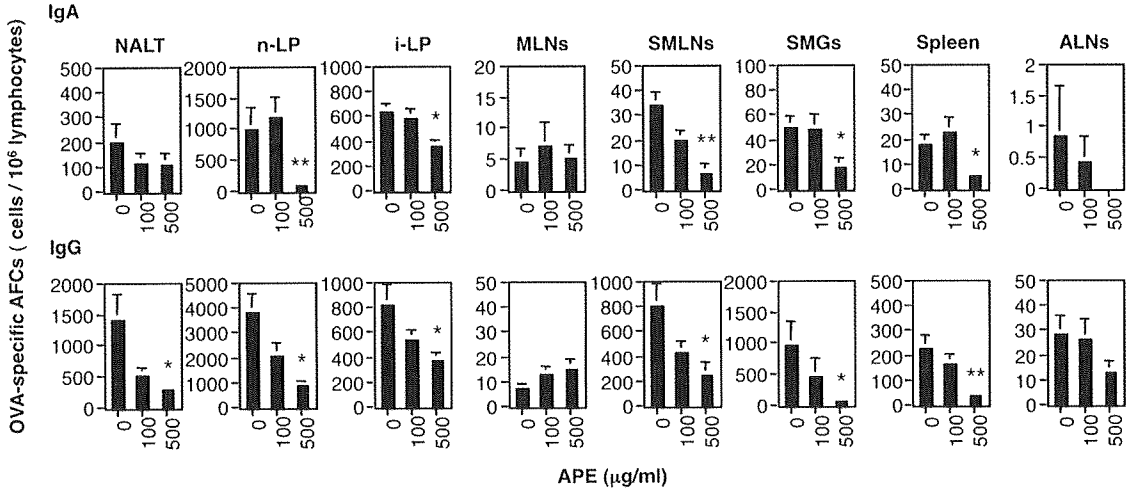

Fig. 8. Analysis of OVA-specific IgA and IgG AFCs in the mucosal and systemic tissues of mice nasally immunized with OVA plus CT with or without APE. The mice were nasally immunized with OVA plus 0.5 μg of CT alone, with 100 μg (1:200) of APE or with 500 μg (1:1000) of APE. Seven days after the last immunization, mononuclear cells isolated from NALT, n-LP, i-LP, MLNs, SMLNs, SMGs, spleen, and ALNs were determined using an OVA-specific ELISPOT assay. The data are shown as the mean number of AFCs/10^6 cells ± one SEM for 12 mice in each experimental group and the data are representative of three separate experiments. Significant differences between the CT-only group and the CT plus APE group are indicated by asterisks ($^*p < 0.05$, $^{**}p < 0.005$).

3.9. GM1 binding responses of APE complexes with CT

When a 1000-fold dosage of APE was nasally administered with CT, CT showed significant alteration of its biological activities including mucosal adjuvanticity. In this regard, we next determined whether APE influences the binding ability of CT to ganglioside GM1 using an *in vitro* binding assay. Our results showed that significant reduction of the GM1 binding ability of CT was initially detected when 10 μg (1:1000) of APE was co-cultured with CT (Fig. 9; $p < 0.05$). When higher doses (50–10,000 μg; 1:5000 to 1:1,000,000) of APE were employed, the GM1 binding ability of CT was drastically decreased ($p < 0.005$) (Fig. 9).

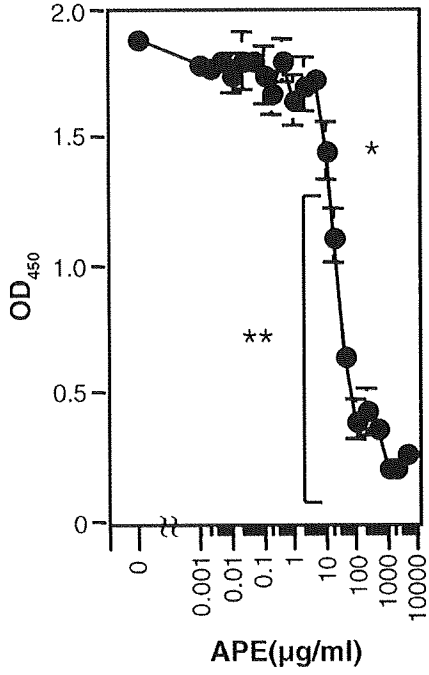

Fig. 9. Analysis of GM1 binding by CT with or without APE. A GM1 coated wells were incubated with 10 ng/ml of CT and different concentration of APE. Mouse anti-CT serum followed by horseradish peroxidase-conjugated goat anti-mouse IgG (H + L) Abs were used to detect CT. The data are shown as the mean OD_{450} ± one SEM for five different experiments. Significant differences between the CT-only group and the CT plus APE group are indicated by asterisks ($^*p < 0.05$, $^{**}p < 0.005$).

4. Discussion

This study provides direct evidence that co-administration of an optimal dose of APE dramatically mitigates CT toxicity without altering mucosal adjuvant activity of native CT to induce Ag-specific humoral immunity in the mucosal and systemic compartments of the mouse model. Our findings showed that the biological effects of APE on adjuvanticity and toxicity of CT were dose-dependent. At the optimal dosages of APE (molar ratio between 1:100 and 1:500 of CT and APE), CT toxicities including inflammatory responses, CNS accumulation, and IgE Ab responses were significantly reduced. Of importance, levels of OVA-specific Abs and OVA-specific AFCs were maintained with an optimal dose of APE. Further, CT binding to GM1 was essentially unchanged (Table 1). In contrast, when low dosages of APE (molar ratio between 1:2 and 1:50 of CT and APE of the combination) were used, toxicities and adjuvanticity of CT were remained intact were (Table 1). When high dosages of APE (molar ratio 1:1000 of CT and APE) were co-administered, CT lost its biological activities including toxicities and adjuvanticity (Table 1). Taken together, these findings show that a dose of APE regulates the optimal efficacy and safety of an adjuvant constituted of CT.

It has been shown that apple condensed tannin (ACT), which is an oligomeric procyanidin containing the dimer to pentadecamer of epicatechin as a unit [40], binds to both CT-A and CT-B [25]. When an optimal dose of APE was mixed with CT, CT-APE complexes were internalized to GM1-expressed cells. However, the CT-APE complex induced significantly lower cAMP levels than CT alone. These results suggest that an optimal dose of APE binds to CT-A but not CT-B subunit. In this regard, it is possible that CT, when administered with a high dose of APE, loses some of its adjuvant effect since it cannot be internalized in GM1-expressed cells. Indeed, our results showed that a high dose of APE significantly reduced CT binding to GM1. Taken together, these results suggest that APE binds first to CT-A as the primary reaction and then binds to CT-B.

It seems that the adjuvant effects achieved by a combination of CT and an optimal dosage of APE result in part from the binding of APE to CT; however, the precise mechanisms of APE in maintaining the adjuvanticity and reducing the inflammatory responses of CT remain to be elucidated. It was reported that adjuvant activity

Table 1
Biological characteristics and potential toxicity of CT/APE mucosal adjuvant.

CT:APE (wt:wt)		Control	Low dosage			Optimal dosage			High dosage
		1:0	1:2	1:5	1:50	1:100	1:200	1:500	1:1000
Toxicity	cAMP	–	–	–	–	*[a]	*	*	**[a]
Adverse reaction	Inflammation	–	–	–	–	*	**	NT[b]	**
	IL-6	–	–	–	–	–	*	**	**
	Total IgE	–	–	–	*	*	*	**	**
	OVA-specific IgE	–	–	–	–	*	*	**	**
CT accumulation	NALT	–	NT	NT	NT	NT	*	NT	*
	ON/E	–	NT	NT	NT	NT	**	NT	**
GM1 binding		–	–	–	–	–	–	–	*
Systemic immunity									
OVA-specific	IgA	–	–	–	–	–	–	–	**
	IgG	–	–	–	–	–	–	–	*
	IgG1	–	–	–	–	–	–	–	**
	IgG2a	–	–	–	–	–	–	–	**
	IgG2b	–	–	–	–	–	–	–	**
	IgG3	–	–	–	–	–	–	–	**
CT-B-specific	IgA	–	–	–	–	**	**	**	**
	IgG	–	–	–	–	*	*	**	**
Mucosal immunity									
OVA-specific IgA	Fecal extract	–	–	–	–	–	–	–	**
	Nasal wash	–	–	–	–	–	–	–	**
	Saliva	–	NT	NT	NT	NT	–	–	**
	Vaginal wash	–	NT	NT	NT	NT	–	NT	*

[a] Significant differences between the CT-only group and the CT plus APE group are indicated by asterisks (*$p < 0.05$, **$p < 0.005$).
[b] Not tested.

of CT is closely related to NF-κB translocation-mediated dendritic cell maturation [41], as well as protein kinase C (PKC)-induced pro-inflammatory cytokine production, such as IL-1β and IL-6 [42]. Apple contains many phytochemicals such as procyanidins, phenol carboxylic acids, catechins, and flavonoids, which possess physiologic and biological functions [28,43–47]. Indeed, apple polyphenol inhibits TNF-α-induced NF-κB activation by inhibiting the proteasomal activities instead of IκB kinase activation [48]. Apple flavonoid also decreases TNF-α-stimulated NF-κB signaling [49]. Further, a polyphenol-rich apple juice extract and phloridzin, the major phenolic glucoside in apple [50], inhibit PKC activity [51,52]. In addition to the above, many plant polyphenols inhibit the activity of eukaryote protein kinase [53,54] and the natural ligand that binds to its receptor [55]. These evidences indicate potential molecular mechanisms of APE for the reduction of CT-induced inflammatory responses.

It should be emphasized that polarized Th2-type T cell responses are often associated with an adverse reaction, the induction of IgE Ab and anaphylactic shock [56–58]. CT [59], mCT [3,15,31], dmCT [16], or mCT-A/LT-B [23] adjuvants are known to induce co-administered Ag-specific Th2-type T cell responses although the mutant and chimeric CTs can reduce adjuvant-induced IgE Ab titers and inflammation [15,16,23]. Our current study and others showed that APE itself did not reduce spontaneous IgE Ab levels in mice and humans [27]. However, an optimal dosage of APE, administered with OVA plus CT, diminished both total and OVA-specific IgE Ab titers in plasma without compromising the ability of CT to induce OVA-specific mucosal and systemic humoral immune responses in mice. APE binds to the high-affinity receptor for IgE Ab (FcεRI) and disturbs binding of IgE Ab to FcεRI [60]. Apple polyphenols have also been reported to suppress auricular swelling in allergic mice [61], and alleviate skin inflammation in atopic patients [27]. Though an optimal dosage of APE did not completely inhibit the production of CT-induced IgE Abs as compared with mice given PBS alone, it could help to reduce adverse reactions such as anaphylactic shock caused by CT-induced IgE Abs.

Native CT and LT pose the risk of serious adverse reactions such as inflammation and physiological epithelial cell barrier disruption in the nasal mucosa. These reactions increase the risk of toxic side effects, including the accumulation of GM1-binding adjuvants and co-administered unrelated proteins into the OBs and brain following nasal immunization [33,62,63]. In the current study, APE greatly reduced CT-induced inflammatory responses in the nasal tissues. In addition to inflammatory responses, accumulation of CT in CNS is a very critical issue in nasal vaccine development using CT as a mucosal adjuvant. Thus, it has been shown that nasal CT accumulated in the CNS tissues and induced toxicity. Indeed, a human vaccine containing inactivated influenza and native LT as an adjuvant resulted in a very high incidence of Bell's palsy [12]. In this regard, dmCTs were developed and showed their safety [16]. Although dmCTs accumulated in the ON/E for a short period, dmCTs were not transferred into the OBs [16]. Furthermore, the dmCTs that accumulated in the ON/E cleared after 24 h and were not seen in the OBs 7 days after the last immunization even though they were given three times in three consecutive administrations at weekly intervals [16]. Similarly, APE significantly reduced levels of CT accumulation in the ON/E of mice administrated CT plus optimal dose of APE nasally although the transfer mechanism of CT-APE complex into the olfactory tissues could differ from that of dmCT. Since the optimal doses of APE did not significantly alter CT binding to GM1, it is possible that nasally co-administered APE prohibits CT migration into the OBs and other CNS tissues.

An ideal effective mucosal adjuvant should induce robust Ag-specific mucosal S-IgA and plasma IgG Ab responses without causing adverse reactions (e.g., IgE Ab production and inflammatory responses). The co-administration of APE together with native CT shows promise as an effective mucosal adjuvant; however, it is essential to perform additional studies in order to determine its stability and its efficacy against pathogens. Though further study is necessary, the concept of a combined native CT and APE nasal adjuvant opens up important new avenues of research for the development of a novel mucosal vaccine strategy.

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Clinical Medicine: Therapeutics

REVIEW

Pegylated Liposomal Doxorubicin for Advanced Ovarian Cancer in Women Who are Refractory to Both Platinum- and Paclitaxel-Based Chemotherapy Regimens

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Abstract: Pegylated liposomal doxorubicin (PLD) is doxorubicin HCl encapsulated in long-circulating STEALTH® liposomes (Doxil®). PLD achieves good response rates and many patients maintain long-lasting stable disease (SD), which is one of the advantages. In addition, the clinical benefit is high in platinum-resistant disease, and PLD is thus considered to be the first option. PLD is associated with a number of adverse events, but these events are mild to moderate. PLD is safer for heavily pretreated patients than topotecan and gemcitabine due to mild bone-marrow toxicity, but that nonhematotoxity, such as PPE, stomatitis, mucositis, and other cutaneous reactions were the most common side effects attributable to PLD. Based on a review of previous studies, there are no differences in efficacy between 50 and 40 mg/m^2 of PLD, therefore, a dose of 40 mg/m^2 is preferable in patients with platinum-resistant disease to reduce adverse events. The 1-hour infusion schedule every 4 weeks makes PLD easy to administer. A rational approach to combine PLD with other drugs should take the slow accumulation and delayed peak of PLD in tumors into consideration. When combined with other useful agents, the lower dose of PLD (30 to 35 mg/m^2) with a 3-week schedule may reduce severe PPE and stomatitis with negligible effects on the level of DI and the therapeutic efficacy.

Keywords: pegylated liposomal doxorubicin, PLD, ovarian cancer

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Introduction

Epithelial ovarian cancer is sensitive to chemotherapy and approximately 75% of patients achieve complete clinical remission after the initial treatment. However, most patients have a recurrence, which results in death after a chronic course. The progression-free survival (PFS) for advanced ovarian cancer patients with optimal residual disease range from 18 to 24 months, while PFS for patients with suboptimal residual disease is 18 months.[1–5] The PFS of dose-dense paclitaxel/carboplatin therapy improved to 28 months for patients with both optimal and suboptimal disease in our study (JGOG3016).[6] In the treatment of recurrent cancer, the issues to consider are the treatment-free interval (TFI), toxicity continuously observed from the initial treatment, recurrent tumor diameter and increased CA125. The TFI is the most important for selecting drugs or regimens, and the longer the TFI, the higher the response rate.[7,8] When the TFI is 6 months or longer, the tumor is considered to be sensitive to chemotherapy, but when the TFI is less than 6 months, the tumor is considered resistant to chemotherapy. However, 6 to 12 months of TFI is considered to be a gray zone, and such tumors require more careful consideration when selecting drugs or regimens. Recommended therapies for tumors sensitive to drugs, based on the results of randomized controlled trials (RCT) and meta-analyses, are carboplatin-combination therapy such as carboplatin/paclitaxel, carboplatin/gemcitabine, and carboplatin/pegylated liposomal doxorubicin (PLD).[9–11] For patients with TFI of 6 to 12 months, a non-platinum drug is one option for prolonging the platinum-free interval and reducing toxicity. However, patients must therefore be carefully observed to determine when the switch from non-platinum chemotherapy to platinum combination therapy should be made. A phase III trial has been recently launched comparing carboplatin/paclitaxel versus PLD in the above cited clinical setting (NCT00657878). On the other hand, for patients with a drug-resistant tumor, a drug without cross-resistance to paclitaxel and carboplatin must be selected. The goal of therapy is to delay progression, relieve symptoms and improve the QOL, and monotherapy is generally chosen for the most favorable toxicity profile. PLD, topotecan, and weekly paclitaxel are drugs that have been approved by the Food and Drug Administration (FDA), and gemcitabine (GEM), oral etoposide, and docetaxel can also be used. In Japan, weekly irinotecan (CPT-11) is widely used. When selecting drugs, the differences in toxicity must be fully understood. It is usually difficult to completely cure recurrent disease with one drug or one regimen with high efficacy and low toxicity, and the drugs must therefore be changed as required while assessing the effect and toxicity. Topotecan and GEM are highly hemotoxic, and patients should be monitored for non-hemotoxic events that reduce the QOL when PLD and irinotecan are used. There is concern about palmar-plantar erythrodysesthesia (PPE) and stomatitis, both of which can occur with PLD treatment, diarrhea due to irinotecan, and peripheral neuropathy and arthralgia during weekly paclitaxel therapy.

PLD was approved in 1999 by the FDA and in 2000 by the European Medicines Evaluation Agency as a treatment for chemorefractory and chemoresistant epithelial ovarian cancer, and has been used worldwide as the first option for patients with chemorefractory and chemoresistant epithelial ovarian cancer.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

PLD consists of doxorubicin encapsulated in N-(carbonyl- methoxypolyethylene glycol 2000)-1, 2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE) coated liposome (STEALTH® liposome) (Fig. 1). Liposomes have the advantage of biocompatibility and versatility of formulation for intravenous use. However, the disadvantage of liposomes are rapid uptake by the reticuloendothelial system (RES) and removal from the circulatory system, thus reducing the amount of drug that reaches the tumor. MPEG-DSPE is a hydrophilic material and characteristically decreases RES uptake. Therefore, the STEALTH® liposome achieves prolonged circulation time without rapid uptake by RES, and PLD has made prolonged delivery of doxorubicin and prolonged circulation time possible. Gabzon et al undertook a pilot clinical study about the pharmacokinetics compared with PLD and free (unencapsulated) doxorubicin (DOX), and reported that the AUC of PLD in plasma was approximately 250-fold higher than that of DOX.[12] Furthermore, the diameter of PLD of approximately 100 μm makes it generally difficult

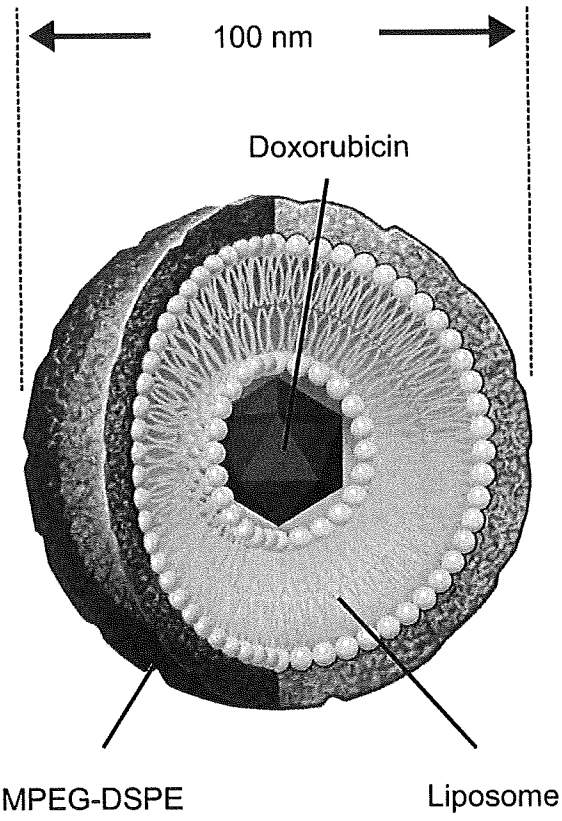

Figure 1. The structure of pegylated liposomal doxorubicin.

to be absorbed into the capillaries. However, tumor tissues have a hypervascular environment compared to normal tissues, and the absence of the basement membrane and of the tight conjunction in the tumor neovessels have to be recognized as possible causes facilitating the extravasation of PLD in tumor tissue. Vaage et al examined the tissue distribution of DOX and PLD in mice with carcinoma, and reported that the AUC of PLD in tumor tissue was approximately 25-fold higher than that of DOX.[13] PLD enables prolonged circulation time and accumulates selectively in carcinoma tissues by intravenous administration, STEALTH® liposomes gradually disintegrate, and doxorubicin is released and metabolized therefore, the metabolic pathway of doxorubicin is the same whether or not the doxorubicin is encapsulated with STEALTH® liposomes. Doxorubicin hydrochloride is metabolized in the liver, and doxorubicinol, the main metabolite, is formed by cytosolic carbonyl reductase. Finally, doxorubicin is formed by deglycosidation. This product is metabolized in the liver and excreted in the urine and feces (bile). The main enzymes that are involved in doxorubicin metabolism are NADPH-dependent aldo-keto reductase and microsomal glycosidase.

Clinical Studies of PLD

Efficacy

The results of phase II and III studies of PLD monotherapy in patients with platinum- and/or taxane-resistant disease are shown in Table 1.[14–26] The response rates of PLD administration at a dose of 50 mg/m^2 every four weeks in 4 phase II studies ranged from 7.7% to 21.0% and the ranges of stable disease (SD) rate and clinical benefit were 40.3% to 51.3% and 57.3% to 61.3%, respectively.[14–23] The response rates in 2 phase III studies were 8.3% and 12.3% with SD rates of 27.7% and 38.5%, respectively, and the clinical benefit was 40.0% and 46.9%.[24–26] The response rates of PLD administration at a dose of 40 mg/m^2 every four weeks in 4 phase II studies ranged from 9.1% to 31.4%, and the ranges of SD rate and clinical benefit were 7.8% to 48.6% and 39.2% to 62.2%, respectively.[16–18,21] The response rate in a phase III study was 15.7% with an SD rate of 42.9%, and the clinical benefit was 58.6%.[26] The time to progression (TTP) ranged from 4 to 19 months with both doses of 40 and 50 mg/m^2. The efficacy of PLD at a dose of 50 mg/m^2 was similar to that at a dose of 40 mg/m^2 (Table 1). The results of a phase III comparative study with topotecan indicated that PLD was more effective in improving survival than topotecan.[24] To be specific, in platinum-resistant disease, the progression-free survival (PFS) and over all survival (OS) were higher with topotecan than with PLD, while in platinum-sensitive disease, in contrast, the PFS and OS were significantly higher with PLD than with topotecan. In 2004, Gordon et al reported long-term follow-up outcomes of patients who were registered in the comparative study that had been done previously.[27] At the time of this evaluation, 87% had died. There was a significant survival advantage for all patients enrolled in this study that the patients who had taken PLD had an 18% reduction in the risk of death. On the other hand, Mutch et al conducted a phase III comparative study with gemcitabine (GEM) that showed no significant differences in PFS and OS between PLD and gemcitabine.[25] Ferrandina et al reported no differences in PFS between PLD and GEM in

Table 1. Response rate in patients with platinum- and/or taxane-resistant disease: Pegylated Liposomal Doxorubicin.

Authors (year)	N	Dose (mg/m²)	RR (%)	SD (%)	Clinical benefit (%)	TTR	Response duration	TTP
Phase II studies								
Muggia (1997)	35	50, q3wk	25.7	NR	NR	5.5 mo	6 mo	5.7 mo
Gordon (2000)	89	50, q4wk	16.9	40.4	57.3	15.4 wk	24.1wk	19.3 wk
Markman (2000)*	44	40, q4wk	9.1	18.2	NR	NR	NR	NR
Campos (2001)*	51	40, q4wk	31.4	7.8	39.2	7.4 wk	NR	5.3 mo
Rose (2001)*#1	37	40, q4wk	13.5	48.6	62.2	NR	NR	4 mo
	39	50, q4wk	7.7	51.3	59.0	NR	NR	4 mo
Lorusso (2004)	17	35, q3wk	18.9	41.2	58.8	12 wk	22.8 wk	28.8 wk
Arcuri (2004)	23	50, q4wk	8.7	NR	NR	NR	3.5 mo	6 mo
Wilailak (2004)	14	40, q3wk	23.1	NR	NR	2 mo	3 mo	6 mo
Chou (2006)*	29	45, q4wk	23.1	34.6	57.7	NR	11.6 mo	5.4 mo
Katsumata (2008)	62	50, q4wk	21.0	40.3	61.3	52d	149d	168d
Phase III studies								
Gordon (2001)	130	50, q4wk	12.3	27.7	40.0	NR	NR	9.1 mo**
Mutch (2007)*	60	50, q4wk	8.3	38.5	46.9	NR	NR	3.6 mo
Ferrandina (2008)#2	70	40, q4wk	15.7	42.9	58.6	11 wk	18 wk	16 wk

Notes: *Including CA125 response, **Progression-free survival, #1Retrospective study, #2Platinum resistant, platinum-free interval <12 mo. Clinical benefit (%): Complete response (%) + partial response (%) + stable disease (%).
Abbreviations: N, number of patients; RR, response rate; SD, stable disease; G, grade. TTR, time to response; TTP, time to progression; Mo, months; Wk, weeks; D, days; NR, not reported.

relapsed patients with a treatment-free interval (TFI) of 12 months or less, but a significant efficacy in OS with PLD compared to GEM (Table 2).[26] From the results of the above phase III studies, PLD was considered to have similar efficacy as other novel drugs on platinum-resistant disease; however, it was more effective at improving the survival rate in patients with recurrent ovarian cancer, including platinum-sensitive cancer, than other drugs.

Safety

PLD is associated with several adverse events, but these events are mild to moderate (Table 3).[14–17,19–26] PLD required fewer dose modifications compared with topotecan and gemcitabine. The superiority of PLD in terms of QOL has been shown.[24–26] PPE, stomatitis, mucositis, and other cutaneous reactions were the most common side effects attributable to PLD. PPE and stomatitis developed in approximately 40% of patients but, grade 2 or higher PPE and stomatitis were found in 19.8% to 31.5% of patients treated with 50 mg/m² of PLD (every 4 weeks), and 2.8% to 15.5% (less than half) of those treated with 40 mg/m² or less of PLD (every 3 to 4 weeks). Grade 2 or higher stomatitis developed in 14% to 38% or more of patients treated with 50 mg/m² of PLD[14,15,23] in contrast, it developed in 8.0% of those treated with 40 mg/m².[16] The results of phase III comparative studies of PLD with topotecan or GEM confirmed that PPE and stomatitis developed significantly in patients treated with 50 mg/m² of PLD compared with those treated with topotecan and GEM, while the incidence of PPE was slightly higher in patients treated with 40 mg/m² of PLD compared with those treated with GEM, and no differences were found in the incidence of mucositis between PLD and GEM.[24–26] These toxicities were usually handled by increasing the cycle length or reducing the dose. On the other hand, PLD induced less hematotoxicity than topotecan and GEM. One quarter of patients who received 50 mg/m² of PLD developed grade 3 or 4 neutropenia, but febrile neutropenia was rarely found. The incidence of thrombocytopenia was even less. Cardiac toxicity was also uncommon. The results of a phase II study in Japan showed PPE in 78% (grade 2 or higher: 51%) and grade 3 or higher neutropenia in 68%, suggesting racial differences.[23]

Table 2. Survival in randomized studies.

	Progression-free survival (median, weeks)		Overall survival (median, weeks)	
Gordon et al. (2001)				
Platinum-sensitive				
PLD (n = 109)	28.9	p = 0.037	108	p = 0.008
Topotecan (n = 111)	23.3		71	
Platinum-resistant				
PLD (n = 130)	9.1	p = 0.733	36	p = 0.455
Topotecan (n = 124)	13.6		41	
Mutch et al. (2007)				
Platinum-resistant				
PLD (n = 96)	3.6*	p = 0.870	12.7*	p = 0.997
Gemcitabine (n = 99)	3.1*		13.5*	
Ferrandina et al. (2008)**				
PLD (n = 70)	16**	p = 0.411	56**	p = 0.048
Gemcitabine (n = 63)	20**		51**	

Notes: *Months. **Patients with treatment-free interval, <12 months.

The first adverse effect seen is an infusion-related reaction that is characterized by flushing, facial edema, headache, back pain, rigors, hypotension, chest/throat tightness and dyspnea. These reactions are seen in 7% to 19% of patients during the first cycle, and are all resolved on the day of onset or the following day.[23,28,29] It has been reported that decreasing the infusion rate reduces the risk of reaction.

There were no treatment-related deaths reported in the 657 patients summarized in Table 3.

Clinical Study of PLD Combined with Other Novel Agents

There may be the potential for synergism between topoisomerase II inhibitors PLD and topoisomerase I inhibitors such as topotecan in platinum-resistant

Table 3. Adverse events: Pegylated Liposomal Doxorubicin.

Authors (year)	N	Dose (mg/m²)	Grade 3–4 (%)		Grade 2–4 (%)	
			Neutropenia	Anemia	PPE	Stomatitis
Phase II studies						
Muggia (1997)	35	50, q3wk	20.0	NR	11.0 (G2)	14.0 (G3/4)
Gordon (2000)	89	50, q4wk	15.7	29.2	31.5	22.5
Markman (2000)	44	40, q4wk	2	NR	12	8
Campos (2001)	71	40, q4wk	1.4	11.3	15.5	NR
Lorusso (2004)#	37	35, q3wk	10.8	0	2.8	0
Arcuri (2004)	30	50, q4wk	23.3	NR	10 (G3/4)	NR
Chou (2006)*	29	45, q4wk	11.9	0	1.5	16.4
Katsumata (2008)	62	50, q4wk	67.6	17.6	51.4	37.8
Phase III studies						
Gordon (2001)	130	50, q4wk	12.1	5.4	23.0 (G3/4)	8.4 (G3/4)
Mutch (2007)*	60	50, q4wk	18.8	2.1	19.8	NR
Ferrandina (2008)#	70	40, q4wk	6.9	5.6	5.6 (G3/4)	NR

Notes: *per cycle, #platinum-resistant = platinum-free interval <12 mo.
Abbreviations: N, number of patients; NR, not reported.

disease,[30,31] and *in vitro* data suggested a potential synergistic interaction between PLD and GEM.[32,33] A median total response rate of 28% and clinical benefit of 72% were demonstrated, with a median TTP of 30+weeks in the combination of PLD and topotecan for platinum-resistant disease (Table 4).[34] These data compare favorably to the data of both drugs administered as a single agent. Combination chemotherapy of PLD and GEM achieved good response rates ranging from 22% to 33%; however, the clinical benefit was between 28% and 61%, which was similar to PLD monotherapy.[35–38] As for hematotoxicity, grade 3/4 neutropenia was slightly higher and grade 2/3 PPE was slightly less (Table 5). The combination of PLD and GEM is an active and acceptably tolerated option for the treatment of patients with platinum-resistant ovarian cancer. These combinations at the chosen dosages seem suitable for this patient population. In a comparison of two studies of combination chemotherapy of PLD and oxaliplatin, the response rates of platinum-resistant disease were 28.6% and 38.5% and the clinical benefit was 71.4% and 76.9%, suggesting higher efficacy compared with PLD monotherapy.[39,40] Furthermore, the response rates for platinum-sensitive disease were 66.7% and 81.5% and the clinical benefit was 82.8% and 100%, showing similar or better efficacy than other platinum combination chemotherapies. The incidence of PPE was low and no marked increase in hematotoxicity was found; consequently, toxicity was considered to be acceptable (Table 4). In patients with platinum-sensitive disease, the combination of PLD and trabectedin significantly improved PFS compared to PLD alone (9.2 months vs. 7.5 months, HR = 0.73, p = 0.0170), on the other hand, no significant difference in PFS was found in patients with platinum-resistant disease.[41] A RCT of the combination of PLD and canfosfamide and PLD alone was conducted in patients with platinum-resistant disease. Consequently, the median PFS was significantly longer for canfosfamide/PLD than PLD alone. Canfosfamide may ameliorate the adverse events of stomatitis and PPE associated with PLD.[42]

While these initial phase II trials are encouraging, they contain a relatively small number of patients, and no RCTs have been performed to date to confirm the benefit of combination therapy with PLD over mono therapy with PLD in the platinum-resistant population.

Table 4. Phase II studies of PLD-combination in platinum- and taxane-pretreated patients.

Author (year)	No. of pts	Dose/Schedule	RR (%)	Clinical benefit (%)	Response duration (wk)	Toxicity(%)	
						G3/4 neutro	PPE
Verhar-Langereis (2006)	27*	P: 30 mg/m^2 (d1) T: 1 mg/m^2/d (d1–5) q3wk	28.0*	72.0*	NR	70.4	3.7 (G3)
Katsaros (2005)	32	P: 30 mg/m^2 (d1) V: 30 mg/m^2 (d1) q3wk	43.3	70.0	NR	12.5	6.3 (G3/4)
Nicoletto (2005)	43	P: 30–35 mg/m^2 (d1) O: 70 mg/m^2 (d1) q4wk	66.7** (28.6*)	82.8** (71.4*)	NR	9.3	4.7 (G2)
Recchia (2007)	40	P: 40 mg/m^2 over 2 days O:120 mg/m^2 over 2 days q3wks	81.5** (38.5*)	100** (76.9*)	NR	37.5	10.0 (G2)

Notes: *platinum-resistant patients. **platinum-sensitive patients.
Abbreviations: PLD, pegylated liposomal doxorubicin; T, topotecan; V, vinorelbine; O, oxaliplatin; RR, response rate; G, grade; Neutro, neutropenia; PPE, palmar-plantar erythrodysesthesia; NR, not reported.

Table 5. Phase II studies of PLD + GEM in patients with platinum-resistant disease.

Author (year)	No. of pts with pl-resist	Dose/Schedule	RR (%)	Clinical benefit (%)	Response duration (wk)	Toxicity (%)	
						G3/4 neutro	PPE
D'Agostino	38	P: 30 mg/m^2 (d1) q3wk G: 1000 mg/m^2 (d1,8)	25.0	61.1	18.0	35.6	25.7 (G2/3)
Ferrandina (2005)	66	P: 30 mg/m^2 (d1) G: 1000 mg/m^2 (d1,8) q3wk	21.6	53.6	20.5	28.8	14.4 (G3)
Skarlos (2005)	37	P: 25 mg/m^2 (d1) G: 650 mg/m^2 (d1,8) q4wk	22.0	27.5	2.7*#	18.9	5.4 (G2/3)
Petru (2006)	31	P: 30 mg/m^2 (d1) G: 650 mg/m^2 (d1,8) q4wks	33.0	46.7	3.0#	26.0	16.0 (G2/3)

Notes: *Time to failure. #Months
Abbreviations: PLD, pegylated liposomal doxorubicin; GEM, gemcitabine; PI-resist, platinum resistant or refractory; RR, response rate; G, grade; Neutro, neutropenia; PPE, palmar-plantar erythrodysesthesia.

Patient Preference and Place in Therapy

Patients with platinum-resistant disease have a poor outcome, and most would like to prolong their survival with relieved symptoms and improved QOL. The effects of drugs on these patients are similar, and it is usually difficult to cure recurrent disease with one drug. Based on the performance status (PS), toxicity persisting from the initial treatment, and the bone-marrow function of an individual patient, the drugs that can be administered should be discussed with the patient. Since the results of phase II studies of PLD showed good outcomes,[14–23] a large-scale study of initial chemotherapy with PLD was performed.[6] However, polychemotherapy of PLD associated with paclitaxel/carboplatin (TC) therapy and sequential doublet combination with carboplatin/PLD and TC therapies did not improve survival compared with TC therapy. Consequently, at present, PLD is regarded as a key drug for TC-refractory and resistant ovarian cancer with no cross-resistance to paclitaxel or carboplatin. PLD achieves good response rates, and many patients maintain long-lasting SD, which is one of the advantages. In addition, the clinical benefit is high in platinum-resistant disease and PLD is thus considered to be the first option. Since PLD has mild hematotoxicity, it is appropriate for patients with early recurrence after the completion of TC therapy, as well as heavily pretreated patients. It has also been reported that PLD did not induce multidrug resistance,[43,44] which is one of the reasons for selecting PLD as the first option for patients with platinum-resistant disease. On the other hand, in a crossover study of PLD and GEM, PPE redeveloped when GEM was administered after patients had been treated with PLD.[25] This result suggests that much of the PPE observed in the PLD/GEM cross-over group may be the result of latent or delayed toxicity secondary to initial PLD treatment.

After explaining the characteristics of PLD, that PLD is safer for heavily pretreated patients than topotecan and GEM due to mild bone-marrow toxicity, but that PPE, stomatitis and mucositis frequently develop, the patient's wishes are considered, and the drugs are finally selected. The 1-hour infusion schedule every 4 weeks makes PLD easy to administer.

Conclusions

PLD (Doxil®) is doxorubicin HCl encapsulated in long-circulating STEALTH® liposomes. Although

doxorubicin has been associated with a poor response in recurrent ovarian cancer, PLD is active, and is an emerging option for patients with platinum-refractory and -resistant disease. A phase II study has recently been completed in Japan, and the response rate for recurrent platinum-resistant ovarian cancer was 21.0%, the SD rate was 40.3% and the clinical benefit was 61.3%, which were similar to those in studies in Europe and the United States.[23]

One of the toxicity characteristics of PLD is a low incidence and severity of hematotoxicity such as neutropenia.[14–17,19–23] Also, Growth factor support are not frequently required in PLD, leading to advantages in healthcare costs. Overall, PLD proved to be preferable to topotecan and gemcitabine due to negligible hematologic toxicities.[24–26] On the other hand, another characteristic of PLD is that the incidence of nonhematotoxity, including PPE, stomatitis and mucositis, is high at FDA-approved doses and schedules. PPE, also referred to as hand-foot syndrome, is a cutaneous reaction typically involving the palms of the hands and the soles of the feet. Although the cause of PPE is unknown, it is theorized that the long half-life and small size of the liposomes result in localization of the drug in areas of skin trauma. The incidence of grade 2 or higher PPE, which reduces the QOL, ranged from 20% to 50%; therefore, these adverse events should be appropriately treated during PLD administration. The severity of PPE can be decreased by dose modification, either decreasing the dose or lengthening the dosing interval. Dose modification often allows continued treatment without recurrence of PPE. Various pharmacologic approaches have been used, including topical dimethyl sulfoxide, pyridoxine (B6), and topical or systemic steroids.[45] We are examining the effects of cooling the wrists and ankles during infusion to prevent PPE.[46]

Based on a review of previous studies,[14–26] there are no differences in efficacy between 50 and 40 mg/m^2 of PLD therefore, a dose of 40 mg/m^2 is preferable in patients with platinum-resistant disease to reduce adverse events. To scientifically confirm the dosage, the Japanese Gynecologic Oncology Group (JGOG) plans to conduct a randomized comparative study of 50 and 40 mg/m^2 of PLD in patients with recurrent platinum-resistant ovarian cancer (TFI < 6 months) (accrual of 350 patients, primary endpoint: PFS, secondary endpoints: OS, adverse events).

A rational approach to combining PLD with other drugs should take the slow accumulation and delayed peak of PLD in tumors into consideration. When combined with other useful agents, the lower dose of PLD (30 to 35 mg/m^2) with a 3-week schedule may reduce severe PPE and stomatitis with negligible effects on the level of DI and the therapeutic efficacy. The response rate of combination chemotherapy of 30 mg/m^2 of PLD and 650 to 1000 mg/m^2 of GEM exceeded 20%, and the clinical benefit was similar to that of PLD monotherapy at 50 mg/m^2.[35–38] As for toxicity, hematotoxicity slightly increased but was easy to control, and nonhematotoxicity, such as PPE, slightly decreased. Furthermore, it was confirmed in a study of combination chemotherapy of topotecan,[34] vinorelbine,[47] oxaliplatin,[39,40] trabectedin,[41] or canfosfamide[42] with PLD (30 mg/m^2) that the response rate and clinical benefit were improved with reduced PPE. Drugs such as PLD with specific nonhematotoxicity and low hematotoxicity should be administered by combination chemotherapy rather than monotherapy to reduce the specific toxicity. In patients with platinum-sensitive disease with a TFI of 6 to 12 months (gray zone), PLD was more effective than topotecan or GEM.[24] In addition, in patients with platinum-sensitive disease, the response rate of PLD + GEM was 53.7%, the clinical benefit was 90.2% and the platinum free interval was simultaneously prolonged. Recently, in patients with platinum-sensitive relapsing ovarian cancer, the combination of PLD-carboplatin was not inferior to paclitaxel-carboplatin in terms of PFS, and was even found to be significantly superior.[48] The results of two other studies showed that combination chemotherapy of PLD and oxaliplatin achieved similar efficacy and safety as those of paclitaxel/carboplatin or more. Therefore, the combination chemotherapy of PLD and platinum is one of the options for patients with platinum-sensitive disease with a TFI of 12 months or less.

Disclosures

The authors report no conflicts of interest.

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特集 卵巣がん手術に必要な知識と手技

1．卵巣がん手術のoverview

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要旨

卵巣がんの初回治療は手術療法で，進行期決定と腫瘍減量が主な目的である．初回手術にてoptimal surgeryを目指すことが治療のファーストステップとして非常に重要であり，その後の予後を最も左右する．また，sub-optimal surgeryや試験開腹に終わらざるを得ない進行症例や再発症例に対しては，二次的手術の有用性に関しての検討が進められている．外科的治療は術者の技量や手術アプローチが異なるため，その客観的評価や技術の均てん化は困難な課題であるが，今後も適切なRCTを積極的に進めていくことが卵巣がん予後改善のために必須である．

Key Words primary debulking surgery（PDS），interval debulking surgery（IDS），secondary debulking surgery（SDS）

卵巣がんの推定罹患数は年間約8,000人，死亡数約4,500人と増加を示している．自覚症状に乏しく早期発見が困難なため，大半は進行がんで発見される．治療は外科的手術療法と抗がん剤による化学療法が密接に連動する複合療法として行われる．初回治療は手術療法で，この目的は，①進行期決定（surgical staging）：卵巣がんの進展様式に準じたInternational Federation of Gynecology and Obstetrics（FIGO）staging systemにて決定され，正確な進行期が最も予後を反映する．②初回腫瘍減量術（primary debulking surgery）：進行がんでは，初回術後残存腫瘍径が化学療法効果を予言する．しかしながら，進行がんの割合が約60%と高く，このため初回腫瘍減量術でoptimal disease（1 cm未満の残存腫瘍）にできる確率は50～60%にとどまる．このためinterval debulking surgery（IDS）が実地臨床に導入され，さらにIDSを前提とした術前化学療法の臨床試験も進められている．また，化学療法低感受性腫瘍である明細胞腺癌と粘液性腺癌では，標準レジメンが科学的に確立されておらず，初回手術での完全摘出の成否が予後を最も左右する．これら難治性腺癌では，他の上皮性悪性腫瘍以上に予後改善のために初回手術の完遂度が要求される．

若年者に好発する胚細胞性悪性腫瘍は抗がん剤に高感受性であり，患側付属器の摘出にとどめ（妊孕性温存手術），術後化学療法はブレオマイシン，エトポシドとシスプラチンの併用療法（BEP療法）が標準的である．

以上を中心に，本稿では卵巣がん手術の現況と今後の展望について概説する．

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上皮性悪性卵巣腫瘍

2007年に改訂された『卵巣がん治療ガイドライン』に掲載されている手術療法に関する用語の定義を**表1**に示す[1].

1) 初回手術

基本術式とstaging laparotomy，さらに進行症例の場合，primary debulking surgery（PDS）が行われる.

基本術式とstaging laparotomy

基本術式には両側付属器摘出術・子宮摘出術・大網切除術が含まれ，staging laparotomyとして腹腔細胞診・腹腔内各所の生検・後腹膜リンパ節（骨盤・傍大動脈）郭清もしくは生検が行われる．正確な進行期と組織型の診断が予後を反映するため，正確な術式の遂行が要求される．後腹膜リンパ節の郭清/生検はその診断的意義は確立されているものの，系統的後腹膜リンパ節郭清術に対しての治療的意義は確立されていない．しかし，系統的後腹膜リンパ節郭清術を行ったpT1期症例のリンパ節転移率は5～25%と報告されており，IIIc期に分類される可能性も少なくない[2]．このため，後腹膜リンパ節の取り扱いに関しては術中の視診や触診のみではなく，系統的な郭清/生検が必要である.

初回腫瘍減量術（primary debulking surgery：PDS）

進行症例の初回治療として行われる病巣の完全摘出または可及的な最大限の腫瘍減量を目的とした手術である．周知のように手術の完遂度が手術に関連する最も重要な予後因子で，術後残存腫瘍径が予後に相関することが複数報告されている[3)~5)]．optimal surgeryの定義に関しては，過去の報告などにより残存腫瘍径を1 cm未満とする手術を考えるのが標準的であろう．初回手術での腫瘍減量の成否がその後の化学療法の効果，さらには予後を決定するため，必要であれば腹膜・腸管等の合併切除も積極的に行い，optimal diseaseを目指す．ただし，化学

表1 手術療法に関する用語の定義

基本術式	両側付属器摘出術・子宮摘出術・大網切除術
staging laparotomy	進行期の確定に必要な手技を含む手術
exploratory laparotomy（試験開腹術）	原発腫瘍の摘出が困難で生検と最小限の進行期確認にとどめる手術
debulking（cytoreductive）surgery（腫瘍減量術）	病巣の完全摘出または可及的に最大限の腫瘍減量に必要な手技を含む手術
primary debulking（cytoreductive）surgery（PDS, PCS）	初回治療として病巣の完全摘出または可及的に最大限の腫瘍減量を行う手術
interval debulking（cytoreductive）surgery（IDS, ICS）	初回手術後の残存腫瘍に対し，一連の初回化学療法中に病巣の完全摘出または可及的に最大限の腫瘍減量を行う手術
secondary debulking（cytoreductive）surgery（SDS, SCS）	初回化学療法終了時に認められる残存，あるいは再発腫瘍に対しての病巣の完全摘出または可及的に最大限の腫瘍減量を行う手術
second look operation（SLO）	初回手術後の臨床的寛解例に対する化学療法の効果判定を目的として行われる手術 その際発見された再発腫瘍を切除するのはSLO/SDSと表現

〔文献1）より引用〕

療法低感受性腫瘍である明細胞腺癌や粘液性腺癌では，現在のところ有効な標準レジメンが科学的に確立されておらず，初回手術での完全摘出の成否が最も予後を左右する．Takanoらは，III, IV期明細胞腺癌においては肉眼的完全摘出が行われることで予後改善が得られると報告している[6]．これら化学療法低感受性腫瘍での予後改善には，手術の完遂度が最も重要であることに留意すべきである．

2）二次的手術

interval debulking surgery（IDS）

卵巣がん治療ガイドラインでは“初回手術後の残存腫瘍に対し，一連の初回化学療法中に病巣の完全摘出または可及的に最大限の腫瘍減量を行う手術”と定義されている．卵巣がん治療は前述のようにPDSでoptimal diseaseを目指すのが大原則である．その一方で卵巣がん症例の約60%はIII期以上の進行症例のため，PDSでのoptimal surgery達成率は50～60%前後にとどまっているのが現実であり，IDSの検討も重要課題である[7][8]．IDSの対象となるのはPDSにてsub-optimal surgeryとなった症例とneoadjuvant chemotherapy（NAC）症例である．しかし，いずれにおいてもIDSの有用性に関して現在のところ明らかなエビデンスは存在しない．PDSにてsub-optimal surgery後のIDSに関しての報告では，EORCT試験とGOG152が代表的である[9][10]前者では無増悪生存期間（PFS），全生存期間（OS）ともにIDSによる予後改善が報告されているのに対して，後者ではPFS, OSのいずれにも有意差はなく，IDSの有用性を否定する結果となっている．この結果の相違に関しては，登録症例の進行期のばらつき，PDSでの残存腫瘍径の違いと術式のqualityの問題，化学療法レジメンの相違など様々な条件の違いが指摘されている．IDSの有用性を明らかにするためにも今後術式も含めた適切な条件設定のもとでのさらなる検証が求められる．現時点の実地臨床においてIDSの適応を検討するにあたっての最低条件としては，

①化学療法に奏効しIDSにて残存腫瘍の完全摘出が期待できる

②良好なPSを維持している

③IDS後に速やかに化学療法の再開が可能である

④十分なインフォームド・コンセントが得られている

…などが挙げられる．これらを踏まえ，慎重にその適応を決定すべきである．

NACの対象は，明らかな進行症例やそれに伴う胸腹水等でPSが低下した症例などで，これらの症例ではPDSにてsub-optimal surgeryや試験開腹になる可能性が高く，また手術侵襲による術後合併症にて化学療法の開始遅延が懸念される．NACに引き続くIDSの目的は，NACを行うことによりPSを改善し，chemical debulking後のIDSでのoptimal surgery率の向上，術後合併症の減少などにより進行がんの予後改善を期待することである．前述のように有用性に関して明確なエビデンスは存在しないが，NACの効果に期待せざるを得ない進行症例も存在しているのも事実であり，NCCNガイドラインでも明らかな切除不能症例に対して細胞診結果に基づいたNAC施行を許容している[11]．Bristowらは計48の報告についてレビューを行った[12][13]．そのすべてが後方視的検討であるが，NACの有用性に関して否定的な見解を述べている．その他の後方視的検討でも，PFSの延長やQOL改善の有用性が一部に指摘されているものの，OS改善に関しての報告は少ない．前方視的検討としては，EORTCにてNACに関するRCT（EORTC55971）が行われ，2008年のIGCSでその結果の一部が報告された．それによると，標準的治療法であるPDSと比較して，生存に関して有意差はなかったものの，周術期の副作用などQOLの面からIIIc・IV期に

おけるNACの有用性を支持しており，今後の動向が注目される結果となった．また，わが国では，JCOG0206（III期/IV期卵巣がん・卵管がん・腹膜がんに対する術前化学療法のfeasibility study）を経て，現在JCOG0602（III期/IV期卵巣がん・卵管がん・腹膜がんに対する手術先行治療vs化学療法先行治療のランダム化比較試験）が進行中である．これらの結果によってNACの方向性が明確にされる期待がある．したがって現時点では，NAC後にIDSを行う方法はあくまで実験的アプローチであること，原発巣や進行期，組織型などが不明確のまま治療を行うリスクや，NACに奏効しない場合は標準治療の機会さえ奪ってしまう可能性があることなどに留意し，安易な施行は避け，その適応には慎重を期さなければならない．

secondary debulking surgery（SDS）

卵巣がん治療ガイドラインでは“初回化学療法終了後に認められる残存，あるいは再発腫瘍に対して病巣の完全摘出または可及的に最大限の腫瘍減量を行う手術”と定義されている．現実的な対応の多くは再発症例であろう．再発卵巣がんにおける治療の第一選択は化学療法である．しかし有用なsecond-line chemotherapyが確立されておらず，根治も困難な現状では，予後改善の一方法としてSDSの検討も進められている．IDS同様，現在のところ再発がんに対するSDSの有用性を示したRCTは存在していない．しかし，一定の条件を満たした症例に関しては，SDSの有用性を示唆する報告も複数認められており[14)~16)]，NCCNのガイドラインでも無病期間（disease-free interval:DFI）が6カ月以上かつ局所再発もしくは体積の小さい再発腫瘍の場合，SDSを推奨している[11)]．多くの報告から，前治療からDFIが6～12カ月以上，最大残存腫瘍径1 cm以下などがSDSの適応条件である．OndaらはSDSを施行した44例に対して多変量解析を行い，SDSによる予後改善因子として，①DFI 12カ月以上，②肝転移なし，③単発性腫瘍，④最大再発腫瘍径6 cm未満を挙げ，これら4因子のうち3因子以上を有する症例に対してはSDSを積極的に考慮すべきと報告している[15)]．また，Chiらは DFI 6カ月以上で，画像診断にて摘出可能と判断し，SDSを施行した再発がん153例を対象に再発後の予後因子について検討を行った．多変量解析の結果，再発腫瘍の数，optimal surgeryの可否，DFIなどが独立した予後因子である報告をした．さらにこれらの結果をもとに再発卵巣がんに対するSDSの適応基準を提唱している（**表2**）[14)]．ただしこれらを満たす症例においても，化学療法より予後良好であると証明される明確なエビデンスは存在せず，今後さらなる前方視的な検証が必要である．また，この基準以外にも，十分なインフォームド・コンセントが得られていることはもちろん，良好なPSを維持しSDSによりQOLを低下する可能性が少ないことなどが，SDSの適応を決めるうえでの必要条件として挙げられるであろう．

表2　DFIと再発腫瘍数に基づいたSDSの推奨基準

DFI（月）	単発腫瘍	複数 非癌性腹膜炎	複数 癌性腹膜炎
6～12	推奨	検討	非推奨
12～30	推奨	推奨	検討
＞30	推奨	推奨	推奨

DFI:disease free interval
〔文献14）より改変〕

second look operation（SLO）

“初回手術後の臨床的寛解例に対する化学療法の効果判定を目的として行われる手術”と定義される．治療の効果判定としては最も正確に評価できる方法であるが，治療的意義に乏しく，予後への貢献はない．過去にはわが国でも頻繁に行われていたが，現在はルーチンには行われず，卵巣がん治療ガイドラインにおいても現時点では臨床試験以外には適応されないと記載さ

れている．

胚細胞性悪性腫瘍

本腫瘍は，全卵巣がんの5%に満たないまれな腫瘍であるが，10～20歳代の若年層に好発し，未分化胚細胞腫（10～15%に両側発生）以外はほとんどが片側性であるなどの臨床的特徴を有しており，妊孕性温存治療を考慮する機会が多い．本腫瘍はVAC（vincristine/actinomycin-D/cyclophosphamide）療法や放射線治療からシスプラチン（CDDP）をベースとした化学療法の導入により奏効率が向上し，その予後は飛躍的に改善した[17)~19)]．現時点では，ブレオマイシン，エトポシド，シスプラチンの併用療法（BEP療法）が標準レジメンとされている[1)20)21)]．全生存率は80%以上と良好で，進行例でも必要であれば妊孕性温存手術を行うことが標準的となっている．また，本腫瘍はまれであることなどよりランダム化比較試験が困難で，高いエビデンスレベルに基づいた管理方法が構築できていない点にも留意すべきである．手術療法においては，患（片）側付属器摘出術が標準的であるが，妊孕性温存が必要ない女性では上皮性悪性腫瘍に準じて子宮・両側付属器摘出，大網切除，後腹膜リンパ節生検，可及的転移巣摘出が行われる．後腹膜リンパ節や大網に関しては，予後への影響に一定の見解が得られていないため[22)]，生検もしくは部分切除にとどめる．ただし，未分化胚細胞腫に関してはリンパ節転移が比較的高いので注意が必要である[23)]．また，腫瘍減量が予後に貢献するかどうかは不明であり，術後早期の化学療法開始が重要となる．このため，化学療法開始に影響を及ぼすような侵襲性の高い術式は極力避けるべきで，転移・播種巣は侵襲を広げない範囲の摘出にとどめる．妊孕性温存が必要な症例は，進行期にかかわらず患側付属器摘出と術後進行期決定に必要最低限度の生検を行う．ここでも，術後の癒着や残存卵巣機能不全などによる不妊症を惹起しないよう心がけねばならない．また，SLOや二次的腫瘍縮小術に関しては，その有用性に関して議論が分かれており，現在のところ一定の見解が得られていない[22)24)25)]．

おわりに

卵巣がんの患者の予後は，手術療法と化学療法の進歩に伴い，少しずつながら改善を示している．手術療法では，初回手術にてoptimal surgeryを目指すことが治療のファーストステップとして非常に重要であり，その後の予後を最も左右する．さらに，化学療法との有効な組み合わせとしてsub-optimal surgeryや試験開腹におわらざるを得ない症例や再発症例に対して，IDSやSDSの有用性や位置づけをさらに明確にしていく必要がある．外科的治療は化学療法や放射線療法などの内科的治療に比べ，術者の技量や手術アプローチが異なる．その客観的評価や技術の均てん化は困難な課題であるが，今後も手術療法を含めた適切なRCTを積極的に進めていくことが卵巣がん予後改善のために必須である．米国“Society of Gynecologic Oncology（SGO）”では，新鮮献体を用いて手術療法におけるperitoneal stripping，腸管切除，上腹部外科手術等の手術手技の教育を行っている．わが国で直ちにこれを導入することは無理としても，このような教育方法の事実を理解し，日々の臨床のなかで研鑽を積む必要がある．

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