RESEARCH ARTICLE

Salvage Chemotherapy in Recurrent Platinum-Resistant or Refractory Epithelial Ovarian Cancer with Carboplatin and Distearoylphosphatidylcholine Pegylated Liposomal Doxorubicin (Lipo-Dox®)

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Abstract

Background: To evaluate the efficacy and safety of distearoylphosphatidylcholine pegylated liposomal doxorubicin (DPLD) combined with carboplatin for the treatment of platinum resistant or refractory epithelial ovarian cancer (EOC) or fallopian tube cancer. Materials and Methods: A retrospective analysis of women who received DPLD with carboplatin for recurrent EOC or fallopian tube cancer in King Chulalongkorn Memorial Hospital Thailand from January 2006 to August 2011 was conducted. Patients were identified from the medical records and data on demographic factors, stage, histology, surgical findings, cytoreduction status, and prior chemotherapies were abstracted. The efficacy and toxicity of DPLD/carboplatin were evaluated. Progression-free (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method. Results: A total of 65 patients, 64 with platinum resistant or refractory epithelial ovarian cancer and 1 with fallopian tube cancer, were enrolled. DPLD and carboplatin were given for an average of 4.46 cycles per patient with a total of 273 cycles. Among the 65 evaluable patients, 0% achieved CR, 7.69% PR, 15.4% SD and 76.% PD. The overall response rate was 23.1%. With a median follow-up of 27.4 months, the median progression-free and median overall survival in the 36 patients was 4.46 months and 8.76 months respectively. In the aspect of side effects, palmar-plantar erythrodysesthesia (PPE) occurred in 33.3% (Grade I 22.2%, Grade II 11.1%) and mucositis in 41.7% (Grade I 27.8%, Grade II 13.9%) of all treatment cycles, all Grade 1 or 2. Anemia, leukopenia and thrombocytopenia occurred in 58.3% (Grade I 41.7%, Grade II 16.7%), 66.7% (Grade I 47.2%, Grade II 19.4%), and 22.2% (Grade I 16.6%, Grade II 5.56%) of cycle respectively, and were mostly Grade 1 or 2. Conclusions: DPLD, the second-generation PLD drug combined with carboplatin every 4 weeks, is effective and has low toxicity for treatment of patients with recurrent platinum-resistant or refractory epithelial ovarian cancer.

Keywords: Recurrent ovarian cancer - chemotherapy - salvage therapy - pegylated liposomal doxorubicin

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Introduction

Epithelial ovarian cancer is one of the most common gynecologic cancers and the fifth most frequent cause of cancer death in women. The incidence rate was 9.8 per 100,000 woman-year and mortality rate was 4.9 per 100,000 woman-year (Jemal et al., 2009). It is also the sixth most frequent cause of cancer death in Thai women. There is still no proper screening method and most of the patients are diagnosed in advanced stages. The current standard management of epithelial ovarian cancer includes surgical staging and an attempt at optimal and, if possible, complete surgical cytoreduction then followed by platinum-based chemotherapy (McGuire et al., 1996). Unfortunately, although the majority of advanced ovarian cancer patients (70-80%) respond to platinum-based chemotherapy, half of the complete responders will subsequently experience recurrent diseases. In patients whose ovarian cancer are platinum-refractory (cancer has progressed while on a platinum-based regimen) or platinum-resistant (cancer has recurred within 6 months of completion of a platinum-based regimen), a number of single agent anti-neoplastic drugs that have been documented to produce objective response rates in more than 10% of the treated population namely topotecan, liposomal doxorubicin, vinorelbine, docetaxel, gemcitabine, oral etoposide and melphalan are currently available as salvage treatment (Shapiro et al., 1996; Bookman et al., 1998; Rose et al., 1998)

Doxorubicin has a wide spectrum of activity in human malignant tumors and is considered one of the active

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chemotherapeutic agents for advanced ovarian cancer (Fanning, 1992; A'Hern and Gore, 1995). Before the paclitaxel era, doxorubicin in combination with cisplatin and cyclophosphamide had been the standard treatment for epithelial ovarian cancer (Williams, 1992). However, the use of this anthracycline agent is limited by its side effects such as myelosuppression, gastrointestinal toxicity and cumulative cardiac toxicity (Singal and Iliskovic, 1998). Various approaches, including the development of its analogues and its liposome-encapsulated form, have been used to improve the toxicity profiles of doxorubicin. Recent advances using liposome as a carrier have resulted in new formulations of doxorubicin with improved pharmacokinetic and tumor localization properties (Harashima et al., 1983; Herman et al., 1983; Gabizon et al., 1986; Rahman et al., 1990; Papahadjopoulos et al., 1991; Huang et al., 1992; Gabizon et al., 1994; Gokhale et al., 1996). Polyethylene glycol-coated (pegylated) liposomal doxorubicin (PLD) is designed for the delivery of a liposomal form of doxorubicin (Caelyx, Schering Plough International, Kenilworth, NJ, USA) to the sites of solid tumors (Gabizon and Papahadjopoulos, 1988; Muggia et al., 1997). The efficacy of PLD in human has already been proved in studies of various malignant tumors such as ovarian cancer, breast cancer, and Kaposi sarcoma. Lower risks of musculoskeletal toxicity and alopecia, and fewer grade 3/4 toxicities have been shown in women with recurrent ovarian cancer when comparing single-agent PLD with paclitaxel and topotecan respectively (Gordon et al., 2000; Markman et al., 2000; Gordon et al., 2004; Ferrandina et al., 2008). Lipo-Dox® (DPLD), (TTY BioPharm, Taipei, Taiwan) is a second-generation PLD drug containing distearoylphosphatidylcholine that has been commercially available in Taiwan since 1998 (Yuda et al., 1996; Hong, 2001). A Taiwanese gynecologic oncology group has reported, in a multicenter phase II trial, that single agent DPLD at 45 mg/m^2 every 4 weeks is effective against recurrent, platinum resistant epithelial ovarian cancer (Chou et al., 2006). The objective of this study is to evaluate the efficacy and safety of a distearoylphosphatidylcholine pegylated liposomal doxorubicin (DPLD) combined with carboplatin in the treatment of platinum-resistant or refractory epithelial ovarian cancer in Thai patients treated at King Chulalongkorn Memorial hospital ,Thailand.

Materials and Methods

This retrospective study was approved by our institutional Internal Review Board. The medical record of the epithelial ovarian cancer patients in King Chulalongkorn Memorial Hospital Thailand during January 2006 to August 2011 who were not responded to prior chemotherapy treatment with both platinum and paclitaxel-based regimen and received DPLD and carboplatin were collected and retrospectively evaluated.

All patients had histological confirmed epithelial ovarian or fallopian tube cancer. Eligible patients included those with a good Eastern Cooperative Oncology Group (ECOG) performance status (0-2), adequate basal renal, liver, bone marrow and cardiac functions. Patients with a history of severe cardiac disease and another malignancy were excluded.

The DPLD/ carboplatin regimen was given as follows: DPLD 40 mg/m^2, diluted in 250 ml of 5% dextrose/ water, was infused over 1 hour.and after completion of the DPLD infusion, carboplatin equivalent to the area under the concentration–time curve (AUC) of 5 mg min/ml (Calvert formula) was infused over 30 minutes. Treatment cycles were repeated every 4 weeks. Toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria grading system (National Cancer Institute Common Toxicity Criteria).

Tumor response was assessed every 2 cycles of treatment according to Response Evaluation Criteria in Solid Tumors. A complete response (CR) was defined as the disappearance of all assessable target lesions with no evidence of new lesions by two disease assessments at least four weeks apart. Partial response (PR) defined as at least 30% decrease in the sum of the longest dimensions of all the target lesions by two disease assessments at least four weeks apart. Progressive disease was defined as at least a 20% increase in the sum of the longest dimensions of all target lesions or the appearance of new lesions. Stable disease (SD) was defined as any condition not meeting the above criteria.

Progression-free survival (PFS) was measured from the date of the first chemotherapy dose to the date of documented disease progression, death due to other causes, or last follow-up date. Overall survival (OS) was measured from the date of the first chemotherapy dose to the date of death, or the date of last follow-up. PFS and OS were estimated using the Kaplan–Meier method.

Results

A retrospective medical record review of the patients receiving DPLD/carboplatin was performed during January 2006 to August 2011. We recruited 65 patients, 64 of them were ovarian cancer and 1 of them was fallopian tube cancer. Mean age of patients was 54.29 year (range 35-78 years old). All of them received surgical intervention as primary treatment. Complete cytoreduction was achieved in 16.92% of the patients, 55.38% obtained optimal cytoreduction which considered the residual disease less than 1 cm in greatest diameter and 27.69% of the patients had suboptimal cytoreduction. Most common stage of the disease was stage IIIc (64.18%) and the most common cell type was serous carcinoma (46.26%). The details of the stage and cell type were described in Table 1.

The entire patients received adjuvant chemotherapy. Most of them received paclitaxel combined with carboplatin (89.55%). The rest of the patients received single agent carboplatin or carboplatin and docetaxel. Their mean disease free interval was 8.82 months (range 0-40 months). According to the response of first line chemotherapy, they were classified as platinum refractory 47.76%, platinum resistance 25.37% and platinum sensitive 47.76%.

We found that half of the recurred patients appeared the recurrent tumor at the distant location (49.25%). DPLD/

Table 1. Patient Characteristics

Characteristics		No. of patients	%
Age (years)		54.29 (35-78)	
FIGO stage	Ia	1	1.54
	Ic	5	7.69
	IIc	9	13.85
	IIIa	1	1.54
	IIIb	2	3.08
	IIIc	42	64.62
	IV	3	4.62
	Unknown	2	3.08
Histologic subtype	Serous	31	47.69
	Endometrioid	14	21.54
	Clear cell	12	18.46
	Mixed epithelial	7	10.72
	Fallopian tubes	1	1.54
Grade	1	20	30.72
	2	7	10.77
	3	35	53.85
	Unknown	3	4.62
No. of prior chemotherapy	Second line	37	56.92
	Third/fourth line	28	43.08

Table 2. Toxicity (according to the National Cancer Institute Common Toxicity Criteria)

Toxicity	Grade I (%)	Grade II (%)	Total (%)
Anemia	41.67	16.67	58.34
Leucopenia	47.22	19.44	66.67
Thrombocytopenia	16.62	5.56	22.2
PPE	22.2	11.1	33.3
Mucositis	27.78	13.89	41.7

carboplatin were given as second line chemotherapies in platinum resistant and platinum refractory patients. The platinum- sensitive patients who did not have contraindication for these agents were re-challenged with carboplatin and paclitaxel and if recurrence occurred in these patients then DPLD/carboplatin would be administered as third line chemotherapeutic regimen. DPLD/carboplatin were given for average of 4.46 cycles per patient with a total 273 cycles. Overall response rate was 23.07%. As we distributed the response to DPLD/carboplatin, no patient can achieve complete response. The other 7.69% gained partial response. Another 15.38% was stable and 76.92% progressed during chemotherapy administration. Median follow up duration was 27.4 months since first diagnosis. Median progression free survival and overall survival were 4.46 months and 8.76 months respectively.

In the aspect of toxicity, the toxicity grading was considered according to the National Cancer Institute Common Toxicity Criteria (NCIC) grading system. The most common toxicity was leucopenia which occurred in 66.7% (Grade 1 was 47.22% and Grade 2 was 19.44%). Anemia occurred in 58.3%. Another common toxicity such as mucositis, PPE and thrombocytopenia were identified at 41.7%, 33.3% and 22.2% respectively. Most of the toxicity was grade 1-2 and reversible. As we considered the chemotherapy continuation, 22.22% of the patients were still received chemotherapy while 8.33% quit because of the intolerance to chemotherapy and 69.44% quit due to disease progression. At the complete analysis time, 74.67% of the patients died and 25.33% was still alive.

Discussion

About 70 percent of ovarian cancer patients are diagnosed in advanced stages because there are currently no effective screening strategies. With aggressive surgical procedures and platinum-based chemotherapy, most patients can achieve a complete clinical remission. Unfortunately, the majority of patients will ultimately relapse and require treatment for recurrent disease. It has been noted that the time interval from the end of platinum-based chemotherapy to the detection of relapse is a good surrogate marker for secondary response to platinum-based chemotherapy (Markman and Hoskins, 1992). The terms 'platinum sensitive' and 'platinum resistant' have been used to describe these patients for prognostic significance and also for appropriate patients selection for second-line chemotherapy. Generally, the term 'platinum resistant' implies a treatment-free interval of less than 6 months before recurrence and the term 'platinum refractory' implies an incomplete response or progression on primary platinum-based chemotherapy (Stuart et al., 2011). Recurrent platinum-sensitive ovarian cancer is usually treated aggressively with consideration of secondary cytoreductive surgery and combination chemotherapy since it often responses to additional chemotherapy. On the contrary, platinum-resistant ovarian cancer is rarely responsive to salvage treatment and has a poor prognosis.The main goal of treatment in these patients should be the palliation of existing symptoms and maintenance of quality of life, Therefore the ideal chemotherapy for salvage therapy should provide a satisfactory response , low toxicity profile and minimal late effects regarding treatment (Grover et al., 2012).

Second-line chemotherapy still remains a major problem for platinum resistant and refractory patients. Numbers of antineoplastics such as topotecan, gemcitabine, etoposide, liposomal doxorubicin have been used for salvage treatment. Unfortunately, they do not provide adequate response and prolong survival. According to previous studies, the median life expectancy is <12 months. Safra et al. reported a 31% overall response rate in one phase I (N=8) and two phase II (N=44) studies on recurrent ovarian cancers salvaged with first generation pegylated liposomal doxorubicin (PLD), Doxil, with median overall survival of 15 months (Safra et al., 2001). Gordon et al. reported a phase II trial on the salvage chemotherapy, with Doxil 50 mg/m^2 every 4 weeks, for 89 patients with platinum and paclitaxel-refractory epithelial ovarian cancers, and showed a response rate of 16.9%. The median time to progression was 19.3 weeks.They also found that patients who received PLD had significantly better overall survival (108 weeks) than those who received topotecan (71.1 weeks) (Gordon et al., 2000). Chou et al. studied second-generation PLD drug, Lipo-Dox® with a dose of 45 mg/m^2 at a 4-week interval in 26 heavily pretreated resistant or refractory ovarian cancers patients and found the response rate of 23.1% with median progression-free interval and median overall survival time of 5.4 months

and 13.8 months, respectively. They found that Lipo-Dox® provided a response rate comparable with that of Doxil on similar patients (Chou et al., 2006). In our study ,we prescribed Lipo-Dox®, combined with carboplatin which was reported in a number of studies to have synergistic combination and found superior with regard to progression free survival and also safety profile (du Bois et al., 2007; Ferrero 2007; Alberts et al., 2008; Power et al., 2009; Strother and Matei, 2009; Grenader et al., 2012). Although recently, there is a multi-institutional phase II trial regarding combination of PLD to another agent such as panitumumab, the first fully human monoclonal antibody specific to EGF receptor in platinum resistant/ refractory ovarian cancer patients, the progression free and overall survival are still not apparently superior comparing the combination of PLD with carboplatin (Steffensen et al., 2013). According to our study, we found the overall response rate was 23.07% which was similar to previous Taiwanese study (Chou et al., 2006). With a median follow-up of 27.4 months, the median progression-free and median overall survivals in the 36 patients was 4.46 months and 8.76 months respectively which were rather shorter than previous study. It might be the proportion of the platinum refractory patients in our study were much higher (47.76% vs 31%) and might implied more aggressive disease since the beginning.

An ideal chemotherapy for salvage treatment for the patient with platinum-resistant or refractory epithelial ovarian cancer should provide not only a satisfactory response but also superior toxicity profile. The usage of doxorubicin has been limited due to its cardiac toxicity, and the recent developed of liposomal doxorubicin may spare its toxicity and provide a potential resolution. This second generation of liposomal drug is made by coating the surface of liposomal particle with polymethylene glycol to reduce opsonization and subsequently avoid clearance by the reticuloendothelial system (Gabizon and Papahadjopoulos, 1988). These pegylated liposomal drugs have a longer half-life in the circulation after intravenous administration and increased uptake by tumor at an even lower volume of distribution. Hydrogenated soybean phosphatidylcholine (HSPC) is used in some of the second-generation liposomes for its higher stability in plasma than that of the phosphatidylcholine used in conventional liposomes. Doxil is one of the formulations of HSPC pegylated doxorubicin that has demonstrated anti-cancer activity (Muggia et al., 1997) Distearoylphosphatidylcholine (DSPC) is another lipid with uniform acyl chain length and higher phase transition temperature than HSPC, with a subsequently higher stability and longer half-life. The drug used in the current study, Lipo-Dox®, is a DSPC pegylated liposomal doxorubicin. The liposomal pegylated formulation of doxorubicin has been developed for increasing antitumoral activity through increased intracellular accumulation rate and obtaining decreased toxicity. Thereby, a prolonged circulation time, small distribution volume and higher doxorubicin (about 3-15 times) accumulation in tumor site and reduced cardiac side effects are obtained (Gabizon and Martin, 1997). Phase II trials with single agent PLD showed significant activity in platinum resistant or refractory ovarian cancer patients with overall response rates ranging from 12-26 % (Muggia et al., 1997; Gordon et al., 2000; 2001). PPE, mucositis and stomatitis are reported to be the most common serious side effects in these trials. The previous Taiwanese study by Chou HH showed the toxicity when treated with Lipo-Dox® that anemia, leukopenia and thrombocytopenia occurred in 20.9%, 32.8% and 9% of cycle respectively, and were mostly Grade 1 or 2. Skin rash/desquamation occurred in 7.4% of all cycles. Grade1/2 stomatitis and pharyngitis were observed in 28.4% of all cycles. Their patients showed less hand–foot syndrome, but more stomatitis and pharyngitis (Chou et al., 2006). According to our study, we found that the most common toxicity was leucopenia which occurred in 66.7%. Anemia occurred in 58.3%. The bone marrow toxicity in our study was found rather more than previous studies using single agent PLD. This may be from the common side effect of carboplatin which was combined in the treatment regimen in our study. Another common toxicity such as mucositis, PPE and thrombocytopenia were identified at 41.7%, 33.3% and 22.2% respectively which were a little bit more than Taiwanese study. However, most of the toxicity was grade 1-2 and reversible. Very few patients were intoleratable to the treatment.

In conclusion, our study suggests that distearoylphosphatidylcholine pegylated liposomal doxorubicin(DPLD), the second-generation PLD drug, at 40 mg/m^2 combined with carboplatin equivalent to the area under the concentration–time curve (AUC) of 5 mg min/ml. every 4 weeks are effective and have low toxicity for salvage treatment of recurrent platinum-resistant or refractory epithelial ovarian cancer and could be an appropriate option for these patients.

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References

A'Hern RP, Gore ME (1995). Impact of doxorubicin on survival in advanced ovarian cancer. *J Clin Oncol*, **13**, 726-32.

Alberts DS, Liu PY, Wilczynski SP et al (2008). Randomized trial of pegylated liposomal doxorubicin (PLD) plus carboplatin versus carboplatin in platinum-sensitive (PS) patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy (Southwest Oncology Group Protocol S0200). *Gynecol Oncol*, **108**, 90-4.

Bookman MA, Malmstrom H, Bolis G, et al (1998). Topotecan for the treatment of advanced epithelial ovarian cancer: an open-label phase II study in patients treated after prior chemotherapy that contained cisplatin or carboplatin and paclitaxel. *J Clin Oncol*, **16**, 3345-52.

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

du Bois A, Pfisterer J, Burchardi N, et al (2007).Combination therapy with pegylated liposomal doxorubicin and

carboplatin in gynecologic malignancies: a prospective phase II study of the Arbeitsgemeinschaft Gynäekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and Kommission Uterus (AGO-K-Ut). *Gynecol Oncol*, **107**, 518-25.

Fanning J, Bennett TZ, Hilgers RD (1992). Meta-analysis of cisplatin, doxorubicin, and cyclophosphamide versus cisplatin and cyclophosphamide chemotherapy of ovarian carcinoma. *Obstet Gynecol*, **80**, 954-60.

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.

Ferrandina G, Corrado G, Licameli A, et al (2010). Pegylated liposomal doxorubicin in the management of ovarian cancer. *Ther Clin Risk Manag*, **6**, 463-83.

Ferrero JM, Weber B, Geay JF, et al (2007). Second-line chemotherapy with pegylated Liposomal doxorubicin and carboplatin is highly effective in patients with advanced ovarian cancer in late relapse: a GINECO phase II trial. *Ann Oncol*, **18**, 263-8.

Gabizon A, Meshorer A, Barenholz Y (1986). Comparative long-term study of the toxicities of free and liposome-associated doxorubicin in mice after intravenous administration. *J Natl Cancer Inst*, **77**, 459-69.

Gabizon A, Papahadjopoulos D (1988). Liposome formulations with prolonged circulation time in blood and enhanced uptake by tumors. *Proc Natl Acad Sci USA*, **85**, 6949-53.

Gabizon A, Catane R, Uziely B, et al (1994). Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes. *Cancer Res*, **54**, 987-92.

Gabizon A, Uziely B, Lotem M, et al (1997). Doxil in patients with pretreated metastatic breast cancer (MBC): a dose-schedule finding study with pharmacokinetics. *Proc Am Soc Clin Oncol*, **16**, 516.

Gokhale PC, Radhakrishnan B, Husain SR, et al (1996). An improved method of encapsulation of doxorubicin in liposomes: pharmacological, toxicological and therapeutic evaluation. *Br J Cancer*, **74**, 43-8.

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.

Gordon AN, Fleagle JT, Guthrie D, et al (2001). Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol*, **19**, 3312-22.

Gordon AN, Tonda M, Sun S, Rackoff W (2004). Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. *Gynecol Oncol*, **95**, 1-8.

Grover S, Hill-Kayser CE, Vachani C, et al (2012). Patient reported late effects of gynecological cancer treatment. *Gynecol Oncol*, **124**, 399-403.

Harashima H, Midori Y, Ohshima S, et al (1993). Kinetic analysis of tissue distribution of doxorubicin incorporated in liposomes in rats (II). *Biopharm Drug Dispos*, **14**, 595-608.

Herman EH, Rahman A, Ferrans VJ, Vick JA, Schein PS (1983). Prevention of chronic doxorubicin cardiotoxicity in beagles by liposomal encapsulation. *Cancer Res*, **43**, 5427-32.

Hong RL, Tseng YL (2001). Phase I and pharmacokinetic study of a stable, polyethylene-glycolated liposomal doxorubicin in patients with solid tumors: the relation between pharmacokinetic property and toxicity. *Cancer*, **91**, 1826-33.

Huang SK, Lee KD, Hong K, Friend DS, Papahadjopoulos D (1992). Microscopic localization of sterically stabilized liposomes in colon carcinoma-bearing mice. *Cancer Res*, **52**, 5135-43.

Markman M, Hoskins W (1992). Responses to salvage chemotherapy in ovarian cancer: a critical need for precise definitions of the treated population. *J Clin Oncol*, **10**, 513-4.

Markman M, Kennedy A, Webster K, et al (2000). Phase 2 trial of liposomal doxorubicin (40 mg/m^2) in platinum/paclitaxel-refractory ovarian and fallopian tube cancers and primary carcinoma of the peritoneum. *Gynecol Onco*, **78**, 369-72.

McGuire WP, Hoskins WJ, Brady MF, et al (1996). Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med*, **334**, 1-6.

Muggia FM, Hainsworth JD, Jeffers S, et al (1997). Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. *J Clin Oncol*, **15**, 987-93.

Papahadjopoulos D, Allen TM, Gabizon A, et al (1991). Sterically stabilized liposomes: improvements in pharmacokinetics and antitumor therapeutic efficacy. *Proc Natl Acad Sci USA*, **88**, 11460-4.

Power P, Stuart G, Oza A, et al (2009). Efficacy of pegylated liposomal doxorubicin (PLD) plus carboplatin in ovarian cancer patients who recur within six to twelve months: a phase II study. *Gynecol Oncol*, **114**, 410-4.

Rahman A, Treat J, Roh JK, et al (1990). A phase I clinical trial and pharmacokinetic evaluation of liposome-encapsulated doxorubicin. *J Clin Oncol*, **8**, 1093-100.

Rose PG, Fusco N, Fluellen L, Rodriguez M (1998). Second-line therapy with paclitaxel and carboplatin for recurrent disease following first-line therapy with paclitaxel and platinum in ovarian or peritoneal carcinoma. *J Clin Oncol*, **16**, 1494-7.

Safra T, Groshen S, Jeffers S, et al (2001). Treatment of patients with ovarian carcinoma with pegylated liposomal doxorubicin: analysis of toxicities and predictors of outcome. *Cancer*, **91**, 90-100.

Shapiro JD, Millward MJ, Rischin D, et al (1996). Activity of gemcitabine in patients with advanced ovarian cancer: responses seen following platinum and paclitaxel. *Gynecol Oncol*, **63**, 89-93.

Singal PK, Iliskovic N (1998). Doxorubicin-induced cardiomyopathy. *N Engl J Med*, **339**, 900-5.

Steffensen KD, Waldstom M, Pallisgard N, et al (2013). Panitumumab and pegylated liposomal doxorubicin in platinum-resistant epithelial ovarian cancer with kras wild-type the palido study, a phase II nonrandomized multicenter study. *Int J Gynecol Cancer*, **23**, 73-80.

Strother R, Matei D (2009). Pegylated liposomal doxorubicin in ovarian cancer. *Ther Clin Risk Manag*, **5**, 639-50.

Stuart GC, Kitchener H, Bacon M, et al (2011). Gynecologic Cancer InterGroup (GCIG) consensus statement on clinical trials in ovarian cancer: report from the fourth ovarian cancer consensus conference. *Int J Gynecol Cancer*, **21**, 750-5.

Williams CJ, Stewart L, Parmar M, Guthrie D (1992). Meta-analysis of the role of platinum compounds in advanced ovarian carcinoma. The advanced ovarian cancer trialists group. *Semin Oncol*, **19**, 120-8.

Yuda T, Maruyama K, Iwatsuru M (1996). Prolongation of liposome circulation time by various derivatives of polyethyleneglycols. *Biol Pharm Bull*, **19**, 1347-51.