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REVIEW

Emerging Pharmacotherapies in Ovarian Cancer: Focus on Pegylated Liposomal Doxorubicin

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Abstract: Pegylated liposomal doxorubicin (PLD) is doxorubicin encapsulated in MPEG-DSPE coated liposomes. PLD shows good response rates and maintains long-lasting stable disease (SD) in patients with recurrent ovarian cancer, and its clinical benefit is also high in platinum-resistant disease. PLD is considered the first option for platinum-resistant disease. A number of adverse events are associated with PLD. Hematotoxicity is generally milder than with topotecan or gemcitabine, especially in heavily pretreated patients, but PLD has characteristic nonhematotoxicities, such as palmar-plantar erythrodysesthesia (PPE), stomatitis, mucositis, and other cutaneous reactions. As for platinum-sensitive disease, non-inferiority of PLD-carboplatin combination in terms of progression-free survival (PFS) and tolerance, but with different toxicity, compared to paclitaxel-carboplatin was reported. However, it may be too early to judge the utility of PLD in combination with other agents because only few studies have been conducted and provided results to evaluate the efficacy of these. Further prospective studies are necessary.

Keywords: pegylated liposomal doxorubicin, chemotherapy, ovarian cancer

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Introduction

The standard primary treatment for ovarian cancer is radical surgery with maximal tumor reduction and combination chemotherapy with carboplatin and paclitaxel. Though more than half of the patients with epithelial ovarian cancer are discovered as advanced cancer, approximately 75% of patients achieve complete clinical remission after the initial treatment, because it is generally sensitive to first-line chemotherapy. However, most patients experience recurrence, which results in death as chemo-resistant disease. Progression-free survival (PFS) of advanced ovarian cancer patients with optimal residual disease range from 18 to 24 months, while it is around 18 months in those with suboptimal residual disease.[1–5] In the treatment of recurrent cancer, factors to consider include treatment-free interval (TFI), recurrent tumor diameter, continued toxicity from the previous chemotherapy, and increased CA125. TFI is the most important factor when selecting anticancer agents or regimens of chemotherapy, because the longer the achieved TFI, the higher the response rate.[6,7] If the TFI is 6 months or longer, the tumor is considered to be sensitive to the previous chemotherapy with platinum agents, but if the TFI is shorter than 6 months, the tumor is considered to be resistant to those. However, a TFI of 6 to 12 months is considered a grey zone, and more careful consideration is required when selecting anticancer agents or regimens in such cases. Based on the results of randomized controlled trials (RCT) and meta-analyses, the recommended treatment for patients with a TFI of 12 months or longer is carboplatin-combination therapy, such as carboplatin/paclitaxel, carboplatin/gemcitabine, and carboplatin/pegylated liposomal doxorubicin (PLD) (Doxil®).[8–10] For patients with a TFI of 6 to 12 months, a clear management method for selecting anticancer agents or regimens is not established yet. On the other hand, for patients with a TFI shorter than 6 months, a drug that does not have cross-resistance with the previous regimen (paclitaxel and/or carboplatin) must be selected. It is not feasible to completely cure recurrent disease. The goal of the therapy is to delay progression, relieve symptoms and improve the QOL. Monotherapy is generally selected to avoid excessive toxicity and deterioration of the QOL. PLD, topotecan, and weekly paclitaxel are approved by the Food and Drug Administration (FDA), and gemcitabine (GEM), oral etoposide, and docetaxel can also be used. In Japan, irinotecan (CPT-11) is also widely selected. Topotecan and GEM are highly hemotoxic. On the other hand, PLD has characteristic non-hemotoxic side effects such as palmar-plantar erythrodysesthesia (PPE) and stomatitis, and these may occasionally become serious and reduce the QOL. Concerning chemotherapy, especially against recurrent disease, the characteristics of the anticancer agents including their toxicity must be fully understood, and agents should therefore be changed as necessary depending on the circumstances while assessing their effect and toxicity. PLD was approved as treatment for chemo-refractory and chemo-resistant epithelial ovarian cancer by the FDA in 1999 and by the European Medicines Evaluation Agency in 2000, and has been used worldwide as the first option for patients with chemo-refractory and chemo-resistant epithelial ovarian cancer. Clinical trials investigating combination therapy including PLD as first line chemotherapy for advanced ovarian cancer, or as 2nd/3rd line chemotherapy for relapsed platinum-sensitive cases are recently conducted.

Pharmacokinetic Profile of PLD

PLD consists of doxorubicin (DOX) encapsulated in N-(carbonyl-methoxypolyethylene glycol 2000)-1, 2-distearoyl-sn-glycero-3-phosphoethanolamine sodiumsalt (MPEG-DSPE)-coated liposomes (STEALTH® liposomes) (Fig. 1). Liposomes have the advantage of biocompatibility and versatility of formulation for intravenous use. However, liposomes also have the characteristic disadvantage of rapid uptake by the reticuloendothelial system (RES) and removal from the circulatory system. It is therefore difficult to sustain the drug in the circulatory system for a long time, and reduces the amount of drug that reaches the tumor. MPEG-DSPE is a hydrophilic material that characteristically suppresses the RES uptake. Therefore, prolonged circulation time of STEALTH®

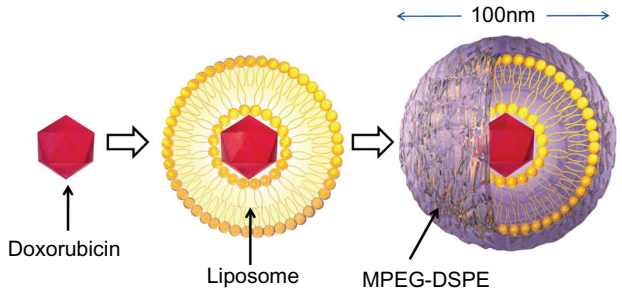

Figure 1. The structure of pegylated liposomal doxorubicin.

liposomes without rapid uptake by RES is achieved, and PLD has made prolonged delivery of DOX with prolonged circulation time possible. The diameter of PLD is approximately 100 μm, a size that is generally difficult to pass through capillaries. However, tumor tissues usually have a hypervascular environment compared to normal tissues, and the absence of a basement membrane and tight conjunctions in tumor neovessels is recognized as possible causes facilitating the extravasation of PLD into tumor tissue. Gabzon et al performed a pilot clinical study to investigate the pharmacokinetics of PLD compared to that of free (unencapsulated) DOX, and reported that the AUC of PLD in plasma was approximately 250-fold that of DOX.[11] Vaage et al investigated the tissue distribution of DOX and PLD in a mouse carcinoma model, and reported that the AUC of PLD in tumor tissue was approximately 25-fold that of DOX.[12]

PLD enables prolonged circulation time and accumulates selectively in carcinoma tissues by intravenous administration, the STEALTH® liposomes gradually disintegrate, and DOX is released and metabolized. The metabolic pathway of DOX is the same as that of free DOX, and is metabolized in the liver and excreted in the urine and feces (bile).

Clinical Profile of PLD

Toxicity

PLD is associated with several adverse events, but these events are mild to moderate. It is generally well tolerated, but PLD has some characteristic toxicities. Compared to doxorubicin, PLD showed significantly reduced cardiotoxicity, but similar efficacy in the past phase III study of first-line chemotherapy for metastatic breast cancer.[13] Nausea, vomiting, and alopecia are also suppressed, but PPE, stomatitis and mucositis showed a higher incidence with PLD than with doxorubicin. PPE and stomatitis are the most common and characteristic nonhematotoxicities of PLD and these are also the most common dose-limiting toxicities of PLD. PPE and stomatitis developed in approximately 40% of patients.[14–26] These adverse events are usually mild to moderate, but if they become serious, QOL is reduced and it is difficult to continue the treatment. Therefore, these should be appropriately treated during PLD administration. It seems that these adverse events tend to appear mostly in early treatment cycles. Comparison between patients treated with 50 mg/m^2 PLD (every 4 weeks) and those treated with 40 mg/m^2 or less PLD (every 3 to 4 weeks) in past studies showed a higher incidence of grade 3/4 PPE among those treated with 50 mg/m^2 PLD (10%–28.6%) than those treated with 40 mg/m^2 or less PLD (0%–8.3%) (Table 1). These results suggest that the frequency of PPE is dependent on the dosage of PLD. As for stomatitis, the same tendency was seen in past studies, but the difference between 50 mg/m^2 PLD and 40 mg/m^2 PLD is smaller than with PPE. These toxicities were usually handled by prolonging the cycle length or reducing the dose. To reduce the incidence and severity of PPE,

Table 1. Adverse events of Pegylated Liposomal Doxorubicin in phase II/III studies.

	N	Dose (mg/m^2)	Grade 3–4 (%)			Grade 3–4 (%)	
			Neutropenia	Anemia	Thrombocytopenia	PPE	Stomatitis
Phase II studies							
Muggia (1997)	35	50, q3wk	20.0	NR	NR	28.6	14.3
Gordon (2000)	89	50, q4wk	15.7	29.2	2.2	20.2	14.6*
Markman (2000)	44	40, q4wk	2	NR	0	0	0
Campos (2001)	71	40, q4wk	1.4	11.3	1.4	8.3***	4.2**
Lorusso (2004)	37	35, q3wk	10.8	0	0	2.7	0*
Arcuri (2004)	30	50, q4wk	23.3	NR	3.3	10	10**
Chou (2006)	29	45, q4wk	11.9	0	0	0	0.7
Katsumata (2009)	62	50, q4wk	67.6	17.6	6.8	16.2	8.1
Phase III studies							
Gordon (2001)	130	50, q4wk	12.1	5.4	1.3	23.0	8.4
O'Byrne (2002)	105	50, q4wk	6	2	NR	16	10
Mutch (2007)	60	50, q4wk	18.8	2.1	5.2	10.4	3.1**
Ferrandina (2008)	70	40, q4wk	6.9	5.6	0	5.6	2.8**

Notes: *Stomatitis+Mucositis, **Mucositis, ***Cutaneous

such pharmacologic approaches as topical dimethyl sulfoxide, pyridoxine (vitamin B6), and topical or systemic steroids, as well as regional cooling (wrists and ankles), behavior restrictions such as avoiding tight clothing, vigorous exercising, rubbing of the skin, hot baths/showers, etc., has been examined.[27,28] As for regional cooling, there are still various opinions about its efficacy and the evidence is not established yet.[29,30] Further prospective studies are necessary. We are examining the effects of cooling the wrists and ankles during infusion to prevent PPE. Infusion-related reactions are also characteristic adverse events of PLD. The major symptoms are 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 resolve on the day of onset or the following day.[22,31,32] It has been reported that a decrease in the infusion rate reduces the risk of reactions. Concerning other nonhematotoxicities, reduced cardiotoxicity, the absence of alopecia and minimal nausea have been reported in many past studies.[13–26] As far as hematotoxicity is concerned, PLD induced myelosuppression less frequently. Most phase II studies also showed grade 3/4 neutropenia in fewer than 20% of patients.[14–22] In the past phase III studies comparing PLD with topotecan or GEM, grade 3/4 neutropenia was found in 6.9% to 18.8% of patients treated with PLD (50 mg/m^2, day 1, every 4 weeks), 77% of those treated with topotecan (1.5 mg/m^2, day 1–5, every 3 weeks), and 22.5% to 38.4% of those treated with gemcitabine (1000 mg/m^2, day 1, 8, every 3 weeks or 1000 mg/m^2, day 1, 8, 15, every 4 weeks).[23–25] Grade 3/4 anemia and thrombocytopenia, respectively, were found in fewer than 6% of patients treated with PLD, approximately 30% of those treated with topotecan, and fewer than 7% of those treated with GEM. No treatment-related deaths were reported among the 762 patients summarized in Table 1.

Efficacy

Platinum-resistant disease

In case of chemotherapy for platinum- and/or taxane-resistant disease, monotherapy is generally selected. The results of past phase II and III studies of PLD monotherapy in patients with platinum-resistant disease are shown in Table 2.[14–26,33] The response rates of PLD administration at a dose of 50 mg/m^2 every 4 weeks ranged from 7.7% to 25.7%, the clinical benefit ranged from 40.3% to 61.3%, and time to progression (TTP) ranged from 3.1 to 9.1 months. The response rates of PLD administration at a dose

Table 2. Response rate of Pegylated Liposomal Doxorubicin in patients with platinum- and/or taxane-resistant disease.

Authors (year)	N	Dose (mg/m^2)	RR (%)	SD (%)	Clinical benefit (%)	TTP
Phase II studies						
Muggia (1997)	35	50, q3wk	25.7	NR	NR	5.7 mo
Gordon (2000)	89	50, q4wk	16.9	40.4	57.3	19.3 wk
Markman (2000)*	44	40, q4wk	9.1	18.2	NR	NR
Campos (2001)*	51	40, q4wk	31.4	7.8	39.2	5.3 mo
Rose (2001)*#1	37	40, q4wk	13.5	48.6	62.2	4 mo
	39	50, q4wk	7.7	51.3	59.0	4 mo
Lorusso (2004)	17	35, q3wk	18.9	41.2	58.8	28.8 wk
Arcuri (2004)	23	50, q4wk	8.7	NR	NR	6 mo
Wilailak (2004)	14	40, q3wk	23.1	NR	NR	6 mo
Chou (2006)*	29	45, q4wk	23.1	34.6	57.7	5.4 mo
Katsumata (2008)	62	50, q4wk	21.0	40.3	61.3	168 d
Phase III studies						
Gordon (2001)	130	50, q4wk	12.3	27.7	40.0	9.1 mo**
O'Byrne (2002)	64	50, q4wk	14.0	NR	NR	16.0 wk
Mutch (2007)*	96	50, q4wk	8.3	38.5	46.9	3.1 mo
Ferrandina (2008)#2	70	40, q4wk	15.7	42.9	58.6	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: RR, response rate; SD, stable disease; G, grade; TTR, time to response; TTP, time to progression; Mo, month; Wk, weeks; D, days; NR, not reported.

of 40 mg/m^2 every 4 weeks ranged from 9.1% to 31.4%, clinical benefit ranged from 39.2% to 62.2%, and TTP ranged from 3.7 to 6 months (Table 2). It seems that there is no significant difference in the efficacy of PLD between the 50 mg/m^2 and 40 mg/m^2 doses. However, there are no prospective studies that have compared 50 mg/m^2 with 40 mg/m^2 PLD for efficacy and toxicity. To scientifically confirm the appropriate dosage, the Japanese Gynecologic Oncology Group (JGOG) has launched a RCT of 50 and 40 mg/m^2 PLD in patients with recurrent platinum-resistant ovarian cancer (TFI $<$ 6 months) (accrual of 350 patients, primary endpoint: PFS; secondary endpoints: OS, adverse events). Gordon et al reported a phase III comparative study of PLD versus topotecan that showed statistically significant improvement of OS in PLD compared to topotecan, but there were no statistically significant differences in PFS.[23,34] In subset analysis of platinum-resistant disease, PFS and OS were similar between the two groups, but in platinum-sensitive disease, in contrast, PFS and OS were significantly higher with PLD than with topotecan. Mutch et al conducted a phase III comparative study with GEM in patients with platinum-resistant disease that showed no significant differences in PFS and OS between PLD and GEM.[24] Ferrandina et al also conducted a phase III comparative study with GEM in patients with a treatment-free interval (TFI) of 12 months or less, and reported no differences in PFS between PLD and GEM, but significant efficacy of OS with PLD compared to GEM.[25] Based on the results of phase III studies showed in Table 2, PLD was considered to have similar efficacy as other novel drugs on platinum-resistant disease, but with a different toxicity profile.

Platinum—sensitive disease

In most past studies of platinum—and/or taxane—sensitive disease, PLD was commonly examined as combination chemotherapy with platinum agents. The results of past phase II and III studies of PLD combination therapy in patients with this disease are shown in Table 3. As for monotherapy against platinum—and/or taxane—sensitive disease, the results have already been described above. Almost all studies were conducted on combination therapy with PLD administration at a dose of 30 to 45 mg/m^2 and carboplatin administration at a dose of AUC = 5. The response rate of PLD+ carboplatin ranged from 51% to 62.5%, and PFS and OS ranged from 9.4

Table 3. Response rate and survival of Pegylated Liposomal Doxorubicin combination therapy in patients with platinum-sensitive disease.

Study	Regimen	Dose/Schedule	n	Response rate	Clinical Benefit	PFS	OS (median)
GINECO (phase 2)	PLD+CBDCA	PLD: 30 mg/m^2 CBDCA: AUC 5 q4wk	104	62.5%	81.7%	9.4 mo	32 mo
SWOG S0200 (phase 3)	PLD+CBDCA	PLD: 30 mg/m^2 CBDCA: AUC 5 q4wk	31	67%*1	NR	12 mo*2	31 mo*3
	CBDCA	CBDCA: AUC 5 q4wk	30	32%*1	NR	8 mo*2	18 mo*3
CALYPSO (phase 3)	PLD+CBDCA	PLD: 30 mg/m^2 CBDCA: AUC 5 q4wk	466	NR	NR	11.3 mo*4	NR
	PTX+CBDCA	PTX: 175 mg/m^2 CBDCA: AUC 5 q3wk	508	NR	NR	9.4 mo*4	NR
Hellenic cooperative Oncology Group (phase2)	PLD+CBDCA	PLD: 45 mg/m^2 CBDCA: AUC 5 q4wk	93	51%*5	67%	11.8 mo*6	24.7 mo*7
	PTX+CBDCA	PTX: 175 mg/m^2 CBDCA: AUC 5 q3wk	96	57%*5	74%	10.8 mo*6	29.4 mo*7

Notes: *1 $P = 0.02$, *2 $P = 0.03$, *3 $P = 0.2$, *4 $P < 0.001$, *5 $P = 0.309$, *6 $P = 0.904$, *7 $P = 0.454$.

to 12 months and 2.47 to 32 months, respectively. The CALYPSO trial, a randomized phase III study of carboplatin plus PLD (C-D) versus carboplatin plus paclitaxel (C-P) in relapsed, platinum-sensitive ovarian cancer, was presented at ASCO 2009, and demonstrated that C-D was not inferior to C-P, and that it was even found to be significantly superior in PFS with a different toxicity profile since neutropenia, neuropathy, alopecia and hypersensitivity were seen more frequently with C-P, and thrombocytopenia, PPE, mucositis and nausea/vomiting were seen more frequently with C-D.[35] The overall survival data are not available yet. Bafaloukos et al recently reported similar results with a randomized phase II study of C-D vs. C-P in platinum sensitive disease.[36] These reports support the efficacy and tolerability of combination therapy of C-D, and it can be set as one of the leading options for platinum- and/or taxane- sensitive disease. As for partially platinum- sensitive relapsed disease (TFI of 6–12 months), there are still few reports about its management. Power et al conducted a phase II study of C-D in patients with TFI of 6 to 12 months and reported 46% objective response rate, 10 months (range 1.5–22.5) median TTP, and 19.1 months (range 2.2–38.9) OS with acceptable toxicity[37]. The subset analysis of the CALYPSO trial in patients with partially platinum-sensitive relapsed ovarian cancer (6–12 months) was presented at ESMO2009, and also demonstrated that C-D was significantly superior to C-P in PFS.[38] Furthermore, a phase III trial that compares C-P versus C-D in the above cited clinical setting is ongoing (NCT00657878 : MITO8).

First-line chemotherapy

As for first-line chemotherapy with PLD, a large-scale study of initial chemotherapy containing PLD was conducted (GOG182-ICON5).[39] However, polychemotherapy of PLD associated with paclitaxel/

Table 4. Phase II studies of Pegylated Liposomal Doxorubicin-combination in platinum- and taxane-pretreated patients.

Author (year)	N	Dose/Schedule	RR (%)	Clinical benefit (%)	Response duration (wk)	Toxicity(%) Neutropenia (G3/4)	PPE
Verhar-Langereis (2006)	27*	P: 30 mg/m2 (d1) T: 1 mg/m2/d (d1–5) q3wk	28.0*	72.0*	NR	70.4	3.7 (G3)
Katsaros (2005)	32	P: 30 mg/m2 (d1) V: 30 mg/m2 (d1) q3wk	43.3	70.0	NR	12.5	6.3 (G3/4)
Nicoletto (2005)	43	P: 30–35 mg/m2 (d1) O: 70 mg/m2 (d1) q4wk	66.7** (28.6*)	82.8** (71.4*)	NR	9.3	4.7 (G2)
Recchia (2007)	40	P: 40 mg/m2 over 2 days O:120 mg/m2 over 2 days q3wks	81.5** (38.5*)	100** (76.9*)	NR	37.5	10.0 (G2)
D'Agostino (2003)	38	P: 30 mg/m2 (d1) q3wk G: 1000 mg/m2 (d1,8)	25.0	61.1	18.0	35.6	25.7 (G2/3)
Ferrandina (2005)	66	P: 30 mg/m2 (d1) G: 1000 mg/m2 (d1,8) q3wk	21.6	53.6	20.5	28.8	14.4 (G3)
Skarlos (2005)	37	P: 25 mg/m2 (d1) G: 650 mg/m2 (d1,8) q4wk	22.0	27.5	2.7***#	18.9	5.4 (G2/3)
Petru (2006)	31	P: 30 mg/m2 (d1) G: 650 mg/m2 (d1,8) q4wks	33.0	46.7	3.0#	26.0	16.0 (G2/3)

Notes: *platinum-resistant patients, **platinum-sensitive patients, ***Time to failure. #Months.
Abbreviations: PLD, pegylated liposomal doxorubicin; T, topotecan; V, vinorelbine; O, oxaliplatin; GEM, gemcitabine; RR, response rate; G ¾, grade3/4; PPE, palmar-plantar erythrodysesthesia; NR, not reported.

carboplatin (TC) therapy and sequential doublet combination with carboplatin/PLD and TC therapies did not improve survival compared with TC therapy. The preliminary results of MITO-2, a randomized phase III study of carboplatin plus paclitaxel (C-P) versus carboplatin plus PLD (C-D) in patients with advanced ovarian cancer, was presented at ASCO 2009.[40] Since the number of events required for final analysis has not been reached yet, final analysis of the primary endpoint (PFS) has not been performed. In response rate, there was no statistically significant difference between CP and CD. There are not enough studies and results to evaluate the efficacy of PLD as first-line chemotherapy. Further investigation is necessary.

Combination chemotherapy with Other Novel Agents

In vitro data suggested a potential synergistic interaction between topoisomerase II inhibitors such as PLD and topoisomerase I inhibitors such as topotecan in platinum-resistant disease,[41,42] and also suggested such interaction between PLD and GEM.[43,44] However, there are only few and small clinical studies of combination chemotherapy with PLD and topotecan, GEM or other agents for recurrent disease. A median response rate of 28% and clinical benefit of 72% were demonstrated, with a median TTP of 30+ weeks with the combination of PLD and topotecan for platinum-resistant disease (Table 4).[45] These data compare favorably with the data of both drugs administered as monotherapy. 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 is similar to that with PLD monotherapy.[46–49] As for hematotoxicity, grade 3/4 neutropenia was slightly higher and grade 2/3 PPE was slightly lower. The combination of PLD and GEM is a potential active option with acceptable tolerance 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 than with PLD monotherapy.[50,51] Furthermore, the response rates of 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, with acceptable adverse events of PPE and hematotoxicity. An RCT of the combination of PLD and trabectedin versus PLD reported that PLD/trabectedin significantly improved PFS compared to PLD alone (9.2 months vs. 7.5 months, HR = 0.73, $P = 0.0170$) in patients with platinum-sensitive disease, but no significant difference in PFS was found in patients with platinum-resistant disease.[52] An RCT of the combination of PLD and canfosfamide versus PLD monotherapy was conducted in patients with platinum-resistant disease. Consequently, canfosfamide/PLD significantly improved PFS compared to PLD.[53] Though these studies are encouraging, they were conducted in a relatively small number of patients, and few RCTs have been performed to date to confirm the benefit of combination therapy with PLD over PLD monotherapy in the platinum-resistant population. Further RCTs are necessary.

Conclusion

PLD (Doxil®) is doxorubicin HCl that is encapsulated in long-circulating STEALTH® liposomes. PLD is regarded as a key drug for TC-refractory and -resistant ovarian cancer without cross-resistance to paclitaxel or carboplatin. Patients with platinum-resistant disease have a poor outcome, the aim of treatment for these patients is to prolong their survival while maintaining or improving the QOL. Thus, an agent that can be administered should be selected based on the performance status (PS), persisting toxicity from the initial treatment, and the bone-marrow function of an individual patient. PLD achieves acceptable response rates and clinical benefit, and in many patients long-lasting SD is maintained, which is one of the advantages. The 1-hour infusion schedule every 4 weeks makes PLD easy to administer. It has also been reported that PLD does not induce multidrug resistance,[54,55] which is one of the reasons for selecting PLD as the first option for patients with platinum-resistant disease. PLD is safer for heavily pretreated patients than topotecan and GEM due to its mild bone-marrow toxicity, but PPE, stomatitis and mucositis develop frequently. 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 prolonging the dosing interval. Dose modification often allows continued treatment without recurrence of PPE. Various pharmacologic approaches including topical dimethyl sulfoxide, pyridoxine (vitamin B6), and topical or systemic steroids, as well as regional cooling have been examined.[27–29] Concerning the assessment of objective response, some reports showed interesting results that seem like a discrepancy between the trend of the CA125 value and the ultimate clinical response on radiographic examination in responding patients treated with PLD, compared to those treated with topotecan or carboptatin.[56,57] The CA125 value in responding patients treated with PLD seemed to decline later than in those treated with topotecan or carboplatin, so early changes in the CA125 may not reflect the ultimate clinical response. It was also recommended to exert caution when assessing response based on CA125 during the first to 2nd cycle of treatment. Based on a review of previous studies,[14–26] there seems to no differences in efficacy between 50 and 40 mg/m^2 PLD, therefore a dose of 40 mg/m^2 is preferable in patients with platinum-resistant disease to reduce the adverse events.[30,33,58] As described above, JGOG has launched an RCT of 50 and 40 mg/m^2 PLD to scientifically confirm the appropriate dosage. As for platinum- and/or taxane-sensitive disease, re-treatment with a combination of platinum and taxane agents is standard. Recently, the CALYPSO trial showed that the PLD-carboplatin combination was not inferior to paclitaxel-carboplatin in terms of PFS and showed tolerance with different toxicity. The combination of PLD-carboplatin is a potential leading option for platinum- and/or taxane-sensitive disease, but further investigation is still needed. When combined with other useful agents, a lower dose of PLD (30 to 35 mg/m^2) with a 3–4 week schedule may reduce severe PPE and stomatitis with negligible effects on the level of DI and the therapeutic efficacy. Further prospective studies are necessary, also of first-line chemotherapy. Recently, some studies of novel molecular target-based agents in combination with PLD are ongoing. A large representative study that is presently ongoing is the AURELIA trial, which is a randomized phase III study of bevacizumab plus either paclitaxel, topotecan or PLD chemotherapy versus only chemotherapy in patients with platinum-resistant ovarian cancer. As for other studies, pazopanib, volociximab, panitumumab, bortezomib, vandetanib, farletuzumab (plus carboplatin) bevacizumab (plus carboplatin) etc., in combination with PLD are being examined in phase I or II studies.[59–62] It is expected that the combination of molecular target-based agents with cytotoxic agents including PLD is an essential next strategy for the treatment of ovarian cancer. These results will attract attention in the future.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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