RESEARCH ARTICLE

Outcomes with Single Agent LIPO-DOX in Platinum-Resistant Ovarian and Fallopian Tube Cancers and Primary Peritoneal Adenocarcinoma - Chiang Mai University Hospital Experience

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Abstract

Background: Single pegylated liposomal doxorubicin (PLD) is commonly used as a salvage treatment in platinum-resistant ovarian cancer, fallopian tube cancer and primary peritoneal adenocarcinoma (PPA) with a satisfactory outcome. However, the data for second generation PLD administered in this setting are still limited. We conducted a retrospective study to evaluate the outcome of patients who received single-agent second generation PLD (LIPO-DOX) after the development of clinical platinum resistance. The study period was between March 2008 and March 2013. LIPO-DOX was administered intravenously 40 mg/m^2 every 28 days until disease progression, but for not more than six cycles. The response rate was evaluated using the Gynecologic Cancer Intergroup (GCIG) criteria while the toxicity was evaluated according to WHO criteria. Twenty-nine patients met the inclusion criteria in the study period with an overall response rate of 13.8%. The median progression free survival and overall survival were three and eleven months, respectively. With the total of 96 cycles of chemotherapy, the patients developed grades 3 and 4 hematologic toxicity as follows: anemia, 0%, leukopenia, 9.6%, neutropenia, 32.3% and thrombocytopenia, 0%. In conclusion, the single agent second generation PLD demonstrated modest efficacy in patients with platinum-resistant ovarian cancer, fallopian tube cancer and PPA without serious toxicity.

Keywords: LIPO-DOX - platinum-resistant ovarian cancer - outcome - toxicity

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Introduction

The majority of epithelial ovarian cancer, fallopian tube cancer and primary peritoneal adenocarcinoma (PPA) patients experience disease recurrence even though they receive standard treatment. The treatment outcome after recurrence depended on the interval time between the time to complete platinum-based chemotherapy until the time to replapse that we called a platinum-free interval. In patients with recurrence with a platinum-free interval of more than six months, the retreatment with platinum-based combined regimens are preferred with the nearly 50% response. However, when the interval time was shorter than six months or tumor progression was identified while receiving the platinum-based regimen, commonly known as platinum-resistant and refractory group , the treatment outcome with various chemotherapies in the literature was nearly ten percent (Bast and Markman, 2010; Markman, 2011).

One of the anti-neoplastic agents given in platinum resistant patients is pegylated liposomal doxorubicin (PLD). This drug is composed of doxorubicin which is encapsulated in a novel proprietary bilayer lipid sphere called "liposome". PLD was investigated in many platinum resistant trials as Phase II and III and showed the activity to have a "non inferior outcome" when compared to another drugs. However, many expert physicians recommend PLD as the first drug to administer in the patients with platinum-resistance due to an effective outcome, minimal toxicity and the convenience of usage (Naumann and Coleman, 2011).

Currently, there are two generations of PLD commercially available. The first one is commonly used in America and Europe with the trade name as "Doxil"or "Caelyx" while the second one named "LIPO-DOX" is commonly used in Taiwan. These two products have the same active ingredient as doxorubicin but a different formulation of liposomes. Caelyx uses hydrogenated soybean phosphatidylcholine (HSPC) while LIPO-DOX uses distearoylphosphatidylcholine (DPLD) compounds. DPLD had a smaller volume of distribution than HSPC resulting a lower clearance rate and a longer half-life. With this character, DPLD revealed a greater stability in plasma than HSPC (Hsiao et al., 2009). However, there are limited clinical trials of LIPO-DOX in recurrent ovarian cancer when compared to Caelyx (Naumann and Coleman,

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2011). Only two publications have reported LIPO-DOX treatment in platinum-resistant ovarian cancer. One study from the Taiwan Gynecologic Oncology Group used single LIPO-DOX and one study from Thailand used LIPO-DOX combined with carboplatin. These two studies revealed a favorable outcome (Chou et al., 2006; Khemapech et al., 2013). In our center, LIPO-DOX was given in platinum-resistant ovarian, fallopian tube cancer and PPA for several years but the outcome has not yet been summarized. Due to the limited data of LIPO-DOX in the literature reveiw, we conducted this retrospective study to evaluate the efficacy and toxicity of single LIPO-DOX in platinum resistant epithelial ovarian cancer patients. These results will enhance the previously published studies regarding the efficacy of LIPO-DOX.

Materials and Methods

After the protocol was approved by the Local Research Ethics Committee, the medical records of the patients with platinum-based resistant epithelial ovarian cancer, fallopian tube cancer and PPA who were administered single agent LIPO-DOX at Chiang Mai University Hospital form March 2008 to March 2013 were retrospectively reviewed.

The protocol of chemotherapy regimen

The schedule of chemotherapy consisted of intravenous (IV) LIPO-DOX 40 mg/m^2 given over one hour every 28 days. Premedication consisted of lorazepam, dexamethasone, ondansetron, ranitidine and diphenhydramine. LIPO-DOX was given until disease progression or intolerable toxicity. A complete blood count, renal function test, liver function test and serum CA 125 were assessed each cycle prior to administration of the chemotherapy. All patients were required to have a hemoglobin (Hb) level of more than ten gm%, an absolute neutrophil count (ANC) of more than 1,500/mm^3, and a platelet count of more than 100,000/mm^3 on the day before beginning LIPO-DOX. The treatment was delayed if blood counts had not returned to acceptable levels prior the next course of chemotherapy. Some patients also received granulocyte-colony stimulating factor (G-CSF) for severe neutropenia. In patients with tumor progression, further treatment depended on the decision of the attending physician. The follow-up after completion of treatment included history taking, pelvic examination and tumor marker evaluation every three months.

Outcome parameters

The objective tumor response was determined by the Gynecologic Cancer Intergroup (GCIG) criteria that used CA 125 criteria for evaluating the outcome (Rustin et al., 2011). Progression-free survival (PFS) was determined as the period of time between the first administration of LIPO-DOX and the date of tumor progression or the date of last contact if the patients did not have a progression of their disease. The overall survival (OS) was determined as the period of time between the first dose given of LIPO-DOX and the date of the last contact or the date of the patients' death. All adverse effects were evaluated by using WHO toxicity criteria (Miller et al., 1981).

Statistical analysis

Descriptive data of all studied patients were presented with measurement data expressed as the mean, with range and discrete data as numbers and percentages. PFS and OS were estimated by the Kaplan-Meier Method. Statistical analysis of the data was done using the SPSS for windows version 17.0 (SPSS Inc.,Chicago, IL, USA).

Results

Twenty-nine patients received LIPO-DOX during the study period. The patient characteristics are noted in Table 1. The mean age of those patients was 54.9 years old and over 80% of them were diagnosed with recurrent ovarian cancer. Two-thirds of the patients were initially diagnosed with Stage III and the most common histology was serous cystadenocarcinoma. The majority of the patients was in

Table 1. Patient Characteristics (N=29)

Clinical data			Number (%)
Mean age (range: years)			54.9(33-76)
Disease			
CA ovary			24(82.8)
CA fallopian tube			1 (3.4)
CA ovary & CA fallopian tube			1 (3.4)
Primary peritoneal adenocarcinoma			3 (10.3)
Stage	I		7 (24.1)
	II		1 (3.4)
	III		18 (62.1)
	IV		3 (10.3)
Surgical type	Complete		5 (17.2)
	Incomplete		24 (82.8)
Residual disease after primary surgery			
No			11 (37.9)
Optimal			3 (10.3)
Suboptimal			10 (34.5)
Unknown			5 (17.2)
Histology	Serous cystadenocarcinoma		15 (51.7)
	Mucinous cystadenocarcinoma		2 (6.9)
	Clear cell carcinoma		7 (24.1)
	Other		5 (16.1)
First line chemotherapy			
Carboplatin+paclitaxel (PT)			28 (96.5)
Carboplatin			1 (3.5)
Cycle of first line administration		1 to 3	4 (13.8)
		4 to 6	24 (82.7)
		9	1 (3.4)
Platinum status			
Sensitive (platinum- free> 6 months)			8 (27.6)
Resistant (platinum –free< 6 months)			14 (48.3)
Refractory (resistant during received platinum)			7 (24.1)
Number of prior chemotherapy regimen		1	12 (41.4)
		2	7 (24.1)
		3	5 (17.2)
		>= 4	4 (13.8)
Recent chemotherapy	Carboplatin & paclitaxel		18 (62.1)
	Gemcitabine		2 (6.9)
	Oral etoposide		5 (17.2)
	Carboplatin		2 (6.9)
	Cisplatin		1 (3.4)
	Ifosfamide		1 (3.4)

Table 2. Outcome of LIPO-DOX (N=29)

Outcome	N (%)
Complete response	1 (3.4)
Partial response	3 (10.3)
Stable of disease	2 (6.9)
Progression	29 (79.3)

*Response rate=13.7%

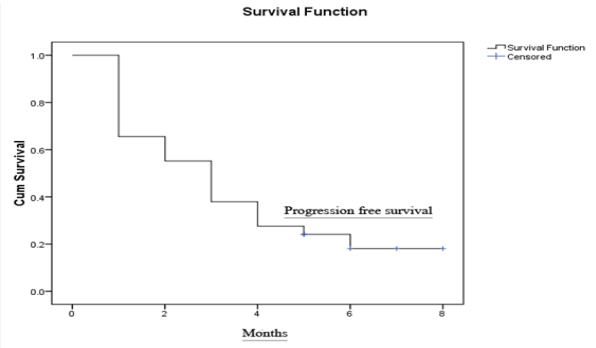

Figure 1. Progression-free Survival of the Studied Patients. The median PFS was 3 months (1-8 months)the median overall survival was 11 months (range 1-65 months)

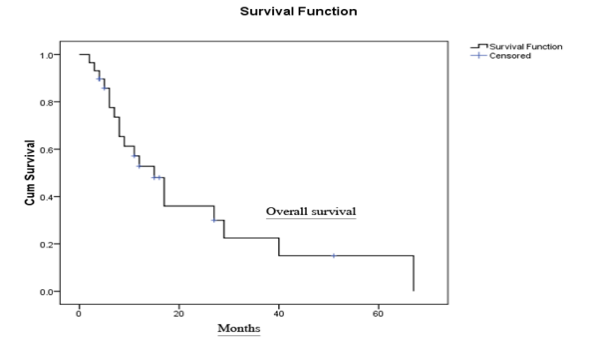

Figure 2. Overall Survival of the Studied Patients. The median overall survival was 11 months (range 2-56 months) 2-year overall survival=30.0%death=18 (62.1%)

Table 3. Grade 3 and 4 Toxicities (96 cycles)

Grade	0(%)	I(%)	II(%)	III(%)	IV(%)
Toxicity					
Anemia	66 (68.8)	27 (28.1)	3 (3.1)	0	0
Leukopenia	58 (60.4)	21 (21.9)	14 (14.6)	3 (3.1)	0
Granulocytopenia	40 (41.7)	30 (31.3)	16 (16.7)	8 (8.3)	2 (2.1)
Thrombocytopenia	96 (100)	0	0	0	0
Non-hematologic toxicity					
Mucositis	74 (80.2)	13 (13.5)	9 (9.4)	0	0
Palmar-plantar erythrodysesthesia	77 (80.2)	17 (17.7)	2 (2.0)	0	0

*Granulocyte stimulating factor (GCSF) used=11 cycles (14.5%)
Grades 3 and 4 hematologic toxicity (per patient): Anemia=o; Leukopenia =3/31=9.6%; Neutropenia=8/31=32.3%; Thrombocytopenia=0

the platinum resistant and refractory group and received no more than two prior chemotherapy regimens. Over 60 percent of the patients were given carboplatin plus paclitaxel before they received LIPO-DOX.

Tumor response and survival

The overall response rate was 13.7% with one complete response observed as noted in Table 2. The patient who achieved complete response was diagnosed as Stage IC ovarian cancer with the histology of mucinous cystadenocarcinoma. She underwent a simple hysterectomy and bilateral salpingo-oophorectomy at the provincial hospital. Afterwards, she was referred to our center and was given three courses of carboplatin and paclitaxel (PT) regimen before re-operation to evaluate retroperitoneal nodal and omental status. After surgical recovery, she was given another three cycles of PT regimen with good response. She was free-of disease for 12 months before developing recurrence and was retreated with one cycle of PT regimen and three cycles of gemcitabine with no observable response. Thus, LIPO-DOX was subsequently given for six cycles with a complete response. However, only two months after LIPO-DOX was discontinued, she developed ascites and revealed a rising of her CA 125.

For another response type, 6.9% of the patients developed a stability of their disease while the rest (79.3%) showed disease progression. After that, further therapy consisted of other chemotherapy (62.1%), pelvic radiation (6.9%), hormone (3.4%) and palliative care (27.6%). With the mean follow up time of 15.2 months, 18 patients (62.1%) died of their disease. The median PFS was three months and median OS was 11 months as showed in Figures 1 and 2, respectively.

Toxicity

Of the 96 courses of LIPO-DOX, the most frequent Grade 3 and 4 hematologic toxicity was neutropenia that developed in 32.3% of patients followed by leukopenia that occurred in 9.6% of patients as noted in Table 3. Granulocyte stimulating factor (GCSF) was given in 11 cycles for those patients with neutropenia while no other non-hematologic serious toxicity was found.

Discussion

LIPO-DOX is the second generation of PLD which is commonly used in Taiwan. The Taiwanese Gynecologic Oncology Group reported the outcome of LIPO-DOX in treated 20 platinum-resistant patients and nine platinum-refractory ovarian cancer patients in the year 2006. LIPO-DOX was started with a dose of 45 mg/m^2 at four week intervals with subsequent escalation of the dosage. With 26 evaluable patients, the overall response rate of their study was 23.1% with one patient that achieved complete response (Chou et al., 2006). This response rate was better than our study that showed the response rate at 13.7%. This distinction might be from the different dosage of LIPO-DOX. In the present study, we used a fixed dose of LIPO-DOX at 40 mg/m^2 while the Taiwanese group used an escalation dose with the starting dose at 45 mg/m^2. About 70% of patients in their study received a dosage of 45 mg/m^2 while the rest received 50-55 mg/m2. However, the median progression free survival (PFS) and median overall survival (OS) in the Taiwanese study compared with the present study were similar with 5.5 and 3 months for PFS and 13.8 and 11.0 months for OS, respectively. In addition, when our results were compared with other clinical trials of platinum-refractory ovarian cancer patients using 40-50 mg/m^2 every four weeks of first

generation PLD (Caelyx®), the outcomes were alike with a response rate of 8.3-16.9%, the median PFS was 3.1-4 months and the median OS was 13.5-14 months (Gordon et al., 2000; Mutch et al., 2007; Ferrandina et al., 2008).

Furthermore, there was a recent retrospective study from Thailand that utilized LIPO-DOX combined with carboplatin in 65 platinum-resistant ovarian cancer patients. This study administered 40 mg/m^2 of LIPO-DOX combined with carboplatin AUC of five every four weeks. The authors reported a very high response rate at 23.1% with 7.7% who achieved complete response. However, with 36 patients who could be evaluated for survival, they found that the median PFS was only 4.5 months while the median OS was only 8.8 months which was shorter than the median OS from our study using only LIPO-DOX (Khemapech et al., 2013).

Regarding toxicity, The Taiwanese group reported Grades 3 and 4 leukopenia and neutropenia occurred at 3.0 and 11.9% of the cycles while none of Grades 3 and 4 anemia, thrombocytopenia, PPE and mucositis were observed in their study (Chou et al., 2006). These results were similar to our study that revealed Grades 3 and 4 leukopenia and neutropenia at 3.1 and 10.4% of the cycles while other Grades 3 and 4 toxicities did not occur. Moreover, when compared to the recent report from Thailand that used a combination of LIPO-DOX and carboplatin, the author did not mention Grades 3 and 4 hematologic toxicity. However, when compared to our study, a greater frequency of Grades 1 and 2 anemia, leukopenia, thrombocytopenia, PPE and mucositis were noted (Khemapech et al., 2013).

The strength of our study was the administration of the unique dosage of LIPO-DOX (40 mg/m^2) with platinum resistance and refraction in one institute. This dosage was comparable to the previous studies that used the first generation of PLD. Many experts suggest a dosage of PLD at 40 mg/m^2 given every four weeks as the standard dose (Pectasides et al., 2006). Thus, the present study became the initial report that revealed the outcome of second generation PLD when administered in the standard dose. However, limitations of the study were the low number of studied patients and the nature of a retrospective study with some incomplete data.

In conclusion, the second generation of PLD (LIPO-DOX) seems to have comparable outcomes with first generation PLD (Caelyx) in treating platinum-resistant and refractory epithelial ovarian cancer with minimal toxicity especially in patients who received the treatment as a salvage drug after resistance to platinum-based chemotherapy.

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References

Bast RC Jr, Markman M (2010). Chemotherapy: A new standard combination for recurrent ovarian cancer? *Nat Rev Clin Oncol*, **7**, 559-60.

Ferrandina G, Ludovisi M, Lorusso D, et al (2008). Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. *J Clin Oncol*, **26**, 890-6.

Gordon AN, Granai CO, Rose PG, et al(2000). Phase II study of liposomal doxorubicin in platinum- and paclitaxel-refractory epithelial ovarian cancer. *J Clin Oncol*, **18**, 3093-100.

Hsiao SM, Chen CA, Lin HH, et al (2009). Phase II trial of carboplatin and distearoylphosphatidylcholine pegylated liposomal doxorubicin (Lipo-Dox) in recurrent platinum-sensitive ovarian cancer following front-line therapy with paclitaxel and platinum. *Gynecol Oncol*, **112**, 35-9.

Khemapech N, Oranratanaphan S, Termrungruanglert W, et al (2013). Salvage chemotherapy in recurrent platinum-resistant or refractory epithelial ovarian cancer with Carboplatin and distearoylphosphatidylcholine pegylated liposomal Doxorubicin (lipo-dox®). *Asian Pac J Cancer Prev*, **14**, 2131-5.

Markman M (2011). Pegylated liposomal doxorubicin: appraisal of its current role in the management of epithelial ovarian cancer. *Cancer Manag Res*, **3**, 219-25.

Mutch DG, Orlando M, Goss T, et al (2007). Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. *J Clin Oncol*, **25**, 2811-8.

Miller AB, Hoogstraten B, Staquet M, et al (1981). Reporting results of cancer treatment. *Cancer*, **47**, 207-14.

Naumann RW, Coleman RL (2011). Management strategies for recurrent platinum-resistant ovarian cancer. *Drugs*, **71**, 1397-412.

Pectasides D, Psyrri A, Pectasides M, et al (2006). Optimal therapy for platinum-resistant recurrent ovarian cancer: doxorubicin, gemcitabine or topotecan? *Expert Opin Pharmacother*, **7**, 75-87.

Rustin GJ, Vergote I, Eisenhauer E, et al (2011). Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). *Int J Gynecol Cancer*, **21**, 419-23.

Taiwanese Gynecologic Oncology Group, Chou HH, Wang KL, et al (2006). Pegylated liposomal doxorubicin (Lipo-Dox) for platinum-resistant or refractory epithelial ovarian carcinoma: a Taiwanese gynecologic oncology group study with long-term follow-up. *Gynecol Oncol*, **101**, 423-8.