase III studies [3,4,14,19] considered patients with platinum-sensitive recurrent disease as eligible. Conversely, patients eligible for our study and that of Mutch et al. [13] were limited to those with platinum-resistant ovarian cancer, so the lower median PFS in our study compared to other investigations was unsurprising.

When PFS or TTP is used as a primary endpoint in late-stage studies, the assessment time used to determine PFS or TTP is very important [19,20]. In particular, assessment time bias can occur if patients are evaluated on different assessment schedules. More frequent assessment could show worse PFS or TTP than less frequent assessment. We strictly performed disease assessment by CT, MRI or serum CA125 at baseline, every two cycles, and every 3 months after the end of treatment.

The main limitations of our study were that the trial was closed, and the data were analyzed before reaching the planned number of events. Some reasons were as follows: the interruption in PLD supply from the company; prolongation of the study; some other

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clinical trials providing treatment with targeted therapy; possible decreases in the interest of participating groups; and spread in the clinical use of 40 mg/m^2 PLD. However, our limited data showed PFS and OS were similar between patients treated with PLD 40 or 50 mg/m^2.

Based on some retrospective studies [2,21-23], no difference in PFS or OS was apparent between PLD 40 or 50 mg/m^2. However, whether PFS or OS were equivalent between the two PLD regimens remained unclear. These retrospective studies concluded that a randomized trial is needed to confirm that efficacy is comparable between the 2 arms. We therefore conducted a phase III randomized, multicenter, non-inferiority study comparing PFS in patients with platinum-refractory or -resistant Müllerian carcinoma.

Furthermore, some retrospective studies have reported that the incidence of PPE or mucositis would be higher in patients receiving PLD at 50 mg/m^2 rather than 40 mg/m^2 [2,21-23], and that specific adverse events of PLD, such as PPE, at standard doses may severely alter the QOL in patients with recurrent ovarian cancer. However, adverse events such as PPE are influenced by pretreatment patient characteristics. Tanyi et al. [22] reported that the incidence of PPE was higher among patients who received a greater number of prior chemotherapy regimens, but the type of chemotherapeutic agent did not show any association with PPE. Although our data were limited due to the premature closure, hand-foot skin reaction ≥grade 2 showed no difference in incidence between arms. However, hand-foot skin reaction ≥grade 3 tended to be more common with PLD at 50 mg/m^2 (p-value of 0.067). If the full number of cases could have been registered, the incidence of hand-foot skin reaction ≥grade 3 might have differed significantly between the two arms. In the AURELIA study [24], the dose of PLD was 40 mg/m^2. In our study, PLD at 50 mg/m^2 resulted in a greater frequency of adverse events than 40 mg/m^2. We think that if PLD is used with bevacizumab, a dose of 40 mg/m^2 might be appropriate for platinum-resistant ovarian cancer.

In our study, the most common reason for study-off was disease progression, and the incidence of withdrawal for this reason was higher in the PLD 40-mg/m^2 arm than in the PLD 50-mg/m^2 arm. Indeed, overall response rates for the two treatment regiments were 17.3% in the PLD 50-mg/m^2 arm and 12.8% in the PLD 40-mg/m^2 arm. However, the incidence of study-off due to adverse events was higher in the PLD 50-mg/m^2 arm than in the 40-mg/m^2 arm. Overall, PFS and OS in both arms were comparable and we thus consider that response rate did not correlate with survival. Since adverse events appeared earlier in the PLD 50-mg/m^2 arm than in the 40-mg/m^2 arm, the reason for study-off may be that adverse events were more frequent in the 50-mg/m^2 arm and progression was more frequent in the 40-mg/m^2 arm.

Mucositis is a common complication of chemotherapy that can affect up to 90% of certain patient populations with cancer [25]. Severe mucositis sometimes requires interruption of treatment or de-escalation of chemotherapy. In particular, oral mucositis involves an extreme decline in QOL, because symptoms can be complicated by uncontrolled pain or loss of appetite in patients with cancer who undergo chemotherapy. If a patient develops oral mucositis, the symptoms are difficult to manage. In patients with platinum-resistant ovarian cancer, the most important concern is QOL. The aim of chemotherapy in these patients is palliation. The GCIG showed that palliative chemotherapy has been shown to reduce symptoms in patients with platinum-resistant ovarian cancer [26]. The 40-mg/m^2 dose of PLD thus appears reasonable.

Results of this non-inferiority clinical trial of 2 PLD dosing schedules cannot be considered confirmed, because the trial was closed prematurely, but PFS and OS were similar.

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Recommendation of dose reduction of PLD in patients with platinum-resistant ovarian carcinoma should be based both on efficacy and safety. The FDA and the Japanese Ministry of Health, Labour and Welfare (MHLW) approved a PLD dosing schedule of 50 mg/m^2 every 4 weeks. However, we hope that the FDA and MHLW will approve a PLD dosing schedule of 40 mg/m^2 every 4 weeks, allowing 40 mg/m^2 doses of PLD to be routinely used as standard-dose chemotherapy in clinical trial for patients with recurrent ovarian cancer.

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REFERENCES

1. Thigpen JT, Aghajanian CA, Alberts DS, Campos SM, Gordon AN, Markman M, et al. Role of pegylated liposomal doxorubicin in ovarian cancer. Gynecol Oncol 2005;96:10-8.
PUBMED | CROSSREF
2. Markman M. Serious ethical dilemma of single-agent pegylated liposomal doxorubicin employed as a control arm in ovarian cancer chemotherapy trials. J Clin Oncol 2010;28:e319-20.
PUBMED | CROSSREF
3. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 2001;19:3312-22.
PUBMED | CROSSREF
4. O'Byrne KJ, Bliss P, Graham JD, Gerber J, Vasey PA, Khanna S, et al. A phase III study doxil/caelyx versus paclitaxel in platinum-treated, taxane-naïve relapsed ovarian cancer. In: Proceedings of the ASCO Annual Meeting; 2002 May 18–21; Orlando, FL; 2002. Abstract 808.
5. Monk BJ, Herzog TJ, Kaye SB, Krasner CN, Vermorken JB, Muggia FM, et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. J Clin Oncol 2010;28:3107-14.
PUBMED | CROSSREF
6. Penson RT, Valencia RV, Cibula D, Colombo N, Leath CA 3rd, Bidziński M, et al. Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation (SOLO3): a randomized phase III trial. J Clin Oncol 2020;38:1164-74.
PUBMED | CROSSREF
7. Herzog TJ, Kutarska E, Bidzińsk M, Symanowski J, Nguyen B, Rangwala RA, et al. Adverse event profile by folate receptor status for vintafolide and pegylated liposomal doxorubicin in combination, versus pegylated liposomal doxorubicin alone, in platinum-resistant ovarian cancer: exploratory analysis of the phase II PRECEDENT trial. Int J Gynecol Cancer 2016;26:1580-5.
PUBMED | CROSSREF
8. Timmermans S, Mauck A. The promises and pitfalls of evidence-based medicine. Health Aff (Millwood) 2005;24:18-28.
PUBMED | CROSSREF
9. Elstein AS. On the origins and development of evidence-based medicine and medical decision making. Inflamm Res 2004;53 Suppl 2:S184-9.
PUBMED | CROSSREF
10. Wilson MK, Pujade-Lauraine E, Aoki D, Mirza MR, Lorusso D, Oza AM, et al.. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: recurrent disease. Ann Oncol 2017;28:727-32.
PUBMED | CROSSREF
11. Rustin GJ, Quinn M, Thigpen T, du Bois A, Pujade-Lauraine E, Jakobsen A, et al. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). J Natl Cancer Inst 2004;96:487-8.
PUBMED | CROSSREF

12. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, 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;92:205-16.
PUBMED | CROSSREF
13. Mutch DG, Orlando M, Goss T, Teneriello MG, Gordon AN, McMeekin SD, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol 2007;25:2811-8.
PUBMED | CROSSREF
14. Uziely B, Jeffers S, Isacson R, Kutsch K, Wei-Tsao D, Yehoshua Z, et al. Liposomal doxorubicin: antitumor activity and unique toxicities during two complementary phase I studies. J Clin Oncol 1995;13:1777-85.
PUBMED | CROSSREF
15. Gordon AN, Granai CO, Rose PG, Hainsworth J, Lopez A, Weissman C, et al. Phase II study of liposomal doxorubicin in platinum- and paclitaxel-refractory epithelial ovarian cancer. J Clin Oncol 2000;18:3093-100.
PUBMED | CROSSREF
16. Katsumata N, Fujiwara Y, Kamura T, Nakanishi T, Hatae M, Aoki D, et al. Phase II clinical trial of pegylated liposomal doxorubicin (JNS002) in Japanese patients with mullerian carcinoma (epithelial ovarian carcinoma, primary carcinoma of fallopian tube, peritoneal carcinoma) having a therapeutic history of platinum-based chemotherapy: a phase II study of the Japanese Gynecologic Oncology Group. Jpn J Clin Oncol 2008;38:777-85.
PUBMED | CROSSREF
17. Markman M, Kennedy A, Webster K, Peterson G, Kulp B, Belinson J. Phase 2 trial of liposomal doxorubicin (40 mg/m^2) in platinum/paclitaxel-refractory ovarian and fallopian tube cancers and primary carcinoma of the peritoneum. Gynecol Oncol 2000;78:369-72.
PUBMED | CROSSREF
18. Ferrandina G, Ludovisi M, Lorusso D, Pignata S, Breda E, Savarese A, 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.
PUBMED | CROSSREF
19. Bhattacharya S, Fyfe G, Gray RJ, Sargent DJ. Role of sensitivity analyses in assessing progression-free survival in late-stage oncology trials. J Clin Oncol 2009;27:5958-64.
PUBMED | CROSSREF
20. Panageas KS, Ben-Porat L, Dickler MN, Chapman PB, Schrag D. When you look matters: the effect of assessment schedule on progression-free survival. J Natl Cancer Inst 2007;99:428-32.
PUBMED | CROSSREF
21. Nakayama M, Kobayashi H, Takahara T, Nishimura Y, Fukushima K, Yoshizawa K. A comparison of overall survival with 40 and 50mg/m^2 pegylated liposomal doxorubicin treatment in patients with recurrent epithelial ovarian cancer: Propensity score-matched analysis of real-world data. Gynecol Oncol 2016;143:246-51.
PUBMED | CROSSREF
22. Tanyi JL, Smith JA, Ramos L, Parker CL, Munsell MF, Wolf JK. Predisposing risk factors for palmar-plantar erythrodysesthesia when using liposomal doxorubicin to treat recurrent ovarian cancer. Gynecol Oncol 2009;114:219-24.
PUBMED | CROSSREF
23. Rose PG, Maxson JH, Fusco N, Mossbruger K, Rodriguez M. Liposomal doxorubicin in ovarian, peritoneal, and tubal carcinoma: a retrospective comparative study of single-agent dosages. Gynecol Oncol 2001;82:323-8.
PUBMED | CROSSREF
24. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol 2014;32:1302-8.
PUBMED | CROSSREF
25. Brown TJ, Gupta A. Management of cancer therapy-associated oral mucositis. JCO Oncol Pract 2020;16:103-9.
PUBMED | CROSSREF
26. Friedlander ML, Stockler M, O'Connell R, Voysey M, Oza A, Gillies K, et al. Symptom burden and outcomes of patients with platinum resistant/refractory recurrent ovarian cancer: a reality check: results of stage 1 of the gynecologic cancer intergroup symptom benefit study. Int J Gynecol Cancer 2014;24:857-64.
PUBMED | CROSSREF