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ORIGINAL ARTICLE

A phase II randomized controlled study of pegylated liposomal doxorubicin and carboplatin vs. gemcitabine and carboplatin for platinum-sensitive recurrent ovarian cancer (GOTIC003/intergroup study)

Hiroyuki Fujiwara[1] · Kimio Ushijima[2] · Shoji Nagao[3,14] · Yuji Takei[1] · Muneaki Shimada[4,13] · Masashi Takano[5] · Kiyoshi Yoshino[6,15] · Yoshiaki Kawano[7] · Yasuyuki Hirashima[8] · Satoru Nagase[9] · Shin Nishio[2] · Tadaaki Nishikawa[3] · Kimihiko Ito[10] · Tadahiro Shoji[11] · Eizo Kimura[12] · Tadao Takano[13] · Toru Sugiyama[11] · Junzo Kigawa[4,16] · Keiichi Fujiwara[3] · Mitsuaki Suzuki[1,17]

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Abstract

Purpose To compare the efficacy, safety, and tolerability profiles of pegylated liposomal doxorubicin and carboplatin (PLDC) with those of gemcitabine and carboplatin (GC) for the treatment of patients with platinum-sensitive recurrent ovarian cancer.

Methods Ovarian cancer patients with recurrence > 6 months after first-line platinum and taxane-based therapies were randomly assigned to PLDC [pegylated liposomal doxorubicin 30 mg/m^2 plus carboplatin area under the curve (AUC) 5 mg/mL/min on day 1] every 4 weeks or GC (gemcitabine 1000 mg/m^2 on days 1 and 8 plus carboplatin AUC 4 mg/mL/min on day 1) every 3 weeks for at least 6 cycles. The primary endpoint was progression-free survival, and overall response rate, overall survival, toxicity, and dose administration were secondary endpoints.

Results One-hundred patients (49 PLDC; 51 GC) were randomly assigned. Over a median follow-up of 24 months, the median progression-free survival was 12.0 months (95% CI 9.2–15.0) for PLDC and 9.8 months (8.9–12.3) for GC [HR 0.69 (0.455–1.047)] with a difference of 2.2 months. The response rate was 57.1% (41.0–72.3) for PLDC and 56.4% (39.6–72.2) for GC. No obvious differences in toxicity (G3/4) were noted between arms. The median relative dose intensity of planned dose per week was 88.9% for pegylated liposomal doxorubicin and 53.1% for gemcitabine ($p < 0.0001$).

Conclusions PLDC and GC are both good treatment candidates for platinum-sensitive recurrent ovarian cancer patients; however, the dose intensity was lower for GC than for PLDC. PLDC had a more favorable risk–benefit profile than that of GC for patients.

Keywords Platinum-sensitive recurrent ovarian cancer · Pegylated liposomal doxorubicin · Gemcitabine · Randomized clinical trial

Introduction

Ovarian cancer is the leading cause of gynecologic cancer death [1, 2]. Chemotherapy has good efficacy as a first-line treatment for ovarian cancer, but many patients experience recurrence [3]. Even in cases of recurrence, the main treatment modality is chemotherapy, and a number of regimens have been developed. Molecular-targeted therapies have been developed, and their effectiveness for the treatment of recurrent ovarian cancer has been reported [4]. Anti-vascular endothelial growth factor (VEGF) monoclonal antibody and poly(ADP-ribose) polymerase (PARP) inhibitors, in particular, prolong progression-free survival [5, 6], and numerous clinical studies are currently underway [4]. The efficacy of immune check point inhibitors in the treatment of recurrent ovarian cancer has also been reported [7].

Anti-VEGF monoclonal antibody and a PARP inhibitor have been approved for clinical use in Japan since November 2013 and January 2018, respectively. However, it is not applicable to all patients because of problems with adverse

✉ Hiroyuki Fujiwara
fujiwara@jichi.ac.jp

Extended author information available on the last page of the article

side effects and expense [8]. Immune check point antibody inhibitors are not approved for use in ovarian cancer in Japan, and these drugs are expensive, which is economically problematic [9]. Thus, it is necessary to provide conventional cytotoxic chemotherapy in Japan and other countries.

Under both Japanese national guidelines [10] and National Comprehensive Cancer Network (NCCN) guidelines [11], the recommended cytotoxic treatment regimen for platinum-sensitive recurrent ovarian cancer is the addition of taxane, pegylated liposomal doxorubicin, or gemcitabine to carboplatin-based therapy. Paclitaxel plus carboplatin [12] is widely used, but it is often not possible to use during recurrence because of adverse effects such as peripheral sensory neuropathy and hair loss. In these cases, pegylated liposomal doxorubicin plus carboplatin (PLDC) therapy [13] or gemcitabine plus carboplatin (GC) therapy [14] is alternative options, but the selection of an appropriate regimen depends on an accurate understanding of efficacy and potential adverse effects. Although there is a systematic review comparing the respective reports of PLDC therapy and GC therapy [15], there are no reports directly comparing these two regimens. Therefore, we compared the efficacy, safety, and tolerability profiles of PLDC with those of GC for the treatment of patients with platinum-sensitive recurrent ovarian cancer.

The registration of this study was between June 2011 and November 2014. Most of the period was before the approval of Bevacizumab in Japan. Therefore, our study is unique, because we evaluated these cytotoxic regimens without the effects of a new therapy.

Materials and methods

This GOTIC (Gynecologic Oncology Trial and Investigation Consortium of North Kanto)/Intergroup, phase II, centrally randomized, multicenter, open-label, parallel noncomparative [16, 17] trial (UMIN 000,005,487) was designed to evaluate the combination of pegylated liposomal doxorubicin and carboplatin (PLDC) and gemcitabine and carboplatin (GC) for the treatment of patients with platinum-sensitive recurrent ovarian cancer. The primary endpoint was progression-free survival. The secondary endpoints were overall response rate, overall survival, toxicity, and drug administration status. In the PLDC group, PLD 30 mg/m^2 in combination with carboplatin area under the curve (AUC) 5 mg/mL/min was administered every 4 weeks. In the GC group, gemcitabine 1000 mg/m^2 on days 1 and 8 and carboplatin AUC 4 mg/mL/min were administered on day 1 every 3 weeks.

Women at least 20 years with recurrent ovarian, fallopian, and peritoneal cancer at least 6 months after the completion of first-line platinum-based therapy were eligible. Patients with measurable disease or assessable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST Ver1.1) were eligible. Other key eligibility criteria included an Eastern Cooperative Oncology Group performance status of ≤ 2; life expectancy of at least 4 months; and adequate bone marrow, renal, and hepatic function. Patients with elevated CA125 without measurable disease or assessable lesions were excluded. Written informed consent was obtained from all patients before enrollment. The study was conducted in accordance with the Declaration of Helsinki. Before patient entry, the appropriate institutional ethics committee for each participating institution approved the protocol.

Before random assignment, patients were stratified based on a therapy-free interval from the prior chemotherapy (6–12 vs. >12 months) and histological type (clear cell carcinoma/mucinous vs. other). Patients were treated for a total of 6 cycles of therapy in the absence of unacceptable toxicity or disease progression.

For dose reduction/withdrawal criteria, the PLDC group followed the CALYPSO trial [13], and the GC group followed the AGO-OVAR trial [14].

Treatment for adverse events was permitted as appropriate. Other anti-neoplastic agents, hormone therapy, radiation therapy, hyperthermia, or surgical therapy for tumors, were not permitted. There were no restrictions on post-treatment after termination or withdrawal from the study.

The primary endpoints included the median progression-free survival, 0.5-year survival rate, 1-year survival rate, and two-sided 95% confidence intervals for each treatment group. The survival function was obtained using the Kaplan–Meier method. Confidence intervals for the survival function were obtained with standard error using Greenwood's formula and using the normal distribution.

The response rate, rate of adverse events, and drug administration status (treatment completion rate, dose intensity, etc.) were analyzed as secondary endpoints. The two-sided 95% confidence intervals based on the binominal distribution were obtained for each item, and no intergroup comparisons were performed. In addition, overall survival time was analyzed. The median survival time, 0.5-year survival rate, 1-year survival rate, and two-sided 95% confidence intervals for each treatment group were determined. The survival function point and interval estimation were performed using the same methods as those for the primary endpoints.

Because this was a noncomparative [16, 17] trial, no statistical test was performed for these analyses. Only the relative dose intensity of the planned dose per week (RDI) was analyzed by Wilcoxon's rank sum test.

The median progression-free survivals were 8–10 months for paclitaxel + carboplatin (TC) therapy [13, 18], 10–11 months for pegylated liposomal doxorubicin + carboplatin therapy [13, 14], and about 9 months for gemcitabine + carboplatin therapy [14]. In addition, the lowest

reported median progression-free survival among the treatments for each group is 5.8 months for carboplatin therapy [14]. Therefore, the efficacy of GEM + carboplatin therapy over carboplatin therapy should exceed this lower confidence limit. The lower confidence limit of median progression-free survival was 5.3, 5.8, 6.0, and 6.1 when the number of events per group was 20, 30, 40, or 50, respectively, for a median survival time set at 10 months and 2000 simulations. Therefore, 40 events were necessary to obtain a lower confidence limit of at least 6 months, and because of censoring, the minimum number of events per group should be 50.

Results

One-hundred patients (49 PLDC; 51 GC) were randomly assigned from 22 academic institutions belonging to GOTIC and/or intergroup in Japan. Table 1 shows the patients' background. Baseline characteristics were generally well balanced between two treatment arms.

For progression-free survival assessment, 92 events were observed. Over a median follow-up of 24 months, the median progression-free survival was 12.0 months (95% CI 9.2–15.0) for PLDC and 9.8 months (95% CI 8.9–12.3) for GC [HR 0.69 (95% CI 0.455–1.047)]. The Kaplan–Meier curve for progression-free survival, the 0.5-year survival rate, the 1-year survival rate, and the 95% CI for each are shown in Fig. 1a with no obvious differences observed between the two groups. The overall survival curve is shown in Fig. 1b with no obvious differences observed between the two groups. The response efficiency is shown in Table 2. The response rate was 57.1% (95% CI 41.0–72.3) for PLDC and 56.4% (95% CI 39.6–72.2) for GC with no obvious differences between the two groups. The disease control rate (SDR), including SD (stable disease), was also 83.3% in the PLDC group and 84.6% in the GC group with no difference between the two groups.

Data on adverse events are shown in Table 3. No obvious differences in toxicity (G3/4) were observed between arms. Although there were no significant differences, the rates of thrombocytopenia and allergic reaction were higher in the GC group. Conversely, the rate of palmar–plantar erythrodysesthesia syndrome was significantly higher in the PLDC, when comparing all grades, although all cases in the two groups were G1–2.

A comparison of drug administration for both groups is shown in Table 4. The median relative dose intensity of the planned dose per week (RDI, %) was 88.9% for pegylated liposomal doxorubicin and 53.1% for gemcitabine ($p < 0.0001$). Furthermore, the treatment completion rate for 6 cycles was higher for PLDC (63.3%, 95% CI 48.3–76.6) than for GC (31.4%, 95% CI 19.1–45.9).

Table 1 Patients' background

Subject characteristics	PLDC ($N=49$)	GC ($N=50$)
Treatment-free interval		
6–12 months	29 (59.2)	28 (56.0)
12–24 months	10 (20.4)	12 (24.0)
Over 24 months	10 (20.4)	10 (20.0)
Histologic type		
CCC or mucinous	5 (10.2)	7 (14.0)
Other	44 (89.8)	43 (86.0)
Performance status		
0	44 (89.8)	45 (90.0)
1	3 (6.1)	5 (10.0)
2	2 (4.1)	0

PLDC pegylated liposomal doxorubicin and carboplatin, *GC* gemcitabine and carboplatin, *CCC* clear cell carcinoma

Discussion

We compared PLDC and GC regimens for platinum-sensitive recurrent ovarian cancer directly. Although no significant difference was observed, the median progression-free survival for the PLDC group was 12.0 months and that for the GC group was 9.8 months with a difference of 2.2 months. The average median progression-free survival in systematic reviews [15] of PLDC [19–23] and GC [14, 24–27] is 10.6 months and 8.9 months, respectively, which was comparable to our study.

The results of the phase III trial of PLDC + Bevacizumab vs. GC + Bevacizumab for platinum-sensitive recurrent ovarian cancer are currently reported in AGO-OVAR2.21/ENGOT-ov18 [28]. The median progression-free survival of PLDC + Bevacizumab and GC + Bevacizumab was 13.3 months (95% CI 11.7–14.3) and 11.7 months (95% CI 11.1–12.8), respectively, and the difference was 1.6 months, which may determine the standard treatment for platinum-sensitive recurrent ovarian cancer. We found similar data, and there was a 2.2-month longer median progression-free survival in the PLDC arm without Bevacizumab. Our PLDC and GC arms were 1.3 and 1.9 months shorter, respectively, than the median progression-free survival of ENGOT-ov18.

A comparison of the relative dose intensity of the planned dose per week (RDI, %) between the PLDC group and the GC group revealed that the carboplatin RDI was similar for both groups, whereas the mean gemcitabine RDI was significantly low. This was a result of the fact that gemcitabine on day 8, in particular, was often reduced or skipped, because it did not meet the dosing criteria. The main reason for reducing or skipping gemcitabine on day 8 was neutropenia. In this study, the main reasons for cycle delay in the GC arm were neutropenia (70.6%) and thrombocytopenia (17.6%).

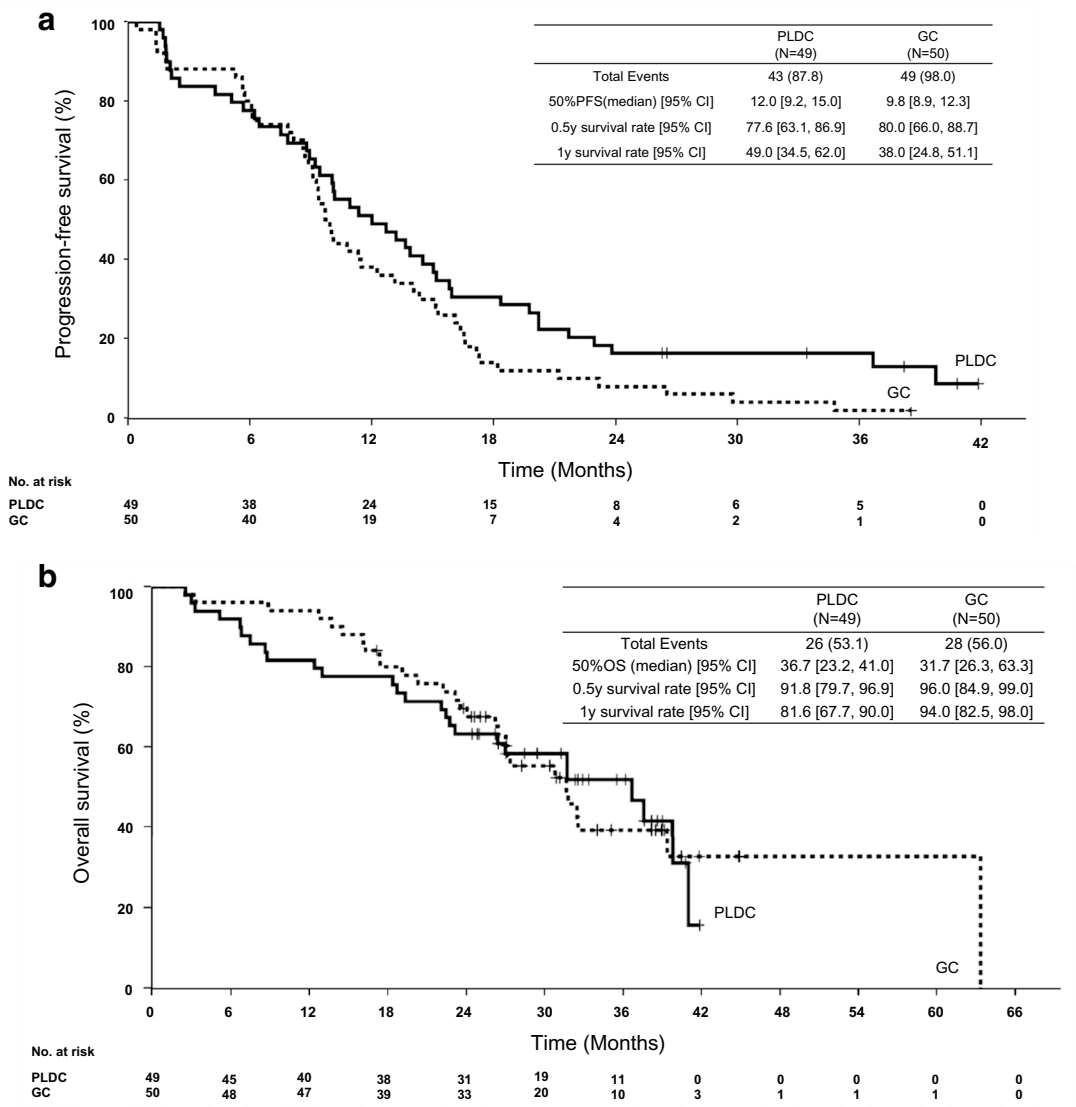

Fig. 1 **a** Kaplan–Meier estimates of progression-free survival. The hazard ratio for recurrence in the PLDC arm compared with that of the GC arm was 0.69 (95% CI 0.455–1.047). **b** Kaplan–Meier estimates of overall survival. The hazard ratio for recurrence in the PLDC arm compared with that of the GC arm was 1.039 (95% CI 0.606–1.783)

Pfisterer et al. also reported that for GC therapy, the gemcitabine RDI was lower than that for carboplatin (76.5% vs. 96.2%) [14].

The treatment completion rate for 6 cycles was also lower in the GC arm than in the PLDC arm (PLDC: 63% vs. GC: 31%). In the GC arm, the main reason for breaking protocol was repeated dose reduction due to adverse events such as neutropenia and thrombocytopenia (51.4%). Disease progression was the second reason for breaking protocol in the GC arm, but the rate was only 14.3%. Among the patients who broke protocol in the GC arm, 53% (16/30) continued GC as post-study therapy without the strict criteria employed in this study. On the other hand, in the PLDC arm, the rate of breaking protocol due to the criteria was only 5.6%, whereas that due to disease progression was 44.4%.

We found that maintaining the dose intensity of gemcitabine using this protocol was difficult in Japanese patients. However, in complying with this protocol, there were no differences in the incidences of Grade 3/4 hematologic and non-hematologic toxicities between the two groups.

The average rates of G3 or higher hematological toxicities in the PLDC group for the treatment of patients with platinum-sensitive recurrent ovarian cancer [15] were as follows: anemia 13.6%, thrombocytopenia 30.6%, neutropenia 45.5%, and febrile neutropenia 4.9%. The rates for the PLDC group in our study were 20.4%, 34.7%, 67.3%, and 2.0%,

Table 2 Response efficacy

Arm				
Response	PLDC ($n=42$*)		GC ($n=39$*)	
	No	%	No	%
NE	0	0	1	2.6
PD	7	16.7	5	12.8
SD	11	26.2	11	28.2
PR	20	47.6	19	48.7
CR	4	9.5	3	7.7
RR (CR + PR) [95% CI]	24	57.1 [41.0, 72.3]	22	56.4 [39.6, 72.2]

PLDC pegylated liposomal doxorubicin and carboplatin, *GC* gemcitabine and carboplatin, *NE* not evaluable, *PD* progressive disease, *SD* stable disease, *PR* partial response, *CR* complete response, *RR* response rate

*Target positive at baseline

respectively, with the rate for neutropenia being higher than that previously reported ($P=0.0049$). The average rates of G3 or higher hematological toxicities for the GC group were as follows: anemia 24.5%, thrombocytopenia 29.7%, neutropenia 62.9%, and febrile neutropenia 1.1% [15]. The rates for the GC group in our study were 13.7%, 45.1%, 82.4%, and 0%, respectively, with rates for thrombocytopenia and neutropenia in the GC group being higher than the previously reported rates ($P=0.023$ and $P=0.0036$). Although no conclusions can be drawn from these different studies, compared with the previous reports from Europe and the United States, both regimens induced neutropenia more often in Japanese patients, with the regimen used for the GC group resulting in an increased incidence of thrombocytopenia.

Peripheral sensory neuropathy is a common problem in TC therapy, and there was a significant difference in the proportion of patients experiencing peripheral sensory neuropathy above Grade 2 between the two groups in this study: 16.3% in the PLDC group and 2.0% in the GC group. The rate of peripheral sensory neuropathy above Grade 2 for TC therapy in the same patient group is 26.9% [13], which suggests that the rate in both groups of our study was low. Although the cause of the higher rate of peripheral sensory neuropathy of Grade 2 or more in the PLDC group than in the GC group was unclear, there was a relationship between palmar–plantar syndrome and the PLDC group. However, there was only 1 case of peripheral sensory neuropathy of Grade 3 or more (2.0%), and no advanced neurological symptoms were observed in association with TC therapy.

Table 3 Adverse events

Toxicity	PLDC ($n=49$)								GC ($n=50$)							
	Grade								Grade							
	1		2		3		4		1		2		3		4	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Hematologic																
Anemia	6	12.2	28	57.1	9	18.4	1	2.0	9	17.6	27	52.9	6	11.8	1	2.0
Neutrophil count decreased	1	2.0	10	20.4	22	44.9	11	22.4	1	2.0	6	11.8	31	60.8	11	21.6
Platelet count decreased	11	22.4	11	22.4	9	18.4	8	16.3	10	19.6	8	15.7	16	31.4	7	13.7
Nonhematologic																
Allergic reaction*	1	2.0	0	0	0	0	0	0	2	3.9	3	5.9	2	3.9	0	0
Alopecia	9	18.4	2	4.1	0	0	0	0	11	21.6	0	0	0	0	0	0
Diarrhea	7	14.3	2	4.1	0	0	0	0	3	5.9	0	0	0	0	0	0
Fatigue	15	30.6	1	2.0	0	0	0	0	24	47.1	1	2.0	0	0	0	0
Febrile neutropenia	0	0	0	0	1	2.0	0	0	0	0	0	0	0	0	0	0
Mucositis oral	18	36.7	6	12.2	0	0	0	0	7	13.7	0	0	0	0	0	0
Nausea	24	49.0	5	10.2	1	2.0	0	0	27	52.9	4	7.8	1	2.0	0	0
Peripheral motor neuropathy	6	12.2	3	6.1	0	0	0	0	2	3.9	0	0	0	0	0	0
Peripheral sensory neuropathy	11	22.4	7	14.3	1	2.0	0	0	16	31.4	1	2.0	0	0	0	0
Palmar-plantar erythrodysesthesia syndrome**	16	32.7	1	2.0	0	0	0	0	2	3.9	1	2.0	0	0	0	0
Vomiting	11	22.4	1	2.0	0	0	0	0	5	9.8	2	3.9	0	0	0	0

PLDC pegylated liposomal doxorubicin and carboplatin, *GC* gemcitabine and carboplatin

*All grade; PLDC 2.0% [95% CI 0.1–10.9] vs. GC 13.7% [95% CI 5.7–26.3]

**All grade; PLDC 34.7% [95% CI 21.7–49.6] vs. GC 5.9% [95% CI 1.2–16.2]

Table 4 Dose administration

	PLDC ($N=49$)		GC ($N=51$)	
	Doxorubicin	Carboplatin	Gemcitabine	Carboplatin
Dose intensity per week (DI) (mg/body/week)				
Median	9.7	97.2	530.0	98.7
Min	7.4	57.2	273.0	52.2
Max	13.0	162.6	948.2	179.0
Relative dose intensity of the planned dose per week (RDI) (%)				
Median	88.9*	88.9	53.1*	85.7
Min	67.6	52.8	28.1	47.5
Max	100.4	100.0	95.5	100.0
Cumulative dose intensity (CDI) from the total of 6 cycles doses (%)	81.4	79.8	42.3	56.8
Treatment completion rate for 6 cycles (%)	63.3		31.4	
95% CI	(48.3, 76.6)		(19.1, 45.9)	

PLDC pegylated liposomal doxorubicin and carboplatin, *GC* gemcitabine and carboplatin

*Wilcoxon's rank sum test: $p<0.0001$

Therefore, it may be beneficial for patients to change to GC or PLDC in cases, where peripheral sensory neuropathy associated with previous TC therapy remains unresolved.

Allergic reactions of Grade 2 or more were observed in 9.8% of patients in the GC group and 0% of patients in the PLDC group. A low allergic response to PLDC has been reported previously [13]. Although the reason remains unclear, the combination of PLD and carboplatin causes few allergic reactions, which suggests that this regimen is particularly suited for long-term treatment.

There were several limitations of this study. First, regimens included only cytotoxic drugs. Nowadays, several new drugs are recommended as a targeted therapy for platinum-sensitive recurrent ovarian cancer. Our regimens may have been old, but these cytotoxic regimens are still used and selected for platinum-sensitive recurrent ovarian cancer therapy. Second, we have no QOL data, and we only obtained data from a Japanese population. Therefore, it is important to reveal differences in nationalities by examining international clinical data in the future.

In conclusion, PLDC and GC are both good treatment candidates for platinum-sensitive recurrent ovarian cancer patients, but the dose intensity was lower for GC than for PLDC. PLDC had a more favorable risk–benefit profile than GC for the patients in this study. Our results for conventional cytotoxic chemotherapy may have implications in the treatment of platinum-sensitive recurrent ovarian cancer patients who have no indications for molecular-targeted medicine.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Medical institutions Jichi Medical University, Kurume University School of Medicine, Saitama Medical University International Medical Center, Tottori University School of Medicine, National Defense Medical College Hospital, Osaka University Graduate School of Medicine, Kyushu University, Shizuoka Cancer Center Hospital, Yamagata University School of Medicine, Kansai Rosai Hospital, Iwate Medical University, Kosei Hospital, The Jikei University School of Medicine, Kashiwa Hospital, Hirosaki University School of Medicine & Hospital, Nara Medical University Hospital, Niigata University Medical and Dental Hospital, Mie University Hospital, Ehime University Hospital, Hyogo Medical College Hospital, Miyoshi Central Hospital, Nagaoka Red Cross Hospital, NHO Shikoku Cancer Center, Niigata Cancer Center Hospital, Tottori Municipal Hospital.

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Affiliations

Hiroyuki Fujiwara[1] · Kimio Ushijima[2] · Shoji Nagao[3,14] · Yuji Takei[1] · Muneaki Shimada[4,13] · Masashi Takano[5] · Kiyoshi Yoshino[6,15] · Yoshiaki Kawano[7] · Yasuyuki Hirashima[8] · Satoru Nagase[9] · Shin Nishio[2] · Tadaaki Nishikawa[3] · Kimihiko Ito[10] · Tadahiro Shoji[11] · Eizo Kimura[12] · Tadao Takano[13] · Toru Sugiyama[11] · Junzo Kigawa[4,16] · Keiichi Fujiwara[3] · Mitsuaki Suzuki[1,17]

[1] Department of Obstetrics and Gynecology, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke 329-0498, Tochigi, Japan

[2] Department of Obstetrics and Gynecology, Kurume University School of Medicine, Fukuoka, Japan

[3] Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Saitama, Japan

[4] Department of Obstetrics and Gynecology, Tottori University School of Medicine, Tottori, Japan

[5] Department of Obstetrics and Gynecology, National Defense Medical College Hospital, Saitama, Japan

[6] Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine, Osaka, Japan

[7] Department of Obstetrics and Gynecology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

[8] Department of Gynecology, Shizuoka Cancer Center Hospital, Shizuoka, Japan

[9] Department of Obstetrics and Gynecology, Yamagata University School of Medicine, Yamagata, Japan

[10] Department of Obstetrics and Gynecology, Kansai Rosai Hospital, Hyogo, Japan

[11] Department of Obstetrics and Gynecology, Iwate Medical University, Iwate, Japan

[12] Department of Obstetrics and Gynecology, Kosei Hospital, Tokyo, Japan

[13] Department of Obstetrics and Gynecology, Tohoku University School of Medicine, Miyagi, Japan

[14] Department of Gynecologic Oncology, Hyogo Cancer Center, Akashi, Japan

[15] Department of Obstetrics and Gynecology, University of Occupational and Environmental Health, Kitakyushu, Japan

[16] Department of Obstetrics and Gynecology, Matsue City Hospital, Matsue, Japan

[17] Department of Obstetrics and Gynecology, Shin Yurigaoka General Hospital, Kawasaki, Japan