

Liposome Encapsulated Doxorubicin Citrate (Ledc) as an Alternative Therapeutic Option for Patients with Recurrent Ovarian Cancer Suffering from Doxorubicin-Related Cutaneous Toxicity

Roberto Angioli¹, Michela Angelucci^{1*}, Francesco Plotti¹, Corrado Terranova¹, Roberto Montera¹, Patrizio Damiani¹, Ester Valentina Cafa¹, Pierluigi Benedetti Panici² and Angiolo Gadducci³

¹Department of Obstetrics and Gynecology Campus Bio Medico University of Rome, Rome, Italy

²Department of Obstetrics and Gynecology, "Sapienza" University of Rome, Rome, Italy

³Department of Obstetrics and Gynecology, University of Pisa, Rome, Italy

Abstract

Introduction: Pegylated liposomal doxorubicin (PLD) is considered to be the single-agent of first choice for patients with recurrent ovarian cancer following paclitaxel/carboplatin-based chemotherapy. However, this drug is associated with a local inflammatory tissue reaction, called palmoplantar erythrodysesthesia (PPE). A new liposomal formulation, known as Liposome Encapsulated Doxorubicin Citrate (LEDC), has been developed in the past decades to limit PPE. In this study we report our experience with LEDC in patients with recurrent ovarian cancer who discontinued doxil due to severe PPE.

Methods: The present retrospective study included 43 patients with recurrent ovarian cancer who were treated with LEDC administered at the dose of 50 mg/mq every 3 weeks until disease progression or unacceptable toxicity. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria Version 3. Response was graded according to Response Evaluation Criteria in Solid Tumors (RECIST).

Results: A total of 32 patients completed planned 6 cycles of chemotherapy. A complete response was achieved in 6%, partial response in 20%, stable disease in 37% and progression in 9% of patients. No cutaneous toxicity was reported.

Conclusion: LEDC is a well tolerated drug and a valid therapeutic option for patients with ovarian cancer suffering from doxil-related cutaneous toxicity.

Keywords: Cutaneous toxicity; Chemotherapy; Refractory disease; Ovarian cancer

Introduction

In spite of recent progress in treatment strategies, 70% of advanced stage ovarian cancer cases relapse [1]. Patients with recurrent disease are commonly characterized as platinum sensitive or platinum resistant. The definition of platinum-resistant disease includes patients who progress while receiving initial chemotherapy or within 6 months of completing initial platinum-based chemotherapy. If platinum free interval is less than 3-month, patients are defined as refractory disease and they have very little chance to respond to a platinum-based therapy.

Platinum-sensitive patients are defined by recurrence after 6 or more months of the completion of initial chemotherapy. For a better subdivision of platinum sensitive group, patients with a more than 12-month interval are defined as highly sensitive disease and patients with 6 to 12 months are considered intermediate sensitive disease. Response to platinum retreatment increases with a longer interval from prior platinum treatment.

Whereas combination treatment with a platinum-doublet is frequently used for recurrent platinum-sensitive patients, especially those with a prolonged disease-free interval, numerous agents are available that can be used as single-agent therapy. Epirubicin, Etoposide, Topotecan, Gemcitabine and Pegylated Liposomal Doxorubicin [2-6] are some of the single-agent treatment options. Single-agent treatment is currently the preferred approach for platinum-resistant patients with a response rate ranging from 9% to 33%. The goal of treatment in these patients is controlling the disease and the disease-related symptoms,

limiting treatment-related toxicity and maintaining or improving quality of life. Therefore, toxicity profile of these drugs is crucial.

Anthracyclines have demonstrated cytotoxic activity in advanced ovarian cancer. Response rate is between 14% and 20% [2,7]. Despite its efficacy substantial toxicity related to its myelosuppressive and cardiotoxic effects has limited its use [8].

Pegylated liposomal doxorubicin (PLD) has been developed to obtain equal benefit without the several side effects of doxorubicin [9,10]. Pegylation of liposomal capsules alters the pharmacokinetic profile, decreasing volume of distribution and extending circulation time [11].

Phase 2 studies established PLD to be an active cytotoxic agent in platinum refractory ovarian cancer when administered at a dose of 50 mg/m² every 3 weeks [12]. At this dosage, however, the most common grade 3-4 non hematological toxicities associated with PLD were

***Corresponding author:** Michela Angelucci, Department of Obstetrics and Gynecology, University of Rome "Campus Bio-Medico", Via Álvaro del Portillo, 200 - 00128 Rome, Italy, E-mail: m.angelucci@unicampus.it

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palmoplantar erythrodysesthesia (PPE) (37%) requiring in most cases, dose reductions and treatment delays. Indeed, because of liposomes small size, PLD extravasates through endothelial cells of tumor vasculature: this property, combined with its longer half life, promotes targeted drug delivery to the tumor site but extravasation may occur in other areas of microvascular permeability [13].

In the past decades, a new liposomal formulations, Liposome-Encapsulated Doxorubicin Citrate (LEDC), has been developed to improve toxicity profile of chemotherapy with anthracyclines. LEDC is a complex of doxorubicin citrate encapsulated in nonpegylated liposomes. Because of their bigger size than PLD, the LEDC liposomes do not pass through the capillary beds of normal tissues, while they enable accumulation of the drug at sites of neoplasia, due to the leaky vasculature present in this area [14]. In several prospective studies LEDC showed antitumor efficacy with low toxicity [15].

Only one study has been conducted on use of LEDC in gynecological malignancies, showing promising results in terms of disease control and toxicity rate [16]. This is the first multicenter study that examines the potential role of LEDC in treating recurrent metastatic ovarian cancer in patients who discontinued previous CT regimen due to severe cutaneous toxicity (palmoplantar erythrodysesthesia) after multiple chemotherapy regimens.

Patients and Methods

We have retrospectively assessed 43 patients who developed PPE during doxil-based chemotherapy for recurrent epithelial ovarian cancer from January 2000 to December 2008 at Policlinico Campus Bio Medico, Department of Reproductive Medicine, Division of Gynecology and Obstetrics, University of Pisa, and Department of Gynecology, Perinatology and Pediatric Nursing of Policlinico Umberto I University “La Sapienza” of Rome. The study has been approved by a Policlinico Campus Bio Medico ethics committee.

Eligibility criteria were: two or more prior chemotherapy regimens; discontinuation of a previous regimen due to grade III-IV palmar-plantar erythrodysesthesia (PPE); presence of measurable disease; adequate organ function (as evidenced by white blood cell count of 3000/KL or greater, granulocyte count of 1000/KL or greater, platelet count of 100,000/KL or greater, creatinine level of 2.0 mg/100 mL or less, bilirubin level of 1.5 times the institutional normal or less); no previous or concomitant other malignancy; performance status ≤ 2 . The performance status assessment was performed using the ECOG (Eastern Cooperative Oncology Group) score [17]. Measurable disease was defined as lesions measured by means of imaging techniques (CT scan; MRI) as recommended by the protocol of Response Evaluation Criteria in Solid Tumors [18].

Patients enrolled in this study received a first-line treatment with carboplatinum. Platinum-sensitive disease was defined as a response to initial platinum-based therapy followed by a progression-free interval of 12 months. Platinum-resistant disease was defined as progression or stable disease during the initial platinum-based therapy or relapse within 6 months after completion of platinum-based therapy. Partial platinum sensitivity was defined as a progression between 6-12 months after completion of chemotherapy.

All patients enrolled in the study were treated with Liposomal Encapsulated Doxorubicin Citrate (LEDC). LEDC was administered intravenously over 1 hour-period at the dose of 50 mg/mq every 3 weeks until disease progression or unacceptable toxicity.

Tumor response was assessed every three chemotherapy cycles

(three weeks after the last administration) by means of imaging techniques according to the target lesion site (CT scan; MRI) and of blood dosage of CA125. According to Response Evaluation Criteria In Solid Tumors (RECIST), complete response was defined as a disappearance of all target lesions. Partial clinical response was defined as a lesion major diameter reduction of 30%. A decrease or increase in size below 30% in absence of new lesions diagnosis was defined as stable disease. An increase of more than 30% or the appearance of new lesions were defined as progressive disease. Clinical response duration or steady disease duration were calculated from the beginning of the treatment to the diagnosis of progression.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria Version 3 during treatment, complete blood cell count, differential, and platelet count were repeated at 7th, 11th, 15th days after chemotherapy cycle and hematologic toxicity grading was based on nadir counts. Blood chemistry analyses were performed on the 15th day after chemotherapy. A dose reduction of 25% was performed when a grade III-IV hematologic toxicity was observed [19].

Chemotherapy was discontinued if toxicity lasted longer than 2 weeks. Cardiac toxicity was based on echocardiographic left ventricular ejection fraction (LVEF) measurements and a 12-lead electrocardiogram that were performed at baseline and every 12 weeks (3 months) [20].

Results

Table 1 summarizes patients characteristics. The median age was 65 (range 42-79), most patients (83%) had performance status 0, forty patients were affected by recurrent disease, while 3 patients had metastatic disease. Most common sites of relapse were peritoneum (51%) and pelvis (34%). Platinum sensitive patients are 34 (80%), platinum resistant patients are 7 (16%) and partial platinum sensitive are 2 (4%).

After initial three cycles of chemotherapy, 3 out of 43 patients showed a complete response (6%), 9 patients showed a partial response

Characteristics	
Number of patients	43
Median Age (range)	65 (42-79)
ECOG performance status, n (%)	
0	36 (83)
1	7 (16)
2	-
Metastatic Ovarian Cancer, n (%)	3 (6)
Recurrent Ovarian Cancer, n (%)	40 (94)
Platinum Sensitive, n (%)	34 (80)
Platinum Resistant, n (%)	7 (16)
Partial Platinum Sensitive, n(%)	2 (4%)
Site of Relapse, n (%)	
Lung	2 (4)
Liver	5 (11)
Peritoneum	15 (34)
Pelvis	13 (30)
Retroperitoneum	8 (19)
Previous CT lines, n (%)	
I line	4 (9%)
II line	29 (67%)
III line	10 (23%)
Previous Side Effects, n (%)	
PPE	43 (100%)

Table 1: Characteristics of patients.

(20%), 21 patients (46%) achieved a stable disease and 10 patients (23%) had progressive disease. These latter stopper LEDC treatment and received other palliative chemotherapy. No treatment-related deaths were recorded. The most common toxicity was myelosuppression. G1, G2, G3 neutropenia occurred in 23%, 34%, 11% of the patients, respectively (Table 2), and only one patient (2%) suspended the treatment for febrile neutropenia G4. Therefore we excluded this patient from the study and then she was submitted to different schedules of palliative chemotherapy. Moreover G1 and G2 anaemia were encountered, respectively, in 12 (27%) and in 10 (23%) patients. G3 anaemia was observed in only 2 patients (5%). The nadir counts were observed more frequently at the 15th day after chemotherapy.

In 7 (16%) patients the dose was reduced by 25% after neutropenia or G3 anemia. No cutaneous toxicity was reported. There were no episodes of cardiac dysfunction (>10% reduction in ejection fraction) in all of patients. Overall toxicity profile after 3 cycles is showed in Table 2.

Patients with complete, partial or stable disease were treated with 3 successive cycles of LEDC, followed by disease reevaluation. Thus a total of 32 patients (74%) completed the planned 6 cycles of chemotherapy. After 6 cycles of chemotherapy, 3 out of 43 patients (6%) continued to show a complete response, 9 patients (20%) evidenced partial response, 16 patients (37%) showed stable disease and 4 patients (9%) suffered disease progression.

No severe G3–G4 hematologic toxicity was showed in this group, but neutropenia and anemia continued to be the most common side effects after 6 cycles of LEDC. In particular G1 neutropenia was encountered in 20 patients (46%) and G2 neutropenia was encountered in 15 patients (34%). G1 anaemia was encountered in 22 patients (51%) and G2 only in 10 patients (23%).

There were no episodes of G3–G4 toxicity in all of patients (Table 3). No cutaneous toxicity were reported. There were no episodes of cardiac dysfunction (>10% reduction in baseline ejection fraction) in all of patients.

Discussion

Advances in the treatment of ovarian cancer over the past decade, have led to emphasize the concept of managing ovarian cancer as a chronic disease. Indeed, patients are generally undergo a series of treatments, associated with progressively treatment-free intervals, with an increased median survival but a long-term management of these patients [21].

Treatment of patients with metastatic or recurrent ovarian cancer is often palliative. The value of a second-line therapy and its impact on survival is very poor [22] Many active agents such epirubicin (2),

Side Effects	G1	G2	G3	G4
Neutropenia	10 (23%)	15 (34%)	5 (11%)	1 (2%)
Anemia	12 (27%)	10 (23%)	2 (5%)	-
Thrombocytopenia	3 (7%)	2 (5%)	-	-
Nausea and Vomiting	6 (14%)	2 (5%)	-	-
Cutaneous	-	-	-	-
Stomatitis	-	-	-	-
Alopecia	5 (11%)	16 (37%)	-	-
Cardiac (reduction of EF>10%)	-	-	-	-

(one patient could have more than one side effects)

Table 2: Side Effects after 3 cycles of LEDC.

Side Effects	G1	G2	G3	G4
Neutropenia	20 (46%)	15 (34%)	-	-
Anemia	22 (51%)	10 (23%)	-	-
Thrombocytopenia	3 (7%)	2 (5%)	-	-
Nausea and Vomiting	4 (9%)	2 (4%)	-	-
Cutaneous	-	-	-	-
Stomatitis	-	-	-	-
Alopecia	5 (11%)	16 (37%)	-	-
Cardiac (reduction of EF>10%)	-	-	-	-

(one patient could have more than one side effects)

Table 3: Side effects after 6 cycles of LEDC.

etoposide (3), topotecan (4), gemcitabine (5) and pegylated liposomal doxorubicin (6) show response rate ranging from 9% to 33%, but prolonged remissions are uncommon.. The goal of treatment in these patients is controlling the disease and the disease-related symptoms, limiting treatment-related toxicity and maintaining or improving quality of life. Therefore, toxicity profile of these drugs is crucial.

Pegylated liposomal doxorubicin (PLD) is considered to be the single agent of first choice for patients with recurrent ovarian cancer following paclitaxel/carboplatin based chemotherapy, when administered at a dose of 50 mg/m² every 3 weeks [6,10]. Because of its size, PLD extravasates through endothelial cells of tumor vasculature. This property, combined with its longer half-life, promotes targeted drug delivery to the tumor site but extravasation may occur in other areas of microvascular permeability, in particular from the microcapillaries of the hands and feet. This local accumulation may cause a skin inflammatory reaction, called PPE, often requiring dose reduction and/or treatment delays [23].

In the mid-1980s, the Liposome Company developed LEDC, a stable, non pegylated liposomal formulation of doxorubicin. The strategy that allowed doxorubicin to be loaded into relatively small liposomes (150 nm) is a mechanism of passive encapsulation. Sodium carbonate was added to an aqueous suspension of liposome in a proton rich environment (citrate buffer) creating a pH of 7.8 outside the liposome and pH 4 within the liposome. When doxorubicin was added to these liposomes, its accumulation to the vesicle interior was driven by the lower internal pH since the doxorubicin formed a unique complex with citrate anions in the vesicle interior [19]. Liposomal entrapment alters the pharmacokinetics of doxorubicin and allows targeted chemotherapy as demonstrated in previous studies, where accumulation of LEDC in tumour tissue was more persistent than that conventional doxorubicin or PLD.

Compared to PLD, LEDC has a reduced half-life compared to recently reported for PLD [24]. This difference in half-life between LEDC and PLD is likely to contribute to the difference in toxicity profiles between the two formulations, such as reduction of PPE frequency and/or severity, and reduction of cardiac toxicity. The combination of LEDC plus cyclophosphamide showed a better therapeutic index, with reduced cardiotoxicity, reduced myelotoxicity and similar antitumor activity, when compared with the combination of PLD plus cyclophosphamide as first-line chemotherapy for metastatic breast cancer [25]. Grade 3–4 PPE, which is a dose limiting toxicity with PLD, was not observed in LEDC treated patients.

Only one study in gynecologic oncology showed activity of LEDC at dose of 75 mg/m² every 3 weeks in advanced/recurrent gynecological cancer patients, with an overall response rate of 17% with a duration of response of 27 weeks. In particular the drug obtained a partial response and a stabilization of disease in 20% and 33%, respectively,

of patients with recurrent ovarian cancer. Treatment with LEDC in these patients was well tolerated: only one patient developed PPE (G3), while hematologic toxicity G3-G4 was encountered in 22 patients of 36 (22%). Only two patients (11%) suspended therapy following an episode of febrile neutropenia and nine patients (50%) required a dose reduction of 25% for hematologic toxicity. As a result, the next 18 patients were treated at a reduced dose 60 mg/m² of LEDC [16].

Thus in the management of ovarian cancer there is not a standard dosage of LEDC. In previous study on gynecologic malignancies [16] the authors used LEDC at dose of 75 mg/m² every 3 weeks. In consideration of their hematologic toxicity noticed in this study we decide to use LEDC at dose of 50 mg/m² every 3 weeks.

Therefore, the aim of our study was to investigate the toxicity profile, especially in terms of dermatological toxicity, of LEDC administration at the dose of 50 mg/m² q21 in a population of metastatic/recurrent ovarian cancer patients, who discontinued previous CT regimen due to severe PPE.

In our study a total of 32 patients (74%) completed the planned 6 cycles of chemotherapy.

Concerning response rate, our study shows that after 6 cycles of LEDC, 3 out of 32 patients (9%) showed a complete response, 9 patients (28%) evidenced partial response, 16 patients (50%) showed stable disease and 4 patients (12%) suffered disease progression. These results are positive if compared to the data reported in the literature with other second-line agents [4,6].

Moreover, the toxicity profile of LEDC appears to be very promising. Only one patient stopped the treatment because of severe neutropenia, and no patients developed cardiac dysfunction, cutaneous toxicity, or stomatitis.

The main toxicities associated with topotecan are haematological, including neutropenia, thrombocytopenia and anaemia. Markman et al firstly evaluated topotecan at the dose of 1.5 mg/m² days 1-3 q3 weeks in a population of 29 recurrent ovarian cancer patients [26]. Severe neutropenia occurred in 24% of patients. In a phase III randomized trial, patients were randomized to receive topotecan 1.5 mg/m² for 5 days vs paclitaxel 175 mg/m² day 1 every weeks [4]. This study demonstrated a significant benefit in the group treated with topotecan in terms of time to progression (23 weeks vs. 14 weeks) while high hematological toxicity was registered. Neutropenia was significantly more frequent on the topotecan arm 79% versus paclitaxel arm 23% (P<0.1).

PPE and mucositis are the most common serious side-effects of pegylated liposomal doxorubicin. Conversely, mielotoxicity and especially severe neutropenia, often occurs in patients treated with topotecan [27], and PPE and mucositis are common serious side-effects in those treated with PLD [28,29].

Conclusions

In this first report of LEDC in the treatment of metastatic-recurrent ovarian malignancies, toxicity data are very encouraging. In fact, despite its efficacy on ovarian cancer, PLD causes a severe cutaneous toxicity called palmar plantar erythrodysesthesia requiring often dose reduction or treatment delays. PPE is an invalidating cutaneous toxicity reaction that severely reduces the quality of life of patients.

Only our previous study has been conducted on use of LEDC in gynecological malignancies, showing promising results in terms of disease control and toxicity rate [16].

This is the first study that aimed at assessing the efficacy and safety of LEDC in treating recurrent metastatic ovarian cancer in patients. In our study LEDC was generally well tolerated even in patients forced to suspend previous chemotherapy protocols because of several cutaneous side effects. In conclusion, our results indicate that the use of LEDC is a well tolerated drug and a valid alternative in patients affected by ovarian cancer suffering from cutaneous toxicity by other drugs.

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