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Gemcitabine Plus Pegylated Liposomal Doxorubicin in Patients with Advanced Epithelial Ovarian Cancer Resistant/Refractory to Platinum and/or Taxanes. A HeCOG Phase II Study

DIMOSTHENIS V. SKARLOS[1], HARALABOS P. KALOFONOS[2], GEORGE FOUNTZILAS[3], MELETIOS A. DIMOPOULOS[4], NICHOLAS PAVLIDIS[5], EVANGELIA RAZIS[6], THEOFANIS ECONOMOPOULOS[7], DIMITRIOS PECTASIDES[7], HELEN GOGAS[8], PARIS KOSMIDIS[6], DIMITRIOS BAFALOUKOS[9], GEORGE KLOUVAS[1], GEORGE KYRATZIS[10] and GERASIMOS ARAVANTINOS[10]

[1]Second Department of Medical Oncology, "Henry Dunant" Hospital, Athens;
[2]University Hospital of Patras, Rio, Patras; [3]"Papageorgiou" Hospital,
Aristotle University of Thessaloniki School of Medicine, Thessaloniki;
[4]"Alexandra" Hospital, Department of Clinical Therapeutics, University of Athens School of Medicine, Athens;
[5]Department of Medical Oncology, Ioannina University Hospital, Ioannina;
[6]"Hygeia" Medical Center, Athens; [7]"Attikon" Hospital, Athens;
[8]"Laikon" Hospital, Athens; [9]Metropolitan Hospital, Oncology Department, Athens;
[10]Third Department of Medical Oncology, "Agii Anargiri" Cancer Hospital, Athens, Greece

Abstract. *Background: A phase II study was conducted to evaluate the efficacy and toxicity of the combination of gemcitabine (GEM) and pegylated liposomal doxorubicin (PLD) in patients with platinum- and/or taxane-resistant/refractory advanced epithelial ovarian cancer (AEOC). Patients and Methods: Patients (pts), who had been treated with platinum or paclitaxel and met the criteria of resistant/refractory AEOC, received GEM 650 mg/m^2 days 1 and 8 and PLD 25 mg/m^2 day 1 every 4 weeks up to a total of 6 cycles, unless disease progression or adverse effects prohibited further therapy. Results: Thirty-seven patients entered the study. There was 1 complete (3%) and 7 partial responses (19%) for an overall response rate of 22%. Two patients had stable disease (5.5%). After a median follow-up of 16.2 months, the median survival was 8.4 months and time to treatment failure 2.7 months. The most frequent severe toxicity was myelosuppression recorded in 13 (35%) patients. Severe stomatitis was recorded in only 2 (5%) cases and severe palmar-plantar erythrodysesthesia in 1 patient. One severe allergic reaction (grade 4) to PLD was recorded following the third cycle of treatment. Conclusion: The combination of GEM and PLD in patients with AEOC, who are resistant/refractory to platinum and/or Taxanes, did not show any superiority over monotherapy. However, in view of the acceptable toxicity profile, the above combination may deserve further investigation in a randomised setting.*

Correspondence to: D.V. Skarlos, MD, Second Dept. of Medical Oncology, "Henry Dunant" Hospital, 107, Mesogion Av., 11526, Athens, Greece. Tel: +30210-6972613, Fax: +30210-6972435, e-mail: hecogiat@otenet.gr

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The current standard of treatment for newly diagnosed advanced epithelial ovarian cancer (AEOC) is cytoreductive surgery followed by systemic chemotherapy with platinum compounds in combination with taxanes (1-3). However, despite the initial good response obtained in up to 70% of patients, 50-70% will eventually relapse. For relapsing patients a number of cytotoxic agents have been investigated with the goal of re-achieving a new response, improving the quality of life and/or prolonging survival (4). Patients who relapse are classified as being platinum-sensitive, if the relapse occurs >6 months after the initial response to platinum-based chemotherapy, or platinum resistant, if the relapse occurs ≤6 months, and refractory if no response is observed during platinum-based chemotherapy (5).

For platinum-sensitive tumors, re-challenge with cisplatin, carboplatin, or oxaliplatin with/ or without taxanes is often recommended; however, this approach leads to a 20-40% overall response rate (ORR) (6). Unfortunately, limited therapeutic options are available for platinum- and/or taxane-resistant and refractory disease. Drugs that have been tested and shown to have activity include hexamethyl-melamine (7), oral etoposide (8), ifosfamide (9), vinorelbine (10), topotecan (11), gemcitabine (12) and the anthracyclines (13). ORRs with these agents, usually partial

and of short duration, range from 10-26%, while the median survival ranges from 6 to 16 months. At present, topotecan is regarded as a reasonable treatment option for those patients (11).

Studies with combination chemotherapy such as ifosfamide and oral etoposide (13) or vinorelbine and docetaxel (14) have also been tested extensively. The results have shown that combined chemotherapy was not superior in terms of efficacy, while it was associated with meaningful toxicity.

Gemcitabine (GEM), a pyrimidine antimetabolite, exhibits cell phase specificity, primarily by killing cells undergoing DNA synthesis and also by blocking the progression of cells through the G1/ S-phase boundary (15). The drug has been found to be active against M_5 ovarian cancer cells, as well as in preclinical models bearing human ovarian cancer (16). GEM has also been investigated in patients with relapsed AEOC, with responses rates of the order of 20% being reported (12).

The polyethylene-glycol-coated liposomal formulation of doxorubicin (PLD) avoids uptake by the reticuloendothelial system, resulting in enhanced delivery of doxorubicin to the tumor and improved specificity. The consistent low plasma levels of the drug lead to lower frequency of alopecia, nausea/ vomiting and myelosupression, while the dose-limiting toxicity is palmar-plantar erythodysesthesia (PPE) syndrome (17). Liposomal doxorubicin has been tested in a small study of resistant/ refractory AEOC where a 26% ORR was reported (18). PLD has been compared to topotecan in relapsed ovarian cancer and the results were similar, while PLD had better tolerability (19). Furthermore, cost-minimization analyses performed in the U.S.A. / U.K. (20), Spain (21) and Italy (22) favour PLD.

Considering the single agent activity of GEM and PLD in relapsed AEOC, and the fact that they have different mechanisms of action, as well as non-overlapping toxicity, makes the combination a very attractive option to other agents. Therefore, the Hellenic Cooperative Oncology Group (HeCOG) has conducted a phase II study in order to assess the activity and safety of the GEM and PLD combination in patients with resistant/ refractory AEOC.

Table I. *Patient characteristics.*

	N	%
Number	37	
Age (years)		
Median	63	
Range	29-82	
Performance status		
0	17	46
1	14	38
2	6	16
Resistant/Refractory		
Resistant[1]	20	54
Refractory[2]	17	46
Histology		
Serous	29	78
Endometrioid	3	8
Clear cell	1	3
Adenocarcinoma	4	11
Grade		
II	8	22
III	23	62
IV	2	5
Unknown	4	11
Baseline CA-125 (units)		
Median	217.5	
Range	(8.5-5848)	
Measurable or evaluable disease		
No	1	3
Yes	36	97
Interval from previous treatment (months)		
Median	3.15	
Range	0.5-6	

[1]Resistant: If relapse occurred ≤6 months after initial response to platinum and/or Taxane.
[2]Refractory: If no response or progression occurred during platinum-based chemotherapy

Patients and Methods

Eligibility criteria. Patients entered the protocol if they had histologically or cytologically proven epithelial ovarian cancer resistant/refractory to platinum/taxane treatment. Patients were required to have measurable or evaluable disease, absolute neutrophil count (ANC) ≥1,500/μl, platelets ≥100,000/μl, creatinine ≤1.5 times the upper limit of normal, AST and alkaline phosphatase ≤2.5 times the upper limit of normal, ejection fraction of left ventricular ≥50% and performance status (PS) of 0-2 according to the Eastern Cooperative Oncology Group scale.

Patients were excluded from the study if they had had other malignancies during the previous 5 years (with the exception of non-melanoma skin cancers and *in situ* carcinoma of the cervix), life expectancy ≤3 months, history of prior radiotherapy, prior chemotherapy with GEM or anthracycline or any history of serious cardiac disease, even medically controlled.

Before entering the study, patients provided informed consent. The study was approved by the HeCOG Protocol Review Committee and conducted according to the Declaration of Helsinki.

Treatment plan. Patients who fulfilled the above-mentioned criteria were further treated with GEM 650 mg/m^2 in a 30-minute infusion given on days 1 and 8 followed by PLD (25 mg/m^2 in a 30-minute

Table II. *Incidence (%) of toxicities.*

	Grade			
Toxicities	1	2	3	4
Anemia	10 (27%)	10 (27%)	5 (13.5%)	-
Granulopenia	5 (13.5%)	9 (24%)	4 (11%)	3 (8%)
Leukopenia	11 (30%)	7 (19%)	6 (16%)	1 (3%)
Thrombocytopenia	4 (11%)	2 (5%)	-	1 (3%)
Nausea/Vomiting	10 (27%)	10 (27%)	-	-
Stomatitis/ Oesophagitis	2 (5%)	2 (5%)	2 (5%)	-
Pulmonary	-	1 (3%)	1 (3%)	-
Alopecia	3 (8%)	5 (13.5%)	1 (3%)	-
Skin	4 (11%)	1 (3%)	1 (3%)	-
Nephrotoxicity	1 (3%)	-	-	-
Neurotoxicity	7 (19%)	2 (5%)	-	-
Fever	1 (3%)	6 (16%)	-	-
Pain	4 (11%)	1 (3%)	-	-
Fatigue	4 (11%)	8 (22%)	-	-
Arthalgias/ Myalgias	3 (8%)	1 (3%)	-	-
Constipation	5 (13.5%)	3 (8%)	-	-
Diarrhea	4 (11%)	-	-	-
PPE*	2 (5%)	1 (3%)	1 (3%)	-
Allergic**	-	-	-	1(3%)**

*Palmar-plantar Erythrodysesthesia
**Grade 4 allergic reaction to PLD

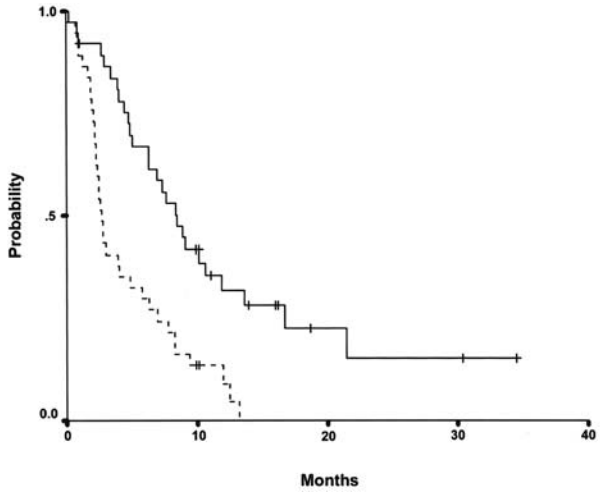

Figure 1. *Time to treatment failure (- - -) and overall survival (— — —).*

infusion) on day 1 every 4 weeks. Treatment was given up to 6 cycles providing that no tumor progression was established.

Treatment was delayed for up to 15 days if ANC were <1,500/μl and/or platelets <100,000/μl. A 25% reduction in drug dose was administered on subsequent cycles. If grade 3 or 4 neutropenia or thrombocytopenia occurred at any time, then 75% of the initial dose was re-administered on subsequent cycles.

The dose of PLD was also modified if palmar-plantar erythrodysesthesia (PPE) or stomatitis occurred. For PPE or stomatitis grades 1 and 2 a delay until recovery was permitted without any dose modification. A re-challenge with a 25% decrease of the doses for both drugs was performed in case of grade 3 PPE or stomatitis. In case of grade 4 PPE or stomatitis, patients were taken off the study.

Assessment of response. Before initiation of treatment, patients had full blood count (FBC), renal and liver function tests, CA-125 levels, left ventricular ejection fraction (LEVF) and computer tomography (CT) of the abdomen and thorax. Blood laboratory tests, including CA-125, were repeated before each cycle while LEVF and CT's were repeated every 3 cycles. In case of fever, blood cultures were performed.

Response was defined according to standard Gynecologic Oncology Group (GOG) criteria as follows: complete response (CR) was the disappearance of all gross evidence of disease for a duration of at least 4 weeks and CA-125 levels within normal limits. Partial response (PR) was a 50% or greater reduction in the product obtained from measurement of each lesion for at least 4 weeks and no appearance of new lesions, with a ≥50% decrease of CA-125 levels. Progressive disease (PD) was defined as a 50% or greater increase in the product from any lesion or the appearance of any new lesions. Stable disease (SD) was defined as any condition not meeting those criteria.

Statistical analysis. The primary end-point of this study was to evaluate the response to chemotherapy. Secondary end-points were survival and toxicity. Sample size was based on ORR. According to Simon's two-stage minimax design (23), assuming that the expected ORR would be at least 40% and the minimum acceptable response rate 20%, a sample of 18 patients was required in the first step. If a minimum of 5 responses were observed, a total of 33 patients would be accrued. Thereby, if at least 11 responses occurred, the probability of accepting a treatment with a real ORR of less than 20% would be 5%. On the other hand, the risk of rejecting a treatment (at the second stage) with a response rate of more than 40% would be 20%.

Following an interim analysis, 6 responses were detected and the study was continued to completion.

Survival was defined as the time from registration on the study to the date of last contact or to the date of death by any cause and it was calculated using the Kaplan-Meier method (24). Time to treatment failure (TTF) was defined as the time from registration to the date progression of disease was first documented (patients who discontinued their treatment for any reason or died from probably disease-related causes were considered, at that time, as treatment failures). Exact confidence intervals (CI) were used to determine the 95% upper and lower CI's of the response rate (25).

Results

Patient characteristics. Thirty-seven patients with AEOC resistant/ refractory to platinum and taxane entered the study. The median age was 63 years, while the vast majority had a good PS. All patients had a left ventricular ejection fraction >50% (Table I).

Drug administration. Nine patients (24%) completed their 6 scheduled chemotherapy cycles. Reasons for treatment discontinuation were; disease progression in 5 patients withdrawal of consent in 3, toxicity and urgent hospitalization due to stroke in 1 case each. There were 5 deaths during the entire treatment period, 3 from tumor progression, 1 from treatment-related toxicity (sepsis) and 1 from cardiac arrest.

Treatment characteristics. A total of 142 cycles of PLD and 263 cycles of GEM were administered. The median delivered dose intensity (DI) of PLD was 5.7 mg/m^2 / week (range 3.2-9.3) and the median relative dose intensity (RDI) was 0.91 (range 0.51-1.0). For GEM, the median delivered DI was 285 mg/m^2 / week (range 153-373) and the median RDI was 0.88 (range 0.47-1.0).

Toxicity. Toxicity was generally mild and patients tolerated their treatment reasonably well. The most frequent severe toxicity was myelosuppression (35%). Of note, only 2 patients had stomatitis grade 3, while severe PPE was recorded in only 1 case. One patient experienced a grade 4 allergic reaction to PLD and discontinued the treatment after the third cycle. One further patient developed febrile neutropenia following the fourth cycle and died from sepsis (Table II).

Response, TTF and survival. Overall, 36 patients with measurable or evaluable disease were included in the analysis of response. Six patients were not evaluable for response: 4 patients refused to be evaluated, 1 died from cardiac arrest and 1 experienced grade 4 allergic reaction to PLD and stopped chemotherapy before response assessment.

There was 1 complete response (3%, 95% CI: 0.07% - 14.5%) and 7 (19%) partial responses (95% CI: 8.2% - 36%) for an ORR of 22% (95% CI: 10% - 39%). Stable disease was recorded in 2 patients (5.5%, 95% CI: 0.7% - 18.7%).

After a median follow-up of 16.2 months (range, 0.16 - 34.5), 27 patients (73%) had died and 26 (70%) demonstrated tumor progression. The median survival was 8.4 months (range, 0.16-34.5), while the median TTF was 2.7 months (range, 0.01-13) (Figure 1).

Discussion

It is well established that the treatment of relapsed AEOC does not yield satisfactory response rates, the duration of response is short and survival is limited. Patients with platinum- and/or taxane-sensitive disease respond better and live longer compared to those with resistant/ refractory disease (5, 6). Due to the poor survival rate, palliation and improved quality of life are important considerations. Unfortunately, for this patient group, combination therapies have not proven superior to single agents and are associated with increased toxicity and less tolerability (13, 14). Therefore, single agent treatment may be the preferable treatment. Among the different chemotherapies tested, topotecan remains the most widely used cytotoxic drug (11). However, when PLD was compared to topotecan in a large phase III trial with both sensitive and resistant refractory patients, the efficacy was almost identical. Furthermore, PLD offered better tolerability than topotecan (19). On the other hand, the GEM and PLD combination seems very attractive, at least theoretically, since: a) the two drugs have different mechanisms of action and thus may act synergistically, b) they are active in resistant/ refractory AEOC, c) are non cross-resistant and d) have non-overlapping toxicities (12, 19).

In the present study, the median TTF was 2.7 months, ORR 22% and median survival 8.4 months. These results were not superior to those achieved when GEM or PLD were administered as single agents (12, 18, 19). Although there is a theoretical rationale for a synergistic effect between these two drugs, our data do not support it. However a definite conclusion cannot be drawn since few studies in relapsed ovarian cancer have separately evaluated sensitive and resistant/ refractory patients. In fact, our study is one of the very few that has included patients with exclusively resistant/ refractory disease. Furthermore, our study population represents a group of resistant/ refractory patients not only to platinum compounds but also to taxanes.

Among 474 patients with relapsed ovarian cancer entered in the previously mentioned phase III trial (19), 254 were platinum-resistant/ refractory. Among 130 patients who had received PLD, ORR was observed in 12% (with 1% CR), TTF was 9 weeks and median survival was 35.6 weeks (19). These results with PLD monotherapy were almost identical to ours with the combination of PLD and GEM. It might be argued that the decreased doses of PLD and GEM that were used in our study did not allow achievement of maximum efficacy.

Our patients tolerated the combination reasonably well and were able to receive 91% and 88% of the scheduled doses of PLD and GEM, respectively. Most of the patients did not complete their treatment program, mainly due to disease progression. The most frequent hematological toxicity was neutropenia. Of note, 2 severe episodes of stomatitis and 1 severe PPE event were recorded. This toxicity profile was consistent with that observed in a phase I study conducted by Tobias *et al.* (26) and the doses of GEM and PLD in our study were identical to those proposed. In that study, 6 out of 14 patients responded for a 43% ORR (5 CR, 1 PR, 5 SD). Toxicity was generally acceptable and only 1 case of severe thrombocytopenia was recorded. However, their phase I study included patients with sensitive and resistant/ refractory disease and, unfortunately, no separate analysis between the two groups was performed.

Based on these results, the same group performed a phase II trial that included 35 patients with resistant/refractory AEOC. The dose of GEM was identical to the previous phase I study, while the dose of liposomal doxorubicin was increased to 30 mg/m^2 on day 1. Activity was assessed by measuring CA-125 levels and clinical benefit by using the EORTC QLQ-30 instrument. A reduction of CA-125 ≥75% in 12 and ≥50% in 4 patients was observed, respectively, for an ORR of 52% for CA-125 reduction. However, 19 out of 34 patients developed grade 3-4 toxicity. One patient died of bowel obstruction (not related to neutropenia) (27).

In an Italian phase I trial, 23 relapsed patients with AEOC were treated with 6 different levels of the GEM and liposomal doxorubicin combination. The maximum tolerated dose (MTD) for GEM was 800 mg/m^2 on days 1 and 8 and for liposomal doxorubicin 35 mg/m^2 on day 1 every 3 weeks. Five patients responded partially and 5 had stable disease. Once again, both platinum-sensitive and -resistant/refractory patients were included in this study, while no separate analysis was performed (28). This study was followed by a phase II trial, conducted by the same group, with liposomal doxorubicin 30 mg/m^2 on day 1 every 3 weeks followed by GEM 1,000 mg/m^2 on days 1 and 8 every 21 days. Fourteen responses were recorded (4 CRs and 10 PRs) among the 46 patients assessable for response. Eight responses (3 CRs, 5 PRs) were recorded in platinum-sensitive, 4 in -resistant and 2 in -refractory patients, respectively. Therefore, the ORR for resistant/refractory disease was 9%. Grade 3/4 neutropenia was observed in 25% and 7.7% of the patients, grade 3/4 anemia in 5.7% and 3.8% and grade 3/4 thrombocytopenia in 5.7% and 0%, respectively. Furthermore, grade 3/4 PPE was noticed in 11.5% of patients (29).

In conclusion, this phase II study with the combination of PLD and GEM in patients with platinum-/taxane-resistant/refractory ovarian cancer suggests that the combination is not superior to single agent monotherapy with either GEM or PLD. However, in view of its acceptable toxicity profile, and the limited published information on this issue, further investigation in randomized studies with monotherapies such as PLD, topotecan or even GEM may be worthy of consideration.

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