Pegylated Liposomal Doxorubicin versus Gemcitabine in Progressive or Recurrent Platinum-Resistant Ovarian Cancer (phase III study)

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Abstract

Aim of the study: to investigate the efficacy & tolerability, of pegylated liposomal doxorubicin (PLD) versus gemcitabine (Gem) in the salvage treatment of progressive or recurrent platinum-resistant ovarian cancer.

Patients and Methods: A randomized phase III study planned to compare PLD (40 mg/m2 every 28 days) to Gem (1,250 mg/m2 on days 1 & 8 every 21 days) in ovarian cancer patients who experienced failure after only one platinum/taxane protocol and who had recurrence or progression within 6 months after completion of primary treatment.

Results: Between Feb. 2008 and August, 2010, a total of 49 patients were enrolled, including 24 patients to the PLD arm (arm A) and 25 patients to the Gem arm (arm B). The study remained open to follow-up for survival and other information until July; 2011.Both arms were balanced for clinicopathologic characteristics. The median PFS in PLD arm was 4.5 months while that for Gem arm was 5 months (P=0.2). Median OS for the PLD arm was 13 months while that for Gem arm was12.5 months and the difference was not statistically significant (*P*=0.35). There was no statistically significant difference between both treatment arms in the overall response rate (6 patients in each arm).both haematologic & non haematologic toxicities were comparable in the two treatment arms except for hand & foot syndrome which is significantly higher with PLD (P=0.02).

Conclusion: PLD and Gem are effective agents in platinum-resistant epithelial ovarian cancer with no significant difference in the PFS, OS, and response rate. Also both agents have tolerable & similar toxicity profile with the exception of hand & foot syndrome which is significantly higher with PLD. Lager randomized studies are needed to confirm these results

Introduction

Approximately 90% of ovarian cancer is epithelial in origin and poses significant therapeutic challenges due to the advanced stage of most patients with this disease. Among different gynecologic malignancies, ovarian cancer (OC) is considered as the leading cause of gynecologic cancer mortality. (1) Long-term survival for advanced-stage disease is only 30%, even among women who have had optimal cytoreduction and front-line combination therapy. Despite the advances in surgical efforts and the achievement of high response rates with platinum/paclitaxel front-line treatment, ovarian cancer remains the most lethal gynecologic malignancy, with a 5-year survival rate of 25% to 30% in advanced stage disease. (2) The major determinants of clinical outcome are the extent of residual tumor at primary surgery and sensitivity to platinum-based chemotherapy. (3) Advanced-stage epithelial ovarian cancer is a chemo responsive disease in the majority of cases, although relapse often occurs and resistance eventually develops to most forms of treatment. The platinum compounds remain the single most active drugs in the treatment of this disease. The combination of platinum compound and a taxanes such as paclitaxel is now accepted as an appropriate first-line chemotherapy option for many patients with a primary response rate of 70% to 80%. (4) Treatment goals after failure of first-line treatment for ovarian cancer are controlling or preventing disease-related symptoms, maintaining quality of life, and prolonging progression-free survival. However, the likelihood of benefit from reusing platinum agents in recurrent disease depends on the interval between the last dose of platinum and the time of relapse (i.e., the platinum-free interval, PFI). Patients with a PFI of less than 6 months are less likely to respond to second-line platinum and are often managed with an alternative agent (5). Patients who are platinum resistant, as defined by a short PFI of less than 6 months or progression during platinum-based chemotherapy, are typically treated with a variety of single agents. Indeed, in platinum-resistant ovarian cancer patients, salvage chemotherapy with nonplatinum agents mostly results in short-lived response rates of approximately 10%to25% with poor survival.(6) Potentially non cross-resistant drugs with activity in the platinum-resistant setting include pegylated liposomal doxorubicin (PLD), paclitaxel, docetaxel, topotecan, gemcitabine, or oral etoposide. PLD is a stealth formulation of doxorubicin, in which a polyethylene glycol layer surrounds a doxorubicin-containing liposome. PLD is often well tolerated in doses of 40 mg/m^2 given every 4 weeks, although the development of palmer-plantar erythrodysesthesia (PPE) or hand-foot syndrome may require dose reductions. There is evidence that dose reduction from 50 to 40 mg/m^2 reduces the incidence of PPE without compromising cytotoxic activity. (7) Phase II studies have shown that platinum-Gem doublet and platinum-taxane-Gem triplet regimens are active first-line chemotherapy in advanced OC, with overall response rates (ORR) above 55%. Several phase III studies of Gem-based doublet and triplet chemotherapy in OC are currently underway. Gem is also active as second-line monotherapy in women with recurrent OC, although studies combining Gem with other agents resulted in higher overall response rates (ORR) than Gem alone. These studies show that Gem-based

chemotherapy may have an important role as second-line treatment in women with platinum-resistant OC.(8) As the quality of life of women with recurrent OC in a respectable issue, it is important to assess the prognosis of each patient individually before start the most appropriate chemotherapy.

Patients and methods

Study Design

A randomized, phase III, comparative study of PLD versus Gem in women with epithelial OC recurring within 6 months after completion of a primary platinum/taxane containing regimen. The primary end point was the assessment of progression free survival (PFS) in PLD-treated patients versus Gem-treated patients. Whereas secondary end points were the assessment of overall survival (OS), response rate (RR), and toxicity.

Eligibility Criteria:

- Female ≥ 18 years of age.
- Measurable or assessable OC according to Response Evaluation Criteria in Solid Tumors (RECiST) who had experienced recurrence or treatment failure within 6 months after first-line, platinum/taxane-containing chemotherapy.
- Adequate bone marrow function (platelets≥100,000/μL, hemoglobin ≥ 9 g/dL, and absolute neutrophil count [ANC] ≥1,500 cells/μL), renal function (serum creatinine ≤ 1.5 mg/dL), liver function (AST ≤ 1.5 X the upper limit of normal, alkaline phosphatase ≤1.5X the upper limit of normal, and bilirubin ≤ upper limit of normal), and cardiac function (left ventricular ejection fraction ≥50% or the institutional normal).
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
- No prior malignancies (with the exception of curatively treated skin carcinoma).
- Written consent from the patient or her care-sponsor relative.

Exclusion Criteria:

- Pregnancy or breastfeeding.
- Patients expected to live ≤3 months.
- Patients had a history of cardiac disease that contraindicates the use of any of the treatment protocol medications (the New York State Heart Association, NYHA classification of class II or greater).
- Patients who had received prior PLD or Gem, or had received chemotherapy within 30 days of the first dose of study drug.

Treatment Protocol

Treatment given to patients in arm A is PLD 40 mg/m2 by a 1-hour infusion every 28 days with appropriate premedication (gransetron 3 mg or ondansetron 8 mg, dexamethasone 8 mg, & antihistaminic chlorepheneramine) 30 minutes before drug infusion without cooling manipulation of hands & feet, while in the arm B, Gem was administered at 1,250 mg/m2 as a 30-minute infusion after the same preparation on days1& 8 of a 21-day cycle. In both arms, treatment was discontinued if there is disease progression, grade 3 or 4 non hematologic toxicity (excluding alopecia and nausea/vomiting) or patient's decision to withdraw participation. In case of platelets less than 100,000/μL, hemoglobin less than 9 g/dL, or ANC less than 1,500 cells/μL on day 1 of the next cycle, treatment was postponed 1 week. Granulocyte colony-stimulating factor (G-CSF) is allowed in grade 3 & 4 neutropenia. In case of hemoglobin less than 8.5 g/dL, whole blood or packed RBC transfusion is also allowed, while if there was a delay of more than 3 weeks the patient had to be excluded from the final data.

Patients' evaluation and assessment

All patients in both arms must be assessed within 2 weeks before starting treatment by medical history, physical examination, CBC, serum chemistries, CA-125 analysis, and chest/abdomen computed tomography scan to define and measure the extent of disease. Assessment of response according to the RECiST criteria (9) was performed every two cycles. While toxicity was graded using the National Cancer Institute Common Toxicity Criteria. (10)

Statistical Analysis

Efficacy analysis was performed on all randomly assigned patients based on the intent-to-treat principle. Response rates were compared using an unadjusted normal approximation for the difference of two binomial proportions, and 95% CIs were evaluated. PFS was estimated from the first day of study drug dosing to the date of disease progression or the date last seen, whereas OS was defined as the time interval from the first day of drug administration to death from disease or the date last seen. Medians and life-tables were computed using the product-limit estimate of the Kaplan-Meier method (11) and analyzed using the log-rank test. (12)Cox proportional hazards model (13) was used to assess the effect of treatment after adjusting for other variables. Multivariate analyses including age, CA-125 levels, performance status, and PFI duration were done for both TTP and OS. Software used was GraphPad prism version 5.01

Results

Patient Characteristics

Between Feb. 2008 and August, 2010, a total of 49 patients were enrolled, including 24 patients to the PLD arm (arm A) and 25 patients to the gemcitabine arm (arm B).this final number after exclusion of two patients, one in each arm (in PLD arm, it was patient refusal while in Gem arm it was due to delay in schedule for 3 weeks) and was excluded from all statistical calculations The study remained open to follow-up for survival and other information until July, 2011. The small number of this study is explained by being a monocenter phase III study and being carried out on a special group of patients with recurrent OC i.e. those with platinum-resistant disease. When comparing patient characteristics, both treatment arms had similar distributions based on age, performance status, response to prior platinum therapy, tumour type & grade, recurrence site, and CA-125 levels. So both arms were well balanced for all clinicopathologic characteristics (Table1).

Table 1: the clinicopathologic characteristics.

	Arm A (PLD)	Arm B (Gem)	P value
Number of patients	24	25	0.7
Age			
Median	57	59	0.66
Range	37-70	39-71	
Performance status			
ECOG 0	10	11	0.89
1	11	12	0.84
2	3	2	0.67
Histopathologic type			
Serous	19	18	0.34
Mucinous	2	3	0.67
Undifferentiated	2	1	0.56
Clear cell	-	1	0.50
Endometrioid	1	2	

Tumor Grade			
I	2	2	0.99
II	4	3	0.8
III	18	20	0.34
Platinum-free interval			
>3 months	9	9	0.5
<3 months	15	16	0.67
Site of recurrence			
Pelvis only	4	3	0.77
Abdominal only	8	9	0.89
Lymph nodes only	2	2	0.34
> 1 site	10	11	
CA-125 levels, (U/mL)			
Median	176	183	0.59
Range	5-3220	7-3400	

Primary end point: There was no statistically significant difference in the PFS between both arms. The median PFS in PLD (arm A) was 4.5 months while that for Gem. arm (arm B) was 5 months with a P value of 0.2. Fig.1

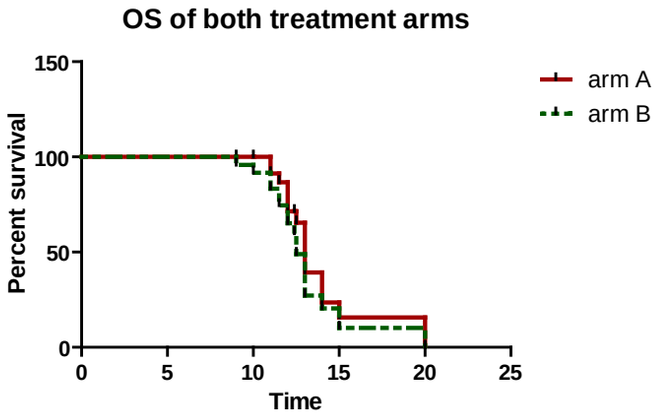

Fig 1: PFS for both treatment arms; (P value calculated by Mantle Cox method was 0 .2045 and HR was 1.66 and interval at 95% was 0.75-3.7).

Secondary end point: I-overall survival (OS): Median OS times for the PLD arm was 13 months while that for gemcitabine arm was12.5 months and the difference was not statistically significant (*P*= .35), figure 2 & table 2.

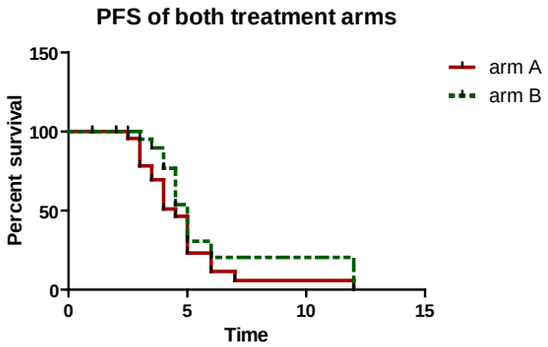

Fig 2: OS for both treatment arms.

Assessment of response: Only one patient in arm A (PLD) had complete response (CR) while there was no CR in arm B (Gem). Regarding the partial responders, they were 5 in arm A and 6 in arm B while the stable disease was observed in 9 patients & 11patients in arm A & B respectively. Unfortunately, 9 patients in arm A as well as 8 patients in arm B had disease progression during the follow up period. There was no statistically significant difference between both treatment arms. table 2

Table 2 : Response rate

Type of response	Arm A (PLD) 24 pts.	Arm B (Gem) 25 pts.	P value
CR	1 (4%)	-- (0%)	0.86
PR	5 (20%)	6 (24%)	0.85
SD	9 (38%)	11 (44%)	0.67
PD	9 (38%)	8 (32%)	0.84
Overall response rate (CR+PR)	6 (25%)	6 (24%)	0.99

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Assessment of toxicity: Non haematologic toxicities: with the exception of hand & foot syndrome which was more in the arm A (PLD) than arm B (Gem), there was no statistical difference between the two treatment arms in all other non haematologic toxicities. Table 3

Table 3: Non haematologic toxicities.

Type of toxicity	Arm A (PLD)24 pt.	Arm B (Gem)25 pt.	P value
Nausea	4	3	0.56
Vomiting	2	1	0.66
Diarrhea	2	2	0.9
Mucositis	2	1	0.77
Constipation	1	1	0.9
Hand & foot syndrome	2	0	.02
Peripheral neuropathy	1	1	0.9
Allergic reaction	1	0	0.23

Haematologic toxicities: there was no statistical difference between the two treatment arms in grade 3 & 4 haematologic toxicities including the need for growth factors & blood transfusion. Table 4

Table 4: Haematologic toxicities.

Type of toxicity	Arm A (PLD)	Arm B (Gem)	P value
Anaemia (grade 3 or 4)	2	3	0.44
Neutropenia (grade 3 or 4)	3	6	0.07
Thrombocytopenia (grade 3 or 4)	1	2	0.56
Blood/RBCs transfusion	3	3	0.9
G-CSF use	4	6	0.09

Discussion

In the time that most patients with epithelial ovarian cancer respond to first-line treatment, 50-75% of these patients will eventually relapse. (14) So, the detection of an active agent in patients with platinum-resistant disease is an important issue. Although till now there is no consensus as to which agent is most active or what schedule is most advantageous, PLD and Gem both are considered as active agents that can be used for the treatment of patients with disease that is refractory to both paclitaxel- and platinum-based regimens. In this

study we investigated the efficacy and tolerability of PLD vs. Gem as a first line chemotherapy in OC patients who relapsed or progressed within 6 months of the primary treatment with platinum/ taxane regimen. Although the small number of patients included in this monocenter study may affect its results, it represents a special group of patients who has bad prognosis among other patients with recurrent OC. The efficacy was assessed by comparing the PFS, OS, & RR in both arms while the haematologic & non-haematologic toxicities were reported also in both treatment arms to evaluate patients' tolerability. In this group of patients, the Ideal agents should lack cross resistance to previously used agents i.e. platinum & taxanes. Also because of the palliative nature of second-line treatment, these agents should also have a favourable toxicity profile. In our study the median PFS in the PLD arm was 5 months while that for the Gem arm was 4.5 months and there was no statistical difference between the two treatment arms (P value=0.2). Comparing these data with the study of David G, et al (15), They found that the median PFS to be 3.6 & 3.1 months respectively for the two arms also without statistical difference. Regarding the median OS, in our study it was 13 months for PLD arm while it was found to be 12.5 months for Gem arm with a P value of 0.35 and again these results are comparable to the results of David & his colleagues who reported a median OS of 12.7 & 13.5 months respectively and the difference was statistically insignificant. It is worthy to note that in David's study the dose of PLD was 50 mg/m2 every 28 days while the Gem dose was 1000 mg/m2 D1, D8, & D15 and these doses are slightly higher than ours. Regarding the ORR, in PLD arm it was 25% and in the Gem arm it was 24% with an insignificant P value. When comparing these data with the above mentioned study of David & his colleagues, the same results were obtained when estimating the difference in the overall response rate (P value=0.589). also in a second similar study carried out in 2008 by Gabriella F et al (16) There was no statistically significant difference in the rate of overall response, according to treatment arms (P = .066). Similar results were obtained in this study when analysing only the subgroup of patients with measurable disease (P =0.221). There was no statistically significant difference in the percentage of overall clinical benefit between GEM- and PLD-treated patients (58% & 71% respectively; P = .085). Once assessing patients' tolerance to treatment, it was found to be well tolerated in both treatment arms (PLD & GEM) and with exception of the hand & foot syndrome which was significantly higher in PLD arm (P =0.02). All other haematologic and non haemalologic toxicities were comparable in both arms. During the first two cycles of treatment, one patient discontinued treatment in each arm (in PLD arm, it was patient refusal while in Gem arm it was due to delay in schedule for 3 weeks) and was excluded from all statistical calculations, and no patients died during study therapy as a result of treatment toxicity.. More patients in the Gem group experienced grade 2, 3, or 4 constipation (P=.004), grade 2, 3, or 4 nausea and vomiting (P=.008), and grade 2, 3, or 4 fatigue (P =.043) compared with PLD patients. While in the grade 3 or 4 hematologic events, neutropenia was significantly higher in the Gem arm (P = .003) compared with PLD. Mostly these differences are attributed to the difference in the Gem. Dose which is higher in their study than ours (1000mg/m2 D1, 8&15 Vs. 1250 mg/m2 D1 &8). Many other trials assessed the tolerability of PLD and Gem in the treatment of platinum resistant ovarian carcinoma either head to head as Gabriella et al (15) or separately as with Gorumlu et al (17), with a conclusion that both PLD & Gem are active and tolerable agent in heavily pretreated epithelial ovarian cancer patients. And even when combined together, PLD & Gem were effective (74.3% disease control rate) and tolerability. (18) We must emphasize that number of patients in our study is relatively small compared to other studies which may explain some discrepancies in the final results and clarify the need for large multicenter studies including larger number of patients. In conclusion PLD as well as Gem are effective agents in platinum-resistant epithelial ovarian cancer with no significant difference in the PFS, OS, and response rate. Also both agents have tolerable toxicity profile- with the exception of hand & foot syndrome which is significantly higher with PLD. Lager randomized studies with larger number of patients are needed to confirm these results.

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