Reduced risk of endometrial cancer from alcohol drinking in Japanese

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The role of alcohol consumption in the etiology of endometrial cancer has not been clarified. To examine the association between alcohol consumption and endometrial cancer risk, we conducted a case-control study with 148 histologically diagnosed incident endometrial cancer cases and 1468 matched non-cancer controls. Median consumption of alcohol was only 19.3 g/week among cases who drank and 28.2 g/week among controls who drank. These values are lower than in Western countries. Relative risk was analyzed in subjects classified into four groups according to weekly alcohol consumption (non-drinkers, 1–24 g/week, 25–175 g/week, and >175 g/week). Confounder-adjusted odds ratios for those consuming alcohol at <25 g/week, 25–175 g/week, and >175 g/week compared to non-drinkers were 0.79 (95% confidence interval (CI), 0.49–1.28), 0.42 (95% CI, 0.23–0.79), and 0.47 (95% CI, 0.14–1.58), respectively. Further analysis was conducted concerning self-reported physical reaction to alcohol. Among women without flushing after drinking, a significant inverse association between risk and alcohol intake was seen (trend $P = 0.001$). In contrast, no protective effect of alcohol was seen among women who experience flushing after drinking. These results suggest the presence of an inverse association between alcohol drinking and endometrial cancer risk among Japanese women, and that this association is evident among those without flushing. Further investigation of these findings is warranted. (*Cancer Sci* 2008; 99: 1195–1201)

Endometrial cancer is a common gynecologic cancer in Japan, and its incidence is increasing, possibly due to the recent Westernization of the Japanese lifestyle.[1] The development of endometrial cancer has been related to exposure to unopposed estrogens.[2–4] Several studies have shown a positive association between alcohol intake and estrogen level in postmenopausal women.[5,6] Although alcohol intake could therefore be expected to increase the risk of endometrial cancer by elevating estrogen levels, epidemiologic studies of this association have been inconsistent. Most previous studies have indicated that alcohol consumption is either weakly or not associated with the risk of endometrial cancer.[7–11] However, several others have shown an increased risk in heavy drinkers[12,13] while a case-control study by Swanson *et al.* suggested an inverse association between moderate alcohol consumption and endometrial cancer risk among young women (<55 years).[14] These inconsistent findings, as well as uncertainties regarding the etiology of endometrial cancer, hamper any coherent understanding of this association.

Here, we conducted a hospital-based case-control study to examine the association between alcohol consumption and endometrial cancer risk among Japanese women, considering other predisposing characteristics, such as body mass index and a history of hormone replacement therapy. In addition, given recent findings that a genetic polymorphism in *aldehyde dehydrogenase2 (ALDH2)*, which has a strong impact on alcohol metabolism, was associated with several cancer risks,[15–17] we also analyzed this risk using self-reported reactions after drinking as a surrogate for *ALDH2* genotyping.

Materials and Methods

Subjects. The subjects were 148 patients newly and histologically diagnosed with endometrial carcinoma between January 2001 and June 2005 at Aichi Cancer Center Hospital (ACCH) in Japan. The distribution of histological subtypes among 148 cases was 93 type I tumor (low-grade endometrioid adenocarcinoma) (62.8%), and 55 type II tumor (high-grade endometrioid adenocarcinoma and other adenocarcinomas) (37.2%). Mixed epithelial and mesenchymal tumors were excluded due to the paucity of knowledge on their etiology. Controls ($n = 1476$) were randomly selected and matched by age (± 3 years) and menopausal status (premenopause or postmenopause) to cases with a 1:10 case-control ratio from 11 814 women who were diagnosed as cancer-free (four cases were matched with nine controls). All subjects were recruited in the framework of the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), as described elsewhere.[18,19] In brief, information on lifestyle factors was collected using a self-administered questionnaire for all first-visit outpatients at Aichi Cancer Center Hospital aged 20–79 who were enrolled in HERPACC between January 2001 and November 2005. Patients were also asked about lifestyle when healthy or before the current symptoms developed. Responses were checked by a trained interviewer. Approximately 90% of eligible subjects completed the questionnaire. Outpatients were also asked to provide blood samples. Our previous study showed that the lifestyle patterns of first-visit outpatients accorded with those in a randomly selected sample of the general population of Nagoya City.[20] The data were loaded into the HERPACC database and routinely linked with the hospital-based cancer registry system to update the data on cancer incidence. All participants gave written informed consent and the study was approved by Institutional Ethical Committee of Aichi Cancer Center.

Assessment of alcohol intake and alcohol reaction. All subjects were asked about their average frequency, beverage type, and amount of drinking per day during the 1-year period before onset of the present disease or before being interviewed. Usual alcohol intake was first reported as frequency of consumption in the five categories of non-drinker, <1 day/week, 1–2 days/week, 3–4 days/week, and 5 or more days per week. Consumption of each type of beverage (Japanese sake, beer, shochu, whiskey,

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Table 1. Characteristics of subjects

Characteristic	Cases		Controls		*P*-values
Number	148		1476		
Age (median, [min–max])	56.0 (26–79)		56.0 (23–80)		0.846
≤39 (%)	22	(14.9)	223	(15.1)	0.986
40–49 (%)	13	(8.8)	136	(9.2)	
50–59 (%)	64	(43.2)	610	(41.3)	
60–69 (%)	36	(24.3)	385	(26.1)	
≥70 (%)	13	(8.8)	122	(8.3)	
Smoking status					
Ever (%)	24	(16.2)	244	(16.5)	0.942
Never (%)	123	(83.1)	1225	(83.0)	
Unknown (%)	1	(0.7)	7	(0.5)	
Body mass index (median, [min–max])	23.2 (13.4–40.9)		21.9 (13.2–42.7)		<0.001
<25 kg/m^2 (%)	104	(70.3)	1211	(82.1)	<0.001
≥25 kg/m^2 (%)	40	(27.0)	257	(17.4)	
Unknown (%)	4	(2.7)	8	(0.5)	
Regular exercise					
No (%)	46	(31.1)	388	(26.3)	0.252
Yes (%)	101	(68.2)	1057	(71.6)	
Unknown (%)	1	(0.7)	31	(2.1)	
Menstrual status					
Premenopausal (%)	51	(34.5)	506	(34.3)	0.965
Postmenopausal (%)	97	(65.5)	970	(65.7)	
Age at menarche (median, [min–max])	14.0 (10–20)		14.0 (10–21)		0.963
≤12 (%)	38	(25.7)	379	(25.7)	0.729
13–14 (%)	75	(50.7)	701	(47.5)	
≥15 (%)	31	(21.0)	365	(24.7)	
Unknown (%)	4	(2.7)	31	(2.1)	
Duration of menstration (median, [min–max])	37.0 (0–49)		36.0 (11–43)		0.390
≤32 (%)	38	(25.7)	395	(26.8)	0.822
33–36 (%)	33	(22.3)	367	(24.9)	
37–39 (%)	38	(25.7)	388	(26.3)	
≥40 (%)	34	(23.0)	284	(19.2)	
Unknown (%)	5	(3.4)	42	(2.9)	
Parity (median, [min–max])	2 (0–4)		2 (0–6)		<0.001
0 (%)	41	(27.7)	207	(14.0)	<0.001
1–2 (%)	82	(55.4)	911	(61.7)	
≥3 (%)	24	(16.2)	348	(23.6)	
Unknown (%)	1	(0.7)	10	(0.7)	
Diabetes history					
No (%)	137	(92.6)	1416	(95.9)	0.056
Yes (%)	11	(7.4)	60	(4.1)	
Hypertension history					
No (%)	121	(81.8)	1273	(86.3)	0.135
Yes (%)	27	(18.2)	203	(13.8)	
Contraceptive usage history					
No (%)	138	(93.2)	1377	(93.3)	0.934
Yes (%)	8	(5.4)	74	(5.0)	
Unknown (%)	2	(1.4)	25	(1.7)	
Hormone replacement therapy history					
No (%)	132	(89.2)	1355	(91.8)	0.247
Yes (%)	15	(10.1)	100	(6.8)	
Unknown (%)	1	(0.7)	21	(1.4)	

and wine) was determined by the average number of drinks per day, which was then converted into a Japanese sake (rice wine) equivalent. One Japanese drink equates to one 'go' (180 mL) of Japanese sake, which contains 23g of ethanol, equivalent to one large bottle (633 mL) of beer, two shots (57 mL) of whiskey, or 2.5 glasses of wine (200 mL). One drink of shochu (distilled spirit), which contains 25% ethanol, was rated as 108 mL. Total alcohol consumption was estimated as the summed amount of pure alcohol consumption (g/drink) of Japanese sake, beer, shochu, whiskey, and wine among current regular drinkers. Weekly ethanol consumption was calculated by combining the amount of ethanol per day and frequency per week. In this study, we used self-reported flushing (yes/no) after a small amount of drinking (a glass of beer) as a stratification factor in the examination of alcohol impact.

Statistical analysis. To assess the strength of associations between alcohol consumption and risk of endometrial cancer, odd ratios (OR) with 95% confidence intervals (CI) were estimated using unconditional logistic models adjusted for potential confounders. For subgroup analysis, subjects were classified by

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Table 2. Odds ratios (OR) and 95% confidence intervals (CI) for endometrial cancer according to frequency and quantitiy of alcohol intake

Category	Cases (n = 148)	Controls (n = 1476)	Age-adjusted OR (95% CI)	Multivariate OR (95% CI)†
Frequency of alcohol intake				
None	108	929	1.00 (Reference)	1.00 (Reference)
<1/week	14	166	0.72 (0.40–1.29)	0.71 (0.39–1.29)
1–2/week	11	119	0.79 (0.41–1.52)	0.77 (0.40–1.50)
3–4/week	8	99	0.69 (0.33–1.46)	0.67 (0.31–1.43)
5-/week	7	154	0.39 (0.18–0.85)	0.37 (0.17–0.82)
unknown	0	9		
P-trends			0.011	0.009
Amount of alcohol consumption				
None	109	933	1.00 (Reference)	1.00 (Reference)
<25 g/week	23	246	0.79 (0.49–1.27)	0.79 (0.49–1.28)
(median, range) (eta g/week)	(8.6, 2.9–24.2)	(8.6, 1.7–24.2)		
25–175 g/week	12	232	0.44 (0.24–0.81)	0.42 (0.23–0.79)
(median, range) (eta g/week)	(54.3, 25.9–96.6)	(69, 25.3–172.5)		
>175 g/week	3	47	0.54 (0.16–1.76)	0.47 (0.14–1.58)
(median, range) (eta g/week)	(201.3, 179.4–552)	(276, 177.1–805)		
unknown	1	18		
P-trends			0.006	0.005

†Multivariate models adjusted for age, smoking, body mass index, regular exercise, menstrual status, age at menarche, duration of menstruation, parity, diabetes history, hypertension history, contraceptive usage history, hormone replacement therapy, and flushing after drinking.

alcohol intake into the four groups of non-drinkers, and weekly ethanol intake of 1–24, 25–175, and >175 g. Among controls, median weekly intake in current drinkers was 25 g. Potential confounders considered in the multivariate analyses were age, smoking habit (never smokers or ever smokers), body mass index (BMI; <25 or ≥25 kg/m^2 based upon our previous study),[21] regular exercise (yes or no), menstrual status (premenopausal or postmenopausal), age at menarche (≤ 12, 13–14, or ≥ 15), duration of menstruation (years, quartiles), parity (0, 1–2, ≥ 3), diabetes history (yes or no), hypertension history (yes or no), contraceptive usage history (yes or no), hormone replacement therapy history (yes or no), flushing after drinking (yes or no), and histological subtype (type I or type II). Missing values for any covariate were treated as a dummy variable in the logistic model. Differences in categorized demographic variables between the cases and controls were tested by the χ^2-test. Age, age at menarche, duration of menstruation, BMI, and parity between cases and controls were compared by the Mann–Whitney test. Stratification analysis was used to estimate risk for subgroups by drinking habit. *P*-values less than 0.05 were considered statistically significant. All analyses were conducted using STATA version 9 (Stata, College Station, TX, USA).

Results

Baseline characteristics of the 148 endometrial cancer patients and 1476 controls are shown in Table 1. Median age was 56 years for both patients and controls. Smoking status did not differ between the two groups. Prevalence of ever smokers was 16.2% and 16.5% in case and controls, respectively. BMI was higher among cases than controls ($P < 0.001$). Regarding reproductive factors, only parity showed a significant difference between two groups. Low experience of delivery was more prevalent among cases than controls ($P < 0.001$). A history of diabetes was more common in cases, although with only marginal statistical significance. Although contraceptive usage did not differ, hormone replacement therapy was more prevalent in cases.

Median consumption of alcohol among cases and controls who drank was only 19.3 and 28.2 g/week, respectively. Table 2 shows the impact of drinking habit on endometrial cancer risk. Frequent drinkers showed a reduced risk: compared with non-drinkers, the age-adjusted OR of those who drank 5 or more days per week was 0.39 (95% CI, 0.18–0.85). Although without significance, all groups except non-drinkers showed OR below unity and their point estimates decreased as frequency increased (P-trend = 0.011). This trend was consistently observed in the multivariate model. Similarly, with regard to the amount of alcohol consumed, those who consumed less than 25 g per week, those who consumed 25–175 g per week, and those who consumed 175 g or more per week showed a lower risk of endometrial cancer than non-drinkers, with OR of 0.79 (95% CI, 0.49–1.27), 0.44 (95% CI, 0.24–0.81), and 0.54 (95% CI, 0.16–1.76), respectively. The multivariate model again showed consistent results.

Table 3 shows a stratified analysis according to potential confounders designed to examine the consistency of association and to explore the possible interaction with weekly alcohol consumption. The inverse association between endometrial cancer risk and alcohol intake persisted after stratification by BMI, regular exercise, menstrual status, age at menarche, duration of menstruation, parity, diabetes history, hypertension history, and type I tumor. In contrast, no associations were seen for ever smokers, oral contraceptive users, hormone replacement therapy users, and type II tumor. Regarding BMI, obese women (BMI ≥ 25) showed a stronger protective effect by alcohol than leaner women (BMI < 25). Among postmenopausal women, the OR for weekly drinking of less than 25, 25–175, and 175 g or more for EC were 0.83 (95% CI, 0.46–1.52), 0.46 (95% CI, 0.21–1.02), and 0.72 (95% CI, 0.17–3.15), respectively, but the P-trend was marginally significant ($P = 0.069$). Generally, endometrial cancer risk was lowest among women with weekly consumption of 25–175 g.

Table 4 shows a stratified analysis according to self-reported reaction to alcohol. Flushing after drinking depends mainly on the activity of aldehyde dehydrogenase, particularly ALDH2, and might therefore reflect lower ALDH2 activity. Among women who did not experience flushing after drinking, an inverse association was seen between endometrial cancer risk and alcohol intake. The age-adjusted OR for weekly drinking of less than 25, 25–175, and 175 g or more for endometrial cancer were 0.51 (95% CI, 0.26–0.98), 0.24 (95% CI, 0.11–0.56), and 0.49 (95% CI, 0.14–1.69), respectively, and the P-trend was statistically significant ($P = 0.001$). By contrast, the protective

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Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for endometrial cancer stratified according to weekly alcohol consumption and lifestyle factors

Category	Alcohol consumption				
	None	<25 g/week	25–175 g/week	>175 g/week	*P*-trends
Total (case/control)[†]	109/933	23/246	12/232	3/47	
OR (95% CI)	1.00 (Reference)	0.79 (0.49–1.27)	0.44 (0.24–0.81)	0.54 (0.16–1.76)	0.006
Smoking					
Never (case/control)	98/829	18/213	5/157	1/16	
OR (95% CI)	1.00 (Reference)	0.70 (0.41–1.18)	0.26 (0.11–0.66)	0.51 (0.07–3.87)	0.002
Ever (case/cotrol)	11/98	4/33	7/75	2/31	
OR (95% CI)	1.00 (Reference)	1.25 (0.36–4.40)	0.89 (0.33–2.46)	0.63 (0.13–3.04)	0.586
Unknown (case/cotrol)	0/6	1/0	0/0	0/0	
Body mass index					
<25 kg/m^2 (case/control)	73/757	17/197	11/202	2/40	
OR (95% CI)	1.00 (Reference)	0.92 (0.53–1.61)	0.58 (0.30–1.12)	0.54 (0.13–2.31)	0.090
≥25 kg/m^2 (case/control)	32/168	6/49	1/30	1/7	
OR (95% CI)	1.00 (Reference)	0.55 (0.21–1.43)	0.15 (0.02–1.13)	0.48 (0.05–4.34)	0.035
Unknown (case/control)	4/8	0/0	0/0	0/0	
Regular exercise					
No (case/control)	36/257	7/40	2/63	1/22	
OR (95% CI)	1.00 (Reference)	1.27 (0.53–3.05)	0.23 (0.05–0.97)	0.34 (0.04–2.57)	0.047
Yes (case/control)	72/654	16/201	10/167	2/25	
OR (95% CI)	1.00 (Reference)	0.70 (0.40–1.24)	0.53 (0.27–1.05)	0.69 (0.16–3.00)	0.053
Unknown (case/control)	1/22	0/5	0/2	0/0	
Menstrual status					
Premenopausal (case/control)	35/280	9/99	5/98	1/23	
OR (95% CI)	1.00 (Reference)	0.72 (0.34–1.57)	0.41 (0.15–1.07)	0.35 (0.05–2.65)	0.038
Postmenopausal (case/control)	74/653	14/147	7/134	2/24	
OR (95% CI)	1.00 (Reference)	0.83 (0.46–1.52)	0.46 (0.21–1.02)	0.72 (0.17–3.15)	0.069
Age at menarche					
≤12 (case/control)	28/236	8/61	1/64	1/13	
OR (95% CI)	1.00 (Reference)	1.04 (0.45–2.40)	0.12 (0.02–0.92)	0.56 (0.07–4.49)	0.053
13–14 (case/control)	53/428	11/127	9/114	1/22	
OR (95% CI)	1.00 (Reference)	0.72 (0.36–1.42)	0.65 (0.31–1.37)	0.38 (0.05–2.90)	0.120
≥15 (case/control)	26/249	2/54	2/48	1/11	
OR (95% CI)	1.00 (Reference)	0.39 (0.09–1.73)	0.44 (0.10–1.91)	1.07 (0.13–8.88)	0.260
Unknown (case/control)	2/20	2/4	0/6	1/0	
Duration of menstruation					
≤32 years (case/control)	27/219	7/77	4/71	0/22	
OR (95% CI)	1.00 (Reference)	0.69 (0.28–1.67)	0.43 (0.15–1.29)	NE	0.029
33–36 years (case/control)	27/246	5/51	1/54	0/9	
OR (95% CI)	1.00 (Reference)	0.93 (0.34–2.55)	0.18 (0.02–1.35)	NE	0.063
37–39 years (case/control)	29/249	3/71	4/57	1/8	
OR (95% CI)	1.00 (Reference)	0.36 (0.11–1.23)	0.60 (0.20–1.78)	1.07 (0.13–8.88)	0.249
≥40 years (case/control)	23/189	6/43	3/43	2/7	
OR (95% CI)	1.00 (Reference)	1.13 (0.43–2.95)	0.56 (0.16–1.95)	2.23 (0.43–11.49)	0.932
Unknown (case/control)	3/30	2/4	0/7	0/1	
Parity					
0 (case/control)	30/115	6/36	4/42	1/10	
OR (95% CI)	1.00 (Reference)	0.63 (0.24–1.65)	0.36 (0.12–1.09)	0.38 (0.05–3.10)	0.046
1–2 (case/control)	58/599	15/147	6/129	2/25	
OR (95% CI)	1.00 (Reference)	1.12 (0.61–2.05)	0.50 (0.21–1.20)	0.90 (0.21–3.93)	0.271
≥3 (case/control)	21/213	2/61	1/59	0/12	
OR (95% CI)	1.00 (Reference)	0.37 (0.08–1.64)	0.19 (0.02–1.43)	NE	0.035
Unknown (case/control)	0/6	0/2	1/2	0/0	
Diabetes history					
No (case/control)	99/894	22/237	12/224	3/45	
OR (95% CI)	1.00 (Reference)	0.81 (0.50–132)	0.47 (0.25–0.87)	0.57 (0.17–1.89)	0.015
Yes (case/control)	10/39	1/9	0/8	0/2	
OR (95% CI)	1.00 (Reference)	0.48 (0.05–4.33)	NE	NE	0.212
Hypertension history					
No (case/control)	87/797	21/225	10/200	2/38	
OR (95% CI)	1.00 (Reference)	0.85 (0.51–1.40)	0.45 (0.23–0.89)	0.47 (0.11–2.00)	0.016
Yes (case/control)	22/136	2/21	2/32	1/9	
OR (95% CI)	1.00 (Reference)	0.54 (0.12–2.47)	0.36 (0.08–1.62)	0.64 (0.08–5.32)	0.178

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Table 3 (*Continued.*)

Category	Alcohol consumption				
	None	<25 g/week	25–175 g/week	>175 g/week	*P*-trends
Contraceptive usage history					
No (case/control)	101/871	23/231	12/216	1/43	
OR (95% CI)	1.00 (Reference)	0.85 (0.53–1.38)	0.47 (0.26–0.88)	0.20 (0.03–1.45)	0.005
Yes (case/control)	6/44	0/11	0/15	2/4	
OR (95% CI)	1.00 (Reference)	NE	NE	3.63 (0.53–24.92)	0.892
Unknown (case/control)	2/18	0/4	0/1	0/0	
Hormone replacement therapy history					
No (case/control)	101/860	18/227	10/212	2/40	
OR (95% CI)	1.00 (Reference)	0.66 (0.39–1.12)	0.39 (0.20–0.77)	0.41 (0.10–1.72)	0.002
Yes (case/control)	7/59	5/15	2/19	1/7	
OR (95% CI)	1.00 (Reference)	2.79 (0.78–10.05)	0.89 (0.17–4.64)	1.21 (0.13–11.31)	0.826
Unknown (case/control)	1/14	0/4	0/1	0/0	
Histological subtype					
Type I (case/control)	68/933	17/246	6/232	1/47	
OR (95% CI)	1.00 (Reference)	0.71 (0.51–1.57)	0.34 (0.14–0.79)	0.27 (0.04–1.97)	0.007
Type II (case/control)	41/933	6/246	6/246	2/47	
OR (95% CI)	1.00 (Reference)	0.60 (0.25–1.43)	0.63 (0.26–1.50)	1.09 (0.25–4.69)	0.323

[1]One case and 18 controls were excluded from analyses due to lack of information on alcohol drinking.
NE, not estimated because of no case in this category.

Table 4. Impact of alcohol consumption according to self-reported reaction to alcohol

Category	Alcohol consumption				
	None	<25 g/week	25–175 g/week	>175 g/week	*P*-trends
Total (case/control)[1]	109/933	23/246	12/232	3/47	
Age-adjusted OR (95% CI)	1.00 (Reference)	0.79 (0.49–1.27)	0.44 (0.24–0.82)	0.54 (0.16–1.76)	0.006
Multivariate OR (95% CI)	1.00 (Reference)	0.79 (0.49–1.28)	0.42 (0.23–0.79)	0.47 (0.14–1.58)	0.005
Flushing after drinking					
No (case/control)	44/292	13/157	7/175	3/36	
Age-adjusted OR (95% CI)	1.00 (Reference)	0.51 (0.26–0.98)	0.24 (0.11–0.56)	0.49 (0.14–1.69)	0.001
Multivariate OR (95% CI)	1.00 (Reference)	0.53 (0.27–1.05)	0.25 (0.11–0.59)	0.48 (0.14–1.67)	0.002
Yes (case/control)	61/574	9/86	5/55	0/10	
Age-adjusted OR (95% CI)	1.00 (Reference)	1.03 (0.49–2.15)	0.89 (0.34–2.30)	NE	0.560
Multivariate OR (95% CI)[2]	1.00 (Reference)	1.07 (0.51–2.27)	0.97 (0.37–2.57)	NE	0.677
Unknown (case/control)	4/67	1/3	0/2	0/1	

[1]One case and 18 controls were excluded from analyzes due to lack of information on alcohol drinking.
[2]Multivariate models adjusted for age, smoking, body mass index, regular exercise, menstrual status, age at menarche, duration of menstruation, parity, diabetes history, hypertension history, contraceptive usage history, and hormone replacement therapy.
CI, confidence interval; NE, not estimated because of no case in this category; OR, odds ratio.

effect of alcohol was not observed among women who had flushing after drinking (age-adjusted *P*-trend = 0.560). The multivariate model again showed consistent results.

Discussion

In this study, we found that a small amount of alcohol consumption was protective against endometrial cancer among Japanese women. This association was consistently observed regardless of potential confounders. OR were lowest among those who consumed 25–175 g per week. In addition, the protective effect of alcohol drinking decreased among women who reported flushing after drinking.

Results to date regarding the relationship between alcohol intake and endometrial cancer risk are inconsistent. Although most previous studies have indicated a null association,[7–9,11,22–25] three have shown a protective effect of alcohol,[10,14,26] while three others have reported that alcohol intake was a risk factor of endometrial cancer.[12,13,27] Newcomb *et al.* suggested a significant inverse association in premenopausal women consuming one drink per day or more (RR = 0.20; 95% CI, 0.06–0.71)[10] while Swanson *et al.* showed an inverse association between moderate consumption and endometrial cancer risk among young women (<55 years), with relative risks for three levels of drinking (<1, 1–4, >4 drinks per week) from lowest to highest of 0.78, 0.64, and 0.41 compared to non-drinkers.[14] Webster *et al.* showed that non-drinkers aged 20–54 years had a higher relative risk (RR = 1.83; 95% CI, 1.11–3.01) than women who consumed an average of 150 g or more of alcohol per week.[26] These results may indicate that light alcohol consumption decreases endometrial cancer risk in younger women. In contrast, Setiawan *et al.* suggested that alcohol consumption equivalent to two or more drinks per day increased the risk of endometrial cancer in postmenopausal women.[12] The other two case-control studies showed similar positive associations between increased alcohol consumption and risk.[13,27]

Here, our study has added to the evidence for a protective effect of alcohol on endometrial cancer. The degree of consumption

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may be an important consideration in determining the impact of alcohol. Average consumption in our study was very low compared with previous studies. Relatively high consumption (≥175 g/week) was seen in only three cases and 99 controls, who showed a protective effect compared with non-drinkers (multivariate OR = 0.47; 95% CI, 0.14–1.58). The provision of stable estimates for this subgroup is hampered by their small sample size.

One possible explanation for these results is that a small amount of drinking might be protective against cancer, as suggested in several prospective cohort studies.[28,32] The biological mechanism of this protective effect for cancer among light-moderate drinkers is not clear. Tsugane *et al.* considered the background characteristics of moderate drinkers to be healthier than those of either non-drinkers or heavy drinkers.[32] It has been reported that alcohol intake increases endogenous serum levels of estrogen in postmenopausal women,[5,6] but it is unclear whether this is due to either a decrease in metabolic clearance or an increase in production.[33] It has thus been hypothesized that alcohol drinking might lead to an increased risk of endometrial cancer risk due via the increased mitotic proliferation of endometrial cells, resulting in increased DNA replication errors and somatic mutations.[34] Our findings here contradict this hypothesized mechanism; nevertheless, we assume that the amount of drinking may differentiate the impact of alcohol on endometrial cancer risk, as stated above.

Of interest was the combined effect of the amount of consumption and physical reaction to alcohol.[19] Subjects who reported flushing did not show the protective effect observed in the non-flushing group. It has been suspected that the oxidative metabolite of ethanol, acetaldehyde, is carcinogenic for humans due to its binding to cellular proteins and DNA, thus leading to carcinogenesis.[35,36] Further, in individuals with ALDH2 encoded by *ALDH2* Glu/Lys, the blood acetaldehyde level after drinking is approximately six-fold that in individuals with active ALDH2.[37] Taking results from our previous study demonstrating sensitivity and specificity of self-reported flushing for ALDH2 genotype as 83.5% and 87.8%,[38] our findings may have resulted from a decrease in the protective effect of alcohol owing to exposure to high levels of acetaldehyde.

Several potential limitations of our study warrant consideration. First, because it was a hospital-based case-control study, the threat of inadequate comparability between cases and controls rested on whether the control population was the source population from which cases arose. In the ACCH, it is assumed that those who are diagnosed as not having cancer at a particular period of time will visit the ACCH in the event that they do develop malignant disease. Our source of controls is therefore assumed to be appropriate for the drawing of causal inferences. Second, as with other case-control studies, this study may have suffered from recall bias. Although the questionnaires, including that on alcohol intake, were completed before diagnosis in our hospital, some case patients referred to the hospital might have known their diagnosis. The fact that alcohol intake is not a well-accepted risk factor for endometrial cancer among the public might preclude this possibility of information bias regarding alcohol Third, our study had a modest sample size, and replication in other studies is required.

In conclusion, our case-control study suggested that alcohol drinking decreases the risk of endometrial cancer among Japanese women who consume small amounts. Further, a similar association was observed after stratification by potential confounders. However, this protective effect of alcohol was modified in those who experienced a flushed reaction to it after drinking. Further investigation of these findings is warranted.

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子宮体癌治療後の経過観察に関する考察

Follow-up after primary treatment for malignancy of uterine body

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Key Words: *endometrial cancer, uterine sarcoma, follow-up*

[概要] 悪性腫瘍の取り扱いは、診断・治療・経過観察の3要素から成り立っている。治療・診断に関する研究や報告は多数あるものの、経過観察に関する報告は非常に少ない。2006年に発行された婦人科腫瘍学会ガイドラインでは1～3年目は1～3ヶ月毎、4～5年目では6ヶ月毎、6年目以降では1年毎の経過観察を推奨しており、2001年に発行されたAmerican Cancer Society's Clinical Oncologyでは1～3年目は3～6ヶ月毎、4年目以降は6ヶ月毎の経過観察を推奨している。これらの根拠は子宮体癌の経過観察に関する後方視的な報告で、主に再発例の初回治療後から再発までの期間と再発時の状況、その治療成績、経過観察時の検査などからこれら結果を示しているが、標準化や推奨するには十分な情報とは言えない。子宮体癌の経過観察期間を検討するために、1991～2000年の当センターでの治療症例296例を検討した。この中で子宮体癌再発を確認した63例を対象とし、再発までの期間と再発部位・予後を検討したので報告する。検討した63例の初回治療開始から再発までの期間の平均は26.4月（95% CI 18.3–30.9）、中央値は14.9月（95% CI 11.1–18.8）であった。再発時期を検討すると、初回治療開始から1年以内の再発が26例（41.3%）、1～2年の間が17例（27.0%）、2～3年の間が8例（12.7%）、3～5年が4例（6.3%）で、5年以降の再発が8例（12.7%）であった。中でも高分化型類内膜腺癌で5年以降の再発が36.4%（4/11）と比較的高率であった。再発後の生存率や生存期間は再発までの期間が長い程延長する傾向にあった。子宮体癌は治療開始後5年以降でも再発する症例が10%以上あり、長期間に渡る経過観察が必要であると考えられた。

[緒　言]

悪性腫瘍の取り扱いは、診断・治療とその後の経過観察の3要素から成り立っている。治療や診断に関する研究や報告は多数あるものの、経過観察に関する報告は非常に少ない。2006年に発行された婦人科腫瘍学会編集の子宮体癌治療ガイドラインでは1～3年目は1～3ヶ月毎、4～5年目では6ヶ月毎、6年目以降では1年毎の経過観察を推奨しており、2001年に発行されたAmerican Cancer Society's Clinical Oncologyでは1～3年目は3～6ヶ月毎、4年目以降は6ヶ月毎の経過観察を推奨している。これらの根拠は子宮体癌の経過観察に関する後方視的な報告[1)–13)]（表1）で、主に再発例の初回治療後から再発までの期間と再発時の状況、その治療成績、経過観察時の検査などからこれら結果を示しているが、標準化や推奨するには十分な情報とは言えない。

今回は子宮体癌の再発時期を検討し、その経過観察方針を検討したので報告する。

[方　法]

子宮体癌の経過観察期間を検討するために、1991～2000年の当センターでの治療症例296例の中で子宮体癌再発を確認した63例を対象とし、再発までの期間と再発部位・予後を検討し

表1：子宮体癌の経過観察に関する文献

著　者	年	症例数	再発例	期　間	＜1年	＜2年	＜3年	＜4年	＜5年	＞6年
Morice *et al.*	2001	351	27	42	3	4	6	12	12	12
Owen *et al.*	1996	97	17		3～4	6	12	12	12	12
Gadducci *et al.*	2000	133	24	53	3～4	3～4	6	6	6	12
Agboola *et al.*	1997	432	50	55	3	4	6	6	6	12
Gordon *et al.*	1997	111	17		3	6	12	12	12	なし
Ng *et al.*	1997	86	14	26	1～2	1～2	3	6	6	
Salvesen *et al.*	1997	249	47	108	3	6	12	12	12	12
Reddoch *et al.*	1995	354	44		3	4	4	6	6	なし
Berchuck *et al.*	1995	398	39		3	3	4	6	6	なし
Shumsky *et al.*	1994	317	53		3	4	4	6	6	6
Podczaski *et al.*	1992	300	47		3	3	3	6	6	12
MacDonald *et al.*	1990	101	19		3	3	3	6	6	なし

た。再発は臨床的・病理学的に診断し、生存率はKaplan-Meier法で推定、統計解析にはSPSS (ver.12) を使用した。

[成　績]

検討した63例の初回治療開始から再発までの期間の平均は26.4月 (95% CI 18.3−30.9)、中央値は14.9月 (95% CI 11.1−18.8) であった。再発時期を検討すると、初回治療開始から1年以内の再発が26例 (41.3%)、1～2年の間が17例 (27.0%)、2～3年の間が8例 (12.7%)、3～5年が4例 (6.3%) で、5年以降の再発が8例 (12.7%) であった (表2)。

進行期別に再発時期を検討すると、5年以降の再発がI−II期で11.1% (3/27)、III期で25.0% (5/20) であったのに対し、IV期では認めなかった (表2)。組織型別の検討では、5年以降の再発が高分化型類内膜腺癌で36.4% (4/11) と比較的高率であったが、中分化型内膜腺癌で9.5% (2/21)、低分化型類内膜腺癌で5.9% (1/17)、その他腺癌で16.7% (1/6)、肉腫で0% (0/8) であった (表2)。

表2：子宮体癌の進行期・組織型別再発時期

			計	＜1年		1～2年		2～3年		3～5年		＞5年	
			n	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
合　計			63	26	41.3	17	27.0	8	12.7	4	6.3	8	12.7
進行期	I−II期		27	8	29.6	9	33.3	4	14.8	3	11.1	3	11.1
	III期		20	7	35.0	4	20.0	4	20.0	0	0.0	5	25.0
	IV期		16	11	68.8	4	25.0	0	0.0	1	6.3	0	0.0
組織型	類内膜	高分化	11	2	18.2	1	9.1	2	18.2	2	18.2	4	36.4
		中分化	21	8	38.1	6	28.6	3	14.3	2	9.5	2	9.5
		低分化	17	9	52.9	6	35.3	1	5.9	0	0.0	1	5.9
	他腺癌		6	3	50.0	1	16.7	1	16.7	0	0.0	1	16.7
	肉　腫		8	4	50.0	3	37.5	1	12.5	0	0.0	0	0.0

(1991～2000年　愛知県がんセンター中央病院婦人科部)

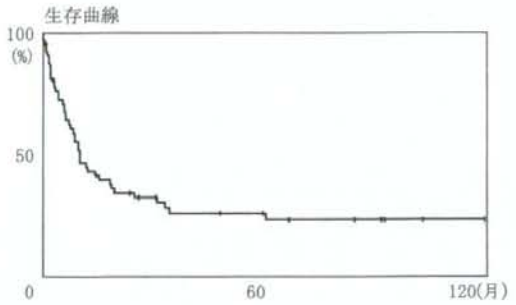
表３：子宮体癌の部位別再発時期

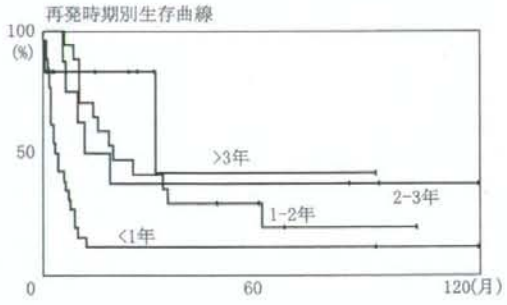
	計	＜1年		1～2年		2～3年		3～5年		＞5年	
	n	n	%	n	%	n	%	n	%	n	%
合計	63	26	41.3	17	27.0	8	12.7	4	6.3	8	12.7
脳	2	2	100.0	0	0.0	0	0.0	0	0.0	0	0.0
肺	18	9	50.0	4	22.2	1	5.6	1	5.6	3	16.7
肝	5	3	60.0	2	40.0	0	0.0	0	0.0	0	0.0
皮膚	3	0	0.0	3	100.0	0	0.0	0	0.0	0	0.0
骨	6	4	66.7	1	16.7	0	0.0	0	0.0	1	16.7
腹腔内	14	7	50.0	3	21.4	2	14.3	1	7.1	1	7.1
骨盤内	17	6	35.3	5	29.4	2	11.8	1	5.9	3	17.6
膣・膣断端	7	2	28.6	3	42.9	1	14.3	1	14.3	0	0.0
頚・縦隔リンパ節	5	2	40.0	0	0.0	2	40.0	0	0.0	1	20.0
傍大動脈リンパ節	11	5	45.5	1	9.1	2	18.2	0	0.0	3	27.3

（1991～2000年　愛知県がんセンター中央病院婦人科部）

部位別に再発時期を検討したが、５年以降の再発部位として頻度が高いのは傍大動脈リンパ節27.3%（3/11）、頚・縦隔リンパ節20.0%（1/5）、骨盤内17.6%（3/17）、肺16.7%（3/18）、骨16.7%（1/6）であった（表３）。

再発症例全体の３年生存率は25.9%で、再発時期別に検討すると、初回治療開始から１年以内の再発で11.5%、１～２年の間で29.4%、２～３年の間で37.5%、５年以降で41.7%であった（図１）。また全体の再発後生存期間の中央値は10.6月（95%信頼区間7.1−14.1月）で、再発時期別に検討すると、初回治療開始から１年以内の再発で中央値が4.0月（95%信頼区間2.4−5.7月）、１～２年の間で19.8月（95%信頼区間7.0−32.7月）、２～３年の間で12.1月（95%信頼区間0.0−24.5月）、５年以降で31.5月（95%信頼区間0.0−74.6月）と、再発までの期間が長い程生存率や生存期間が長い傾向にあった。





		生存率				生存期間		
再発時期	症例数	1年	2年	3年	5年	中央値	95%信頼区間	p
全体	63	46.6%	34.2%	25.9%	25.9%	10.6月	7.1-14.1月	
<1年	26	15.4%	11.5%	11.5%	11.5%	4.0月	2.4-5.7月	<0.001
1-2年	17	70.6%	47.1%	29.4%	29.4%	19.8月	7.0-32.7月	
2-3年	8	62.5%	37.5%	37.5%	37.5%	12.1月	0.0-24.5月	
>3年	12	83.3%	83.3%	41.7%	41.7%	31.5月	0.0-74.6月	

（1991−2000年　愛知県がんセンター病院婦人科統計）

図１：子宮体癌の再発後治療成績

［考　察］

今回の検討では子宮体癌の再発症例中12.7%(8/63)が、治療開始後5年以降に再発していた。悪性腫瘍は一般に治療開始後5年間再発なければ治癒した可能性が高いと考えられており、「5年生存率」が治療成績に用いられる程、5年という期間は重要である。しかし乳癌は再発症例の25%以上が治療開始後5年以降に再発し、これは特にホルモン療法を施行した症例に多いとされるなど[14]、5年に拘らない考えが出てきている。今回の検討で、経過観察5年以降に再発した症例の50%が高分化型類内膜腺癌であったことからも、子宮体癌は治療開始後5年以降でも再発する症例があり、十分な経過観察が必要であると考えられる。

子宮体癌の経過観察に関する研究は、表1に示す様にいくつか報告されているが、必ずしも十分な症例数がある訳ではなく、また長期にわたる経過観察期間で検討している訳ではない[1)-13)]。悪性腫瘍の経過観察は長期間を要するため、前向きな研究が計画しにくく、適確な情報が得にくい。また施行された治療により、再発までの期間や再発部位が変わる可能性があることから、標準治療が変わる度に再検討を要することになる。このように経過観察に関する研究には根本的な問題点が多く、解析が難しいが、主に検討すべき点は経過観察の間隔と来院時に行う検査である。残念ながら今回は検討されておらず、今後の重要な検討課題である。

今回の検討で、治療開始後1年以内で再発した症例が41.3%(26/63)、1～2年で再発した症例が27.0%(17/63)と多いことから、この期間は厳重な経過観察が必要なのかもしれない。しかし1年以内に再発した症例の再発後生存期間の中央値は4.0ヶ月であり、再発を早期に診断することは治療成績の改善や延命に貢献しない様である。逆に初回治療後1年以降に再発した症例は1年程度かそれ以上の生存が期待できることから、再発後の生活の質(QOL)維持が良いほうが望ましく、再発の早期診断のために厳重な経過観察する必要があることになる。しかしこの時期以降は再発の危険性が少なくなっていくため、全ての症例の経過観察を厳重にすべきではなく、今後の重要な検討課題である。

経過観察の間隔と同様に、経過観察時に行うべき検査も重要な論点である。今回の検討では子宮体癌での頻度の高い再発部位は、肺(28.6%)・骨盤内(27.0%)・腹腔内(22.0%)・傍大動脈リンパ節(17.5%)であり、これらを精査するには定期的にCT等の画像診断を行うのが望ましいことになる。しかし経過観察に関する文献をみると、CTを毎年施行しているのは12文献中わずか1つで、腫瘍マーカーCA125を測定している文献はない。また疼痛などの臨床症状により再発が診断される可能性が77%と報告されていること、CTは被爆量が多いことから頻回に行いにくく、これも今後の重要な検討課題である。

緒言にも書いたが悪性腫瘍の経過観察に関する報告は、診断や治療に関する文献に比べて非常に少ない。筆者が10年以上前に検索した時点では参考文献は得られず、欧米の教科書に「6ヶ月毎に全ての検査を行う」と書いてあるのみで、慣習的に上司や先輩の真似をして1年目は1ケ月ごと、2年目は2ケ月ごと、3年目は3ケ月ごと、4～5年目は6ケ月ごと、6年目以降は1年ごと、みたいな間隔で経過観察を行っていた。しかし以後の検討により現在は諸般の事情等も加味して、1～2年目は3ケ月ごと、3年目以降は6ケ月ごとに経過観察している。来院時に行う検査などさらに検討すべき事項が残されており、子宮体癌の経過観察は今後も重要な課題であると考えられた。

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Phase II Clinical Trial of Pegylated Liposomal Doxorubicin (JNS002) in Japanese Patients with Müllerian 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

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Objective: This study was conducted to evaluate the efficacy and safety of pegylated liposomal doxorubicin (PLD) in Japanese patients with Müllerian carcinoma having a therapeutic history of platinum-based chemotherapy.

Methods: Patients who were diagnosed with Müllerian carcinoma (epithelial ovarian carcinoma, primary carcinoma of fallopian tube and peritoneal carcinoma) by histological examination and had received the initial platinum-based chemotherapy were included in the study. The study drug was administered to the patients at 50 mg/m^2 every 4 weeks.

Results: Seventy-four patients were enrolled in the study. All patients had received platinum-based chemotherapy as first-line regimen and more than 90% of patients had also received taxanes. The overall response rate was 21.9% (95% confidence interval, 13.1–33.1%) and 38.4% of patients had stable disease. The median time to progression was 166 days. The major non-haematological toxicities were hand-foot syndrome (Grade 3; 16.2%) and stomatitis (Grade 3; 8.1%). Myelosuppression such as leukopenia (Grade 3; 52.7%, Grade 4; 6.8%), neutropenia (Grade 3; 31.1%, Grade 4; 36.5%) and decreased haemoglobin (Grade 3; 14.9%, Grade 4; 2.7%) were the most common haematological toxicities.

Conclusion: We confirmed that a 50 mg/m^2 every 4 weeks regimen of PLD was active in Japanese patients with Müllerian carcinoma having a therapeutic history of platinum-based chemotherapy and toxicity was manageable by dose modification of PLD or supportive care.

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Key words: pegylated liposomal doxorubicin – Müllerian carcinoma – ovarian carcinoma – hand-foot syndrome – chemo-gynaecology – chemo-phase I-II-III – gynaecology

INTRODUCTION

Approximately 8000 cases of ovarian cancer are newly diagnosed in Japan and more than 4000 women die of this disease (1). From an embryologic perspective, epithelial ovarian carcinoma, primary carcinoma of fallopian tube and peritoneal carcinoma are generally recognized as a similar disease group, which is known as Müllerian carcinoma. In patients with primary carcinoma of the fallopian tube and peritoneal carcinoma, the experience with chemotherapeutic agents is largely limited to case reports and small studies due to the rarity of disease type (2,3). However, the overall experience closely parallels that of ovarian cancer, so treatment of primary carcinoma of the fallopian tube and peritoneal carcinoma is conducted according to that of ovarian cancer (2,3).

Advanced epithelial ovarian cancer is a highly chemosensitive solid tumour with response rates to first-line chemotherapy of ~80%. The majority of patients, however, eventually relapse and treatment with second-line agents becomes necessary. Furthermore, patients with recurrent ovarian cancer ultimately die of chemoresistant disease. Therefore, it is very important to recognize recurrent ovarian cancer therapy as palliative therapy and therapeutic agents are required to show efficacy as well as favourable toxicity profile. However, there are not many drugs approved in Japan for ovarian carcinoma, or recommended by the Japanese clinical practice guideline for as second-line treatment except platinum, taxane and irinotecan.

Pegylated liposomal doxorubicin (PLD) is a formulation of doxorubicin hydrochloride encapsulated in long circulating STEALTH® liposomes and formulated for intravenous administration. STEALTH® liposomes have liquid membranes coated with polyethylene glycol, which attracts water and renders resistance to mononuclear phagocytosis (4). The liposome's small diameter (~100 nm) and their persistence in the circulation allow their penetration into altered and often compromised, leaky tumour vasculature with entry into the interstitial space in malignant tissues (5). Therefore, pegylated liposomes are suitable for prolonged delivery of doxorubicin and have a prolonged circulation time (6,7). At these tumour sites, the accumulating liposomes gradually break down, releasing doxorubicin to the surrounding tumour cells (8,9). PLD has been designed to enhance the efficacy and to reduce the toxicities of doxorubicin such as myelosuppression, alopecia and cardiotoxicity by altering the plasma pharmacokinetics and tissue distribution of the drug.

Based on the data from the Phases II and III clinical trials in Europe and the USA, it is evident that PLD possesses promising activity and a favourable toxicity profile in the second-line treatment of ovarian cancer (10–15). Currently, PLD is provided as one of the standard treatment options in recurrent ovarian cancer treatment guidelines (16–18).

The result of the Phase I clinical trial in Japan was reported (19). In that study, recommended PLD dose was evaluated in 15 Japanese patients with solid tumours and resulted in 50 mg/m^2 every 4 weeks. In addition, one partial response (PR) and one normalization of CA125 were observed among six ovarian cancer patients enrolled in that study, and further trials with Japanese ovarian cancer patients were encouraged.

Based on the result from a Phase I clinical trial in Japan, we conducted the Phase II clinical trial of PLD in patients with recurrent or relapsed Müllerian carcinoma (epithelial ovarian carcinoma, primary carcinoma of fallopian tube, peritoneal carcinoma) having a therapeutic history of platinum-based chemotherapy.

We conducted a multicentre, non-randomized, open-label study to evaluate efficacy and safety of a PLD 50 mg/m^2 every 4-week regimen in Japanese patients with Müllerian carcinoma who had previously been treated with platinum-based chemotherapy.

PATIENT AND METHODS

Study Design

This study was a multicentre non-randomized, open-label trial to evaluate efficacy and safety of PLD in Japanese patients with Müllerian carcinoma previously treated with platinum-based chemotherapy. The primary endpoint was the best overall response (response rate) and secondary endpoints included adverse events and adverse drug reactions (incidence, severity, seriousness and causality), time to response and duration of response. The final evaluation of the antitumour effect was performed by the independent radiological review committee. The study protocol was approved by the institutional review board at each site. This study was conducted based on ethical principles in the Declaration of Helsinki and in compliance with Good Clinical Practice.

Patients

This study included patients who met all the following inclusion criteria: (i) having histological confirmation of Müllerian carcinoma (epithelial ovarian carcinoma, primary fallopian tube carcinoma and peritoneal carcinoma);

(ii) receiving first-line platinum-based chemotherapy and who would receive PLD as a second-line therapy if time to progression was within 12 months from the date of final administration of platinum therapy, excluding patients whose best response to first-line platinum-based chemotherapy was progressive disease (PD), or who received PLD as a third-line therapy; (iii) receiving 1 or 2 regimens with prior chemotherapy; (iv) having measurable lesions that conformed to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria; (v) ECOG performance status (PS) grade of 0–2; (vi) adequate functions of principal organs, defined by white blood cell (WBC) counts 3.0×10^3–$12.0 \times 10^3/mm^3$, neutrophil counts not less than $1.5 \times 10^3/mm^3$, haemoglobin not less than 9.0 g/dl, platelet count not less than $10.0 \times 10^4/mm^3$, serum AST, ALT and AP not more than 2.5 times the institutional upper limit of normal, total bilirubin not more than the institutional upper limit of normal, serum creatinine not more than 1.5 times the institutional upper limit of normal, left ventricular ejection fraction (LVEF) not less than 50%, electrocardiography (ECG) normal or minor change without symptoms that required any therapeutic intervention, and no evidence of cardiac disorder or Class I in New York Heart Association (NYHA) functional classification; (vii) no colony stimulating factor (CSF) agent or blood transfusion received within 2 weeks before the date of blood tests for screening; (viii) no previous treatment with hormonal agents, oral antimetabolic or immunotherapeutic agents for at least 2 weeks, with nitrosourea or mitomycin C at least 6 weeks, or with surgical therapy, radiation therapy or other chemotherapy for 4 weeks or more; (ix) abilities to stay in hospital for 4 consecutive weeks from the initial administration of PLD; (x) survival expectancy 3 months or longer; (xi) 20–79 of age years at enrolment in the trial; and (xii) received an explanation of this trial from the physicians with written informed consent forms and other relevant information and freely provided informed consent before the trial.

Patients who met any of the following exclusion criteria were excluded from the trial: (i) requiring drainage of pericardial fluid; (ii) having experienced myocardial infarction or angina attack within 90 days before the start of trial; (iii) receiving prior therapy with anthracycline (total anthracycline dose of more than 250 mg/m^2 as doxorubicin); and (iv) having known hypersensitivity to doxorubicin or any component of PLD.

Medication

PLD was intravenously administered to each subject at a dose of 50 mg/m^2 as doxorubicin hydrochloride on Day 1 of each cycle, followed by a treatment-free interval of 28 days including Day 1. This was repeated for at least two cycles if the subject did not meet the withdrawal criteria. PLD was administered at a rate of 1.0 mg/min from the start of infusion to completion, using an infusion pump in consideration of risks of development of infusion-related reactions. PLD was used by diluting with 250 ml of 5% glucose injection for a dose of less than 90 mg as doxorubicin hydrochloride or with 500 ml for a dose of 90 mg or more as doxorubicin hydrochloride.

After administration, PLD would be discontinued in subjects who met any of the following withdrawal criteria: (i) desiring to discontinue the study treatment or withdrawing consent; (ii) having LVEF decreased to less than 45% after administration of PLD or decreased by 20% or more than baseline; (iii) having no possibility for a subsequent cycle to be started within 6 weeks from the planned injection date because of adverse reactions or after 8 weeks for hand-foot syndrome (HFS) or stomatitis; (iv) having bilirubin increased to 3.0 mg/dl or more; (v) requiring a repeated reduction in the dose; (vi) the anticipated total dose of anthracycline antibiotics including PLD would exceed 500 mg/m^2 as doxorubicin hydrochloride (including doses from prior chemotherapy and pre/postoperative treatment); (vii) being judged by the physician to have difficulties continuing the trial due to serious (or significant) adverse events; (viii) being assessed to have difficulty continuing the trial due to concurrent illnesses (e.g. complications); (ix) having obvious progression of the underlying disease or development of new lesions (PD); (x) having any of the exclusion criteria which was discovered after enrolment; and (xi) being judged as unfavourable to continue the trial by the physician.

Prior to administration of the study drug in the next cycle, all the subjects were confirmed to meet all the following criteria: (i) HFS or stomatitis $\leq$Grade 1; (ii) neutrophil counts $\geq 1.5 \times 10^3/mm^3$; (iii) WBC counts $\geq 3.0 \times 10^3/mm^3$; (iv) platelet counts $\geq 7.5 \times 10^4/mm^3$; (v) bilirubin $\leq$1.5 mg/dl; and (vi) other adverse drug reactions $\leq$ Grade 2 (excluding fatigue, nausea, vomiting, anorexia, hypokalemia, hyponatremia and lymphopenia). If any of these criteria was not met, the scheduled administration of the study drug for the next cycle would be delayed for 2 weeks at the maximum. If any of the above criteria was still not met after a 2-week delay from the scheduled initial date of each cycle, the trial for the subjects would be discontinued. In case Grade 2 HFS or stomatitis was observed at 6 weeks from the initial date of each cycle, the scheduled administration of the test drug for the next cycle would be delayed for 2 weeks. As a result, when the subjects met all the above criteria, the next cycle would be started. Even if the subjects met all the criteria, the scheduled initial date could be delayed for a maximum of 2 weeks at the investigator's discretion.

As the subjects met any of the following dose reduction criteria, the previous dose would be reduced by 25% (37.5 mg/m^2) for the next cycle: (i) HFS or stomatitis $\geq$ Grade 3; (ii) neutrophil count $<500/mm^3$ or WBC count $<1000/mm^3$ that was maintained for at least 7 days; (iii) neutrophil counts $<1000/mm^3$ with 38.0°C or higher fever; (iv) platelet reduction $<2.5 \times 10^4/mm^3$; (v) other adverse drug reactions $\geq$ Grade 3 (excluding fatigue, nausea, vomiting, anorexia, hypokalemia, hyponatremia, lymphopenia and other adverse events associated with infusion-related reactions); and (vi) the physician judged that the dose should be

decreased. Dose reduction was permitted only once, and it was prohibited to increase the dose after the dose was reduced. If a further dose reduction was required after the dose was reduced, the trial for the subject would be discontinued.

Administration of CSF was admitted when patients met any of the following criteria: (i) neutrophil counts $<1000/mm^3$ with fever ($\geq 38°C$); (ii) neutrophil counts $<500/mm^3$; (iii) experience of either (i) or (ii) in the prior cycle and neutrophil counts $<1000/mm^3$ in the following cycle.

Evaluation of Response and Safety

Tumour response evaluation was performed according to the RECIST guidelines. Confirmed duration of stable disease (SD) was defined as the duration of 8 consecutive weeks or longer after the start of administration.

Severity of adverse events was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

Sample Size and Statistical Analysis

Among the subjects enrolled in this trial, those who received platinum-based chemotherapy as the first-line chemotherapy and experienced disease progression between 6 and 12 months after the completion of the platinum regimen were classified as the platinum-sensitive group, and those who had progression during the first-line chemotherapy, received platinum-based chemotherapy as the first-line chemotherapy and experienced progression less than 6 months after the completion of the platinum regimen, or who would receive PLD as a third-line therapy were classified as the platinum-resistant group. A sample size to produce the expected response rate of 30 and 15% for the platinum-sensitive and platinum-resistant groups, respectively, with the threshold response rate of 5%, a significance level of 5% and power of 80% was determined to be 80 patients in total (20 and 60 patients for the platinum-sensitive and platinum-resistant groups, respectively).

For the response evaluation, statistical analysis was performed based on the evaluation for the full analysis set (FAS) by the independent radiological review committee. The primary endpoint was the response rate, the proportion of patients with complete response (CR) or PR in the response analysis set, and the point estimate and two-sided 95% confidence interval (CI) were calculated. The secondary endpoints included the duration of overall response, time to response and time to progression, and the progression-free survival was analysed using the Kaplan–Meier method, and descriptive statistics (median, minimum and maximum) were calculated. The safety of PLD was evaluated for all the subjects treated with PLD. Statistical analyses were performed using the SAS System for Windows release 8.02.

RESULT

Demographics and baseline characteristics of patients are shown in Table 1. Seventy-four patients were enrolled into the trial between January and December 2005, and 73 patients (11 for the platinum-sensitive group and 62 for the platinum-resistant group), excluding one patient who was confirmed to be ineligible after enrolment, were eligible for the trial, and defined as the FAS. All 74 patients who received PLD were defined as the safety analysis set. Although the targeted number of patients for the platinum-sensitive group was 20, only 11 patients were enrolled. That was because the study was closed at the end of 2005 when the patient enrolment in the platinum-resistant group reached the target number due to slow enrolment.

The median of patients' age was 57.0 years (range, 32–76). Among 74 patients enrolled, 62 had epithelial ovarian carcinoma and 12 had peritoneal carcinoma. Histological, 49 patients had serous carcinoma, eight had endometrioid carcinoma, eight had clear cell carcinoma, one had mucinous carcinoma and eight had other types of carcinoma. All 74 patients had received first-line chemotherapy including platinum regimen, 70 (94.6%) had also received taxanes as the first-line chemotherapy, and only three had received anthracycline in the prior chemotherapy. A total of 334 cycles of PLD was administered to 74 patients, and the median number of cycles administered was 4.0 (range, 1–10 cycles). Administration of PLD was completed or discontinued in all 74 patients before statistical analysis. The dose of PLD was reduced to 37.5 mg/m^2 in 26 of 74 patients (35.1%). The scheduled administration of PLD was delayed in 49 of 74 patients (66.2%) and in 154 of 334 cycles (46.1%).

Response

The antitumour effect (best overall response) and response rate are shown in Table 2. The best overall response in 73 patients of FAS was CR in two patients, PR in 14, SD in 28, PD in 27 and not evaluable (NE) in two patients. The response rate was 21.9% (16 of 73) (95% CI: 13.1–33.1%). The response rate (two-sided 95% CI) by patient group was 27.3% (3 of 11) (95% CI: 6.0–61.0%) in the platinum-sensitive group and 21.0% (13 of 62) (95% CI: 11.7–33.2%) in the platinum-resistant group. The proportion of patients with CR, PR or SD was 60.3% (44 of 73) in FAS, and 54.5% (6 of 11) in the platinum-sensitive group and 61.3% (38 of 62) in the platinum-resistant group.

The results from subgroup analysis sets by platinum-free interval were as follows. In a subgroup analysis set where patients received PLD as a second-line therapy, the response rate by platinum-free intervals was 8.3% (1 of 12) and 27.3% (3 of 11) in patients with the platinum-free interval of within 6 months and of 6–12 months, respectively. In another subgroup analysis set where patients received PLD as a third-line therapy, the response rate was 7.1% (1 of 14),

Table 1. Demographics and baseline characteristics of patients

Characteristics	Total ($n = 74$)	Platinum sensitive ($n = 11$)	Platinum resistant ($n = 63$)
Age, years			
Median (range)	57.0 (32–76)	55.0 (40–72)	58.0 (32–76)
Primary cancer (%)			
Epithelial ovarian carcinoma	62 (83.8)	11 (100.0)	51 (81.0)
Peritoneal carcinoma	12 (16.2)	0 (0.0)	12 (19.0)
Tumour histology (%)			
Serous	49 (66.2)	6 (54.5)	43 (68.3)
Endometrioid	8 (10.8)	3 (27.3)	5 (7.9)
Clear cell	8 (10.8)	1 (9.1)	7 (11.1)
Mucinous	1 (1.4)	0 (0.0)	1 (1.6)
Other	8 (10.8)	1 (9.1)	7 (11.1)
Initial FIGO stage (%)			
I	7 (9.5)	1 (9.1)	6 (9.5)
II	1 (1.4)	1 (9.1)	0 (0.0)
III	50 (67.6)	6 (54.5)	44 (69.8)
IV	16 (21.6)	3 (27.3)	13 (20.6)
Previous chemotherapy (%)			
1 regimen	23 (31.1)	11 (100.0)	12 (19.0)
2 regimen	50 (67.6)	0 (0.0)	50 (79.4)
3 regimen	1 (1.4)	0 (0.0)	1 (1.6)
Previous chemotherapy with antracycline (%)			
Yes	3 (4.1)	0 (0.0)	3 (4.8)
No	71 (95.9)	11 (100.0)	60 (95.2)
Platinum-free interval (days)			
Median (range)	263 (28–2792)	315 (216–441)	235 (28–2792)
CA-125 at baseline (U/ml)			
Median (range)	243.6 (5.8–7809.8)	192.1 (22.2–808.0)	261.0 (5.8–7809.8)

FIGO, Federation Internationale de Gynecologie et d'Obstetrique.

Table 2. Response rate

	Total	Platinum sensitive	Platinum resistant
Number of patients	73	11	62
Best overall response: *n* (%)			
CR	2 (2.7)	0 (0.0)	2 (3.2)
PR	14 (19.2)	3 (27.3)	11 (17.7)
SD	28 (38.4)	3 (27.3)	25 (40.3)
PD	27 (37.0)	4 (36.4)	23 (37.1)
NE	2 (2.7)	1 (9.1)	1 (1.6)
Response rate			
n (%) (95% CI)	16 (21.9) (13.1–33.1)	3 (27.3) (6.0–61.0)	13 (21.0) (11.7–33.2)

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluable; 95% CI, confidence interval.

15.4% (2 of 13) and 36.8% (7 of 19) in patients with the platinum-free interval of within 6 months, of 6–12 months and more than 12 months, respectively.

The response rate by histological type was 29.2% (14 of 48) and 25.0% (2 of 8) in patients with serous carcinoma and with endometrioid carcinoma, respectively. In patients

Table 3. Time to response, duration of response and time to progression

	Total	Platinum sensitive	Platinum resistant
Number of patients	73	11	62
Time to response (day)			
Patient (%)[a]	16 (21.9)	3 (27.3)	13 (21.0)
Median (range)	54.0 (20–162)	56.0 (54–59)	52.0 (20–162)
Duration of response (day)			
Patient (%)[a]	16 (21.9)	3 (27.3)	13 (21.0)
Median (range)	149.0 (56–309)	– (92–159)	149.0 (56–309)
Withdrawal (%)	11 (68.8)	2 (66.7)	9 (69.2)
Time to progression (day)			
Patient (%)[b]	71 (97.3)	10 (90.9)	61 (98.4)
Median (range)	166.0 (14–358)	159.0 (16–217)	168.0 (14–358)
Withdrawal (%)	30 (42.3)	4 (40.0)	26 (42.6)

[a]Responder only. [b]Excluded two patients due to unable calculation for time to progression.

with clear cell carcinoma, SD was observed in two of eight patients, and the time to progression in the two patients was 350+ and 87+ days, respectively. In patients with mucinous carcinoma, SD was observed in one of one patient and the time to progression was 135+ days.

The median and range of the duration of response, time to response and time to progression are shown in Table 3.

The median time to response (CR or PR) was 54.0 days. The median time to response was 56.0 days in the platinum-sensitive group and 52.0 days in the platinum-resistant group.

The median duration of overall response was 149.0 days. The median duration of overall response in the platinum-resistant group was 149.0 days, however, that in the platinum-sensitive group could not be calculated. The Kaplan–Meier curve for time to progression is shown in Fig. 1. The median time to progression was 166.0 days: 159.0 days in the platinum-sensitive group and 168.0 days in the platinum-resistant group. The median survival could not be calculated.

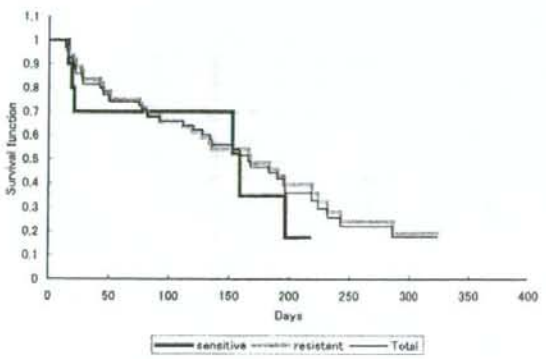

Figure 1. Kaplan–Meier estimates of time to progression.

Safety

Adverse drug reactions were reported from all 74 patients treated with PLD. The major adverse drug reactions observed in the study are shown in Table 4.

The most common Grade 3 or 4 adverse reactions were due to haematological toxicity: neutropenia in 50 patients (67.6%), leukopenia in 44 (52.7%), lymphopenia in 35 (47.3%), decreased haemoglobin in 13 (17.6%), thrombocytopenia in five (6.8%) and erythropenia in three patients (4.1%). The median time to nadir for neutrophils, WBCs, haemoglobin and platelets from the start of administration in the first cycle was 21.0 days, 21.0, 15.0 and 22.0 days, respectively. The median time to recovery to the level at which the administration of PLD in the next cycle was permitted was 7.0–8.0 days for any haematological event.

Grade 3 or 4 adverse drug reactions due to non-haematological toxicity included: HFS in 12 patients (16.2%), stomatitis in six (8.1%), febrile neutropenia, nausea, ALT (GPT) increased and blood potassium decreased in two each (2.7%) and deep venous thrombosis rash, herpes zoster, infection, upper respiratory tract infection, impaired glucose tolerance, diarrhoea, small intestinal obstruction, vomiting, fatigue, AST (GOT) increased, decreased blood sodium and increased γ-GTP in one each (1.4%). Only deep venous thrombosis was Grade 4. The median time to occurrence of HFS, rash and stomatitis from the start of administration was 34.0 days (2.0 cycles), 33.0 days (2.0 cycles) and 16.0 days (1.0 cycle), respectively. The median time to the Grade 2, 3 or 4 adverse reactions (Grade 3 or 4 for rash), which required delay of next administration, was 64.5 (3.0 cycles), 84.0 (3.0 cycles) and 43.0 (2.0 cycles), respectively and the median duration for those reactions was 15.0, 8.0 and 8.0 days, respectively.

Infusion-related reactions were seen in 14 patients (18.9%) only during the first cycle. Serious reactions were not seen.

Table 4. Grades 3 and 4 adverse drug reactions

Adverse Reaction (MedDRA/J Ver9.0)	Number of patients (n = 74)			
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	8 (10.8)	11 (14.9)	23 (31.1)	27 (36.5)
Lymphocytopenia	15 (20.3)	16 (21.6)	29 (39.2)	6 (8.1)
Leukopenia	5 (6.8)	20 (27.0)	39 (52.7)	5 (6.8)
Haemoglobin decreased	23 (31.1)	27 (36.5)	11 (14.9)	2 (2.7)
Thrombocytopenia	27 (36.5)	13 (17.6)	4 (5.4)	1 (1.4)
Deep vein thrombosis	0 (0)	0 (0)	0 (0)	1 (1.4)
Hand-foot syndrome	20 (27.0)	26 (35.1)	12 (16.2)	0 (0)
Stomatitis	29 (39.2)	22 (29.7)	6 (8.1)	0 (0)
Erythropenia	42 (56.8)	11 (14.9)	3 (4.1)	0 (0)
Nausea	37 (50.0)	6 (8.1)	2 (2.7)	0 (0)
ALT (GPT) increased	16 (21.6)	1 (1.4)	2 (2.7)	0 (0)
Blood potassium decreased	10 (13.5)	0 (0)	2 (2.7)	0 (0)
Febrile neutropenia	0 (0)	0 (0)	2 (2.7)	0 (0)
Rash	17 (23.0)	19 (25.7)	1 (1.4)	0 (0)
Fatigue	28 (37.8)	5 (6.8)	1 (1.4)	0 (0)
Vomiting	11 (14.9)	5 (6.8)	1 (1.4)	0 (0)
γ-GTP increased	13 (17.6)	4 (5.4)	1 (1.4)	0 (0)
Diarrhoea	12 (16.2)	4 (5.4)	1 (1.4)	0 (0)
AST (GOT) increased	18 (24.3)	2 (2.7)	1 (1.4)	0 (0)
Upper respiratory tract infection	0 (0)	2 (2.7)	1 (1.4)	0 (0)
Blood sodium decreased	15 (20.3)	0 (0)	1 (1.4)	0 (0)
Small intestinal obstruction	0 (0)	0 (0)	1 (1.4)	0 (0)
Herpes zoster	0 (0)	0 (0)	1 (1.4)	0 (0)
Infection	0 (0)	0 (0)	1 (1.4)	0 (0)
Glucose tolerance impaired	0 (0)	0 (0)	1 (1.4)	0 (0)

Of these patients, one patient had Grade 2 events and other patients had Grade 1 events. Symptoms associated with infusion-related reactions included hot flushes, facial flushing and hot feeling. These symptoms were restored on the day of occurrence or the following day. PLD was discontinued in one patient who had nausea, low back pain, chest tightness and facial flushing as Grade 2 infusion-related reactions. These symptoms were rapidly restored by supportive care with drip infusion of physiological saline. Although slow-down in the PLD infusion rate was required in two patients, the other 11 patients completed the infusion without any intervention. Among 14 patients with infusion-related reactions, 11 patients received the next cycle without recurrence of infusion-related reactions.

Cardiac toxicity was seen in 17 of 74 patients (23.0%), all of which were Grade 1. Increase in the incidence of cardiac toxicity associated with accumulation of PLD was not observed. Alopecia was seen in 18 patients (24.3%), which was Grade 1 in all of them.

There was no death due to adverse events reported during the trial period. Fourteen serious adverse reactions were seen in 11 patients (14.9%): two events each of nausea, HFS, small intestinal obstruction and stomatitis; and one event each of neutropenia, leukopenia, vomiting, pneumonitis, deep venous thrombosis and anorexia.

PLD was discontinued due to adverse reactions in 16 (21.6%). Common adverse reactions that required the discontinuation of PLD included: decreased haemoglobin in six patients (8.1%), leukopenia in four (5.4%) and HFS and neutropenia in three each (4.1%). The PLD dose was reduced in 24 patients (32.4%) due to adverse drug reactions such as HFS in 10 patients (13.5%), decreased haemoglobin and stomatitis in five each (6.8%) and neutropenia in three patients (4.1%). Administration of PLD was delayed in 49 patients (66.2%) in 111 cycles of 334 cycles due to adverse reactions mainly including leukopenia in 68 cycles (20.4%), neutropenia in 56 cycles (16.8%), HFS in 40 cycles (12.0%) and stomatitis in eight cycles (2.4%).

DISCUSSION

We evaluated the efficacy and safety of PLD in Japanese patients with Müllerian carcinoma (epithelial ovarian carcinoma, primary fallopian tube carcinoma and peritoneal carcinoma) previously treated with platinum-based chemotherapy.

Currently, platinum and taxane therapies are used for the standard first-line chemotherapy for treatment of ovarian carcinoma, though the results of Phase III clinical trials conducted in the US and Europe demonstrated the effectiveness of PLD, gemcitabine and topotecan in patients resistant to these drugs (13,14,20). However, these drugs have not been approved and the results from prospective studies of their use in patients with ovarian carcinoma previously treated with platinum and taxane therapy have not been reported in Japan. Our study was intended to provide the outcome in patients who had recurrent Müllerian carcinoma after the standard first-line chemotherapy (90% of patients in our study had received first-line chemotherapy with platinum and taxane).

In this trial, the response rate was 21.9% (95% CI: 13.1–33.1%) for all patients in FAS. The response rate in the platinum-sensitive and platinum-resistant groups was 27.3% (95% CI: 6.0–61.0%) and 21.0% (95% CI: 11.7–33.2%), respectively. Better response was obtained in patients with longer platinum-free interval when PLD was administered as second- or third-line chemotherapy. Clinical studies conducted in the US and Europe showed that the response rate of PLD was 28.4% in the platinum-sensitive group and 6.5–18.3% in the platinum-resistant group (11,12,13). These response rates were similar to those obtained in our trial.

Common adverse reactions reported in this study were haematological toxicities (leukopenia, neutropenia and decreased haemoglobin), HFS and stomatitis.

The median time to nadir for WBC, neutrophils and haemoglobin after the start of administration of PLD was 15–22 days, and the median time to recovery to baseline after reaching the nadir was 7–8 days. Repeated cycles did not lead to worsening the events. Most patients could receive PLD continually by concomitant use of G-CSF and dose modification, such as dose reduction and delay of next administration.

In the previous Phase III study (13), HFS and stomatitis occurred in 49% (Grade 3 or higher: 23%) and 40% (Grade 3 or higher: 8%) of patients, respectively. Although these toxicities were seen in 78.3 and 77.0% of patients in our study, only 16.2 and 8.1% of patients experienced Grade 3 or higher toxicities, respectively. Most patients could continually receive PLD treatment by dose modification of PLD and supportive care, and the patients discontinued due to toxicities were few.

Infusion-related reaction that is known as toxicity specific to PLD was seen in 14 patients (18.9%) during the first cycle, all of which were resolved on the day of the occurrence or the following day. The second cycle was administered in 11 of 14 patients with infusion-related reactions. No recurrence of infusion-related reactions was seen in all 11 patients. It is important to use PLD with close attention to the condition of patients at the first administration of PLD. Infusion-related reaction is related to the initial infusion rate of PLD. It has been reported that decreasing the infusion rate reduces the risk of the infusion-related reaction (21).

It has been reported that cardiac toxicity, which is a significant problem with the use of conventional doxorubicin, associated with PLD is mild (22). Also in this trial, all cardiac toxicities observed were Grade 1, and had no effect on continuation of the trial. Furthermore, no patients experienced Grade 2 or higher alopecia, and Grade 3 or higher gastrointestinal toxicities were rarely seen in our trial. These toxicities are frequently induced by treatment of conventional doxorubicin.

These results suggest that toxicity of PLD is manageable by dose modification of PLD and supportive care.

Most patients with ovarian carcinoma exhibited response to first-line chemotherapy, however, the incidence of recurrence is high and prognosis is poor. It might be important to recognize that the chemotherapy would be palliative treatment for treatment of recurrent ovarian carcinoma. PLD has a safety profile that is different from that of platinum and taxanes, which are used for the standard first-line chemotherapy. PLD has a low risk of enhancing cumulative toxicities (haematological toxicity or neurotoxicity) associated with first-line chemotherapy. PLD is expected to have a beneficial effect against disease progression as the proportion of patients with CR, PR or SD and time to progression were 60.3% and 166 days (median). Furthermore, PLD might make it easy to provide long-term outpatient chemotherapy since PLD would reduce a patient burden by dosing once every 4 weeks.

In conclusion, this trial demonstrated that PLD (50 mg/m^2 every 4 weeks) was expected to have antitumour effect in Japanese patients with Müllerian carcinoma previously treated with platinum-based chemotherapy and that toxicities associated with PLD are manageable by dose modification and supportive care. In the USA and Europe, combination chemotherapy with PLD and platinum has recently been investigated in the platinum-sensitive group where PLD is considered to be more effective (23,24,25). It is desirable to investigate the optimal regimen of the combination therapy in Japan.

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Conflict of interest statement

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