

Tolerability of PLD/Oxaliplatin Regimen in Recurrent Ovarian Cancer Patients With Previous Fragility to Carboplatin/Paclitaxel Treatment

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Objectives: This retrospective analysis aims at describing the safety profile of treatment with pegylated liposomal doxorubicin (PLD) and oxaliplatin in recurrent ovarian cancer patients who experienced myelotoxicity (principally neutropenia) during first line chemotherapy with carboplatin and paclitaxel.

Methods: We reviewed the medical records of patients with relapsed ovarian cancer treated with PLD/Oxaliplatin at the Istituto Oncologico Veneto (IOV)/IRCCS, Padua University between 2002 and 2008.

Results: A cohort of 16 patients who developed myelodepression and other toxicities of grade 3 to grade 4 during first line chemotherapy with carboplatin/paclitaxel, were selected for this retrospective study. Patients had developed predominantly grade 3 to grade 4 neutropenia and grade 1 to grade 3 thrombocytopenia as major toxicities during primary chemotherapy with carboplatin and paclitaxel. Following relapse or disease progression, PLD/oxaliplatin chemotherapy was administered at 30 to 35 and 70 mg/m², respectively, over 2 day, every 4 weeks.

Conclusions: Complete regression and stabilization of bone marrow suppression and no allergic reactions were seen with PLD/oxaliplatin treatment. The estimated median overall survival was 51.2 months. PLD/oxaliplatin chemotherapy did not show hematological toxicity and was feasible and active in this group of pretreated frail patients.

Key Words: ovarian cancer, myelotoxicity, carboplatin, paclitaxel, pegylated liposomal doxorubicin, oxaliplatin

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A number of studies have compared the efficacy of cisplatin/paclitaxel with carboplatin/paclitaxel for the treatment of ovarian cancer, proving ultimately that the carboplatin regimen is better tolerated.^{1–5} Side-effects, such as emesis, nephrotoxicity, ototoxicity, and neurotoxicity, were more favorable with carboplatin, compared with cisplatin. As a result, carboplatin and paclitaxel have become the current standard of care for primary treatment of ovarian cancer.^{6–8} Unfortunately, one of the main drawbacks of the regimen carboplatin/paclitaxel is its dose-limiting and cumulative myelosuppression, characterized by granulocytopenia, thrombocytopenia, and anemia.

Generally, 70% of advanced ovarian cancers relapse after first line chemotherapy, requiring additional treatments. The reintroduction of a platinum-taxane combination, as recommended in particular for platinum sensitive cancer, at first relapse may increase myelosuppression in ovarian cancer patients whose bone marrow reserves are already compromised. These patients could have an

increased risk of clinically relevant events of neutropenia, along with infectious episodes and may not obtain maximal clinical benefits when receiving further therapies.

Therefore, in planning additional chemotherapy regimens for relapsed ovarian cancer patients, factors such as toxicity profiles and cumulative effects produced by previous lines of chemotherapy need to be considered carefully.

In this retrospective analysis, we report good tolerability of a regimen with pegylated liposomal doxorubicin (PLD; Caelyx, Schering-Plough International, Kenilworth, NJ) plus oxaliplatin (Eloxatin, Sanofi-Synthelabo Inc., Paris, France) in a select group of ovarian cancer patients that experienced neutropenia and other hematological adverse events during prior chemotherapy with carboplatin plus paclitaxel.

PATIENTS AND METHODS

The current retrospective analysis examines a cohort of 16 patients with advanced ovarian cancer, treated at our institution (Istituto Oncologico Veneto-IOV/IRCCS, Hospital of the University of Padua) between August 2002 and December 2008, who developed severe hematological toxicities following paclitaxel plus carboplatin regimen chemotherapy. This review specifically describes the regression and complete normalization of neutropenia and/or thrombocytopenia toxicities in this group of “frail” women after treatment with PLD plus oxaliplatin, a regimen regularly approved by the Ethics Committee of our institution.

Carboplatin/Paclitaxel Treatment Schedule

All patients received the following chemotherapy regimen as first line of treatment: paclitaxel at a dose of 175 mg/m² or 135 mg/m² (for elderly women) and carboplatin which was dosed according to the Calvert formula for the desired area under the curve of 5 on day 1 of a 3-week cycle, for 6 courses. All patients received standard antiemetic agents and prophylaxis for paclitaxel-associated hypersensitivity reactions. Carboplatin dose was not modified unless the patients experienced complicated grade 3 or 4 neutropenia or thrombocytopenia requiring platelet transfusion. The treatment was delayed when patients were unable to recover from a hematological toxicity. Granulocyte colony stimulating support (G-CSF) was employed to increase neutrophil counts and the carboplatin dose was reduced to area under the curve 4.

PLD-Oxaliplatin Treatment Schedule

The treatment regimen following relapse consisted of a 1-hour infusion of PLD 30 to 35 mg/m² on day 1 followed by oxaliplatin 70 mg/m² infused over 2 hours on day 2, repeated every 28 days for 6 to 8 cycles. Patients received the following premedication: dexamethasone 8 mg on day 2 and tropisetron 8 mg on day 2 of each cycle.

Assessment of Toxicity

Toxic effects were evaluated before each new treatment cycle and graded according to the National Cancer Institute Common

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Terminology Criteria for Adverse Events v3.0. A Complete blood count was carried out before each cycle of chemotherapy. Patients were required to have an absolute neutrophil count of at least 1500 per cubic millimeter, and a platelet count of at least 100,000 per cubic millimeter on the first day of course.

Statistical Analysis

Data are reported as median and range, counts and percentages when appropriate. OS was defined as the time between start of therapy with PLD-oxaliplatin and last follow-up or death. Differences in OS were estimated using log-rank test. The hypothesis tests, which gave *P* value of 0.05 or less, were considered to provide significant evidence.

RESULTS

Sixteen patients were considered for this review. The main characteristics of the patients are summarized in Table 1. Median age was ~58 years (range, 41–81). At presentation, the majority of patients (87.5%, 14/16) had a histologically confirmed FIGO stage III ovarian cancer, while ~6% of patients had stage IC and ~6% had stage IV. Histology was as follows: 68% serous papillary, 19% endometrioid, 6.5% poorly differentiated, and 6.5% Brenner tumor. All patients had a performance status (ECOG 0–2) which did not exclude treatment. The progression-free interval from the end of first-line chemotherapy to relapse was a median of 16.7 months (range, 1.6–61.1 months). According to Markman's criteria for clinical platinum sensitivity,⁹ 11 patients (~69%) were classified as sensitive and 5 (31%) as resistant to platinum therapy. Thirteen patients (~81%) received 2 or more lines of chemotherapy, including rechallenge treatment with paclitaxel and carboplatin in platinum sensitive patients, hormone therapy, and single-agent paclitaxel treatment. One patient was also treated with radiotherapy. None of the patients considered had a documented diagnosis of immunodeficiency disease or had previous hematological disorders; no predictive factors associated with an increased rate of other toxicities were observed.

During treatment with paclitaxel and carboplatin, significant myelotoxicity occurred among these 16 patients, with ~68% expe-

riencing grade 3 neutropenia, and ~19% developing at least 1 episode of grade 4 neutropenia; grade 1 and grade 3 thrombocytopenia was experienced by ~62% and 12.5% of patients, respectively (Table 2).

PLD/oxaliplatin regimen was well tolerated, with ~81% of subjects completing 6 or more cycles of therapy. The patients received a median of 7 cycles (range, 2–9), versus a median of 5.9 cycles (range, 2–10) of carboplatin/paclitaxel, employed as first line chemotherapy. Median OS (overall survival) of these patients treated with PLD/oxaliplatin was 51.2 months (95% CI: 19.1–83.3). A complete response was obtained in 6 patients (~38%) and a partial response in 5 patients (~31%). Stable disease was observed in 3 patients (~18%) and disease progression in the remaining 2 patients (13%). A low toxicity profile was observed, with no grade 3 to grade 4 toxicities reported.

DISCUSSION

Although carboplatin and paclitaxel are the current standard of primary therapy for ovarian cancer, their long-term side effects represent serious challenges in the treatment of patients with relapsed ovarian cancer. In fact, carboplatin plus paclitaxel regimen is often accompanied by cumulative bone marrow toxicity and hypersensitivity reactions in up to 15% of patients. In previous randomized studies, carboplatin in combination with paclitaxel or docetaxel had led to neutropenia in a significant number of patients.^{5,10} Moreover, women younger than 60 years compared with older women have the same risk of developing severe myelodepression, showing that carboplatin/paclitaxel-induced myelotoxicity is not dependent on age.¹¹

Within the group of patients herein described, the administration of carboplatin/paclitaxel chemotherapy was highly limited by its myelotoxicity. Since there is an unsure evidence that “maintenance dose intensity” could determine an increase in survival or quality of life and in an effort to minimize the risk of neutropenic events, we lowered the doses of carboplatin/paclitaxel over multiple cycles.^{12–14} Despite this rational approach, already adopted successfully in other ovarian cancer patients, myelotoxicity was still ob-

TABLE 1. Main Characteristics of Patients

Patient	Age	dgn, yr	Histology	Grading	Stage	N° Cycles First Line		N° Cycles PLD/
						Platinum Sensitivity	Carboplatin + Paclitaxel	
						2°/3° Lines of Chemotherapy		Oxaliplatin
1	81	SP	3	IIIC	S	5	Tamoxifen	8
2	75	SP	—	IIIC	S	5	Carboplatin + paclitaxel	8
3	61	SP	3	III	S	6	—	8
4	59	SP	3	IIIC	S	2	Tamoxifen	7
5	57	Undifferentiated	3	IIIC	R	9	Tamoxifen	9
6	70	SP	3	IIIA	S	7	Carboplatin + paclitaxel	8
7	62	SP	3	IIIB	S	5	Tamoxifen/carboplatin + paclitaxel	7
8	39	E	3	IIIB	R	6	Paclitaxel	8
9	52	E	3	IIIC	R	7	Paclitaxel	8
10	58	SP	3	IC	S	6	Topotecan + carboplatin/RT	2
11	47	SP	2	IIIC	S	3	—	8
12	69	E	ND	IV	R	10	Tamoxifen/paclitaxel	5
13	41	SP	3	IIIC	S	6	Carboplatin + paclitaxel	7
14	42	Brenner tumor	2	IIIC	S	6	—	9
15	54	SP	3	IIIC	S	6	Carboplatin + paclitaxel	3
16	62	SP	—	IIIC	R	6	Carboplatin + paclitaxel	8

SP indicates serous papillary; E, endometrioid; RT, radiotherapy para-aortic lymph nodes.

TABLE 2. Bone Marrow Toxicity

16 Patients Adverse Events Grading	Carboplatin/Paclitaxel				PLD/Oxaliplatin			
	WBC		Thrombocytes		WBC		Thrombocytes	
	N	(%)	N	(%)	N	(%)	N	(%)
0	—		2	(12.5)	—		—	
G1	—		10	(~62)	2	(12.5)	—	
G2	2	(12.5)	1		—		—	
G3	11	(~68)	2	(12.5)	—		—	
G4	3	(~19)	—		—		—	

served in this patient population. During treatment, growth factor supports G-CSF and broad-spectrum antibiotics were used in presence of grade 4 neutropenia. Notwithstanding the use of secondary prophylactic G-CSF, treatment delays were often necessary. We observed that if significant neutropenia occurred during 1 cycle, that patient was then at high risk for neutropenia during the following cycles of carboplatin-based chemotherapy.

In contrast, even though all patients had received previous carboplatin-based treatments leading to a reasonable concern for cumulative hematological toxicity, the subsequent administration of PLD/oxaliplatin in recurrent ovarian cancer patients was well tolerated. Pegylated liposomal doxorubicin, a formulation of doxorubicin encapsulated within long-circulating, polyethylene(glycol)-coated liposomes, has a mild hematologic toxicity with no cross-resistance to platinum compounds, due to its different mechanism of action. Moreover, several studies have demonstrated that the combination chemotherapy of PLD with a platinum compound is an effective regimen for improving response rate and clinical benefit in patients with both platinum-sensitive and platinum-resistant ovarian cancer.^{15,16} We chose oxaliplatin, a diaminocyclohexane platinum analogue, combined with PLD because of its favorable toxicity profile and efficacy in ovarian cancer, largely supported by a number of in vitro and in vivo studies.^{17–22} Oxaliplatin exhibits minimal hematologic side effects at recommended doses.²³ Its main adverse effect is acute, cold-triggered dysesthesias, and cumulative peripheral sensory neuropathy. Gastrointestinal toxicities, such as nausea, vomiting, and diarrhea, are also common with oxaliplatin therapy but are predominantly of mild-to-moderate severity. The incidence of these events increases when oxaliplatin is specially used in combination with fluorouracil/folinic acid for treatment of advanced colorectal cancer.^{24,25} Other minor side effects that may occur during treatment with oxaliplatin are changes in taste sensation, mouth sores, nosebleeds, fatigue, headache, dizziness, or trouble sleeping.

The toxicity profile associated with PLD/oxaliplatin treatment in our group of ovarian cancer patients was indeed markedly favorable, with no events of myelosuppression observed. The most common toxicity of PLD-oxaliplatin was mucositis (grade 1, 3/16, 18%). “Hand-foot syndrome” grade 2 occurred only in 1 patient (1/16, 6%). “Hand-foot” syndrome, also called palmar-plantar erythrodysesthesia (PPE) or hand-to-foot syndrome, and mucositis or stomatitis are some of the most common mucocutaneous reactions after the use of PLD. PPE may evolve from a light erythema accompanied by dysesthesia/paresthesia of the hands and feet (toxicity-grade 1) into a painful edematous erythema (toxicity-grade 2) followed by blistering ulcerations and desquamation that strongly influence daily activities (toxicity-grade 3). PPE typically involves the palms of the hands and the soles of the feet but may also affect other body surfaces, especially those subjected to pressure and friction, such as the sacral area, groin, and axillae. Though the etiology of PPE is still not well understood, the long half-life of

about 48 hours and the small size of the pegylated liposomes facilitate the accumulation of PLD in skin regions with a high density of capillaries. In addition, the increased PLD-concentration detected in the eccrine sweat glands of the palms and soles and the regional temperature gradients in the distal extremities have been postulated as contributors to the development of PPE. To reduce the frequency of PPE, all our patients, treated with PLD-oxaliplatin, received premedication with dexamethasone before each cycle of chemotherapy and oral pyridoxine (vitamin B6) at a dosage of 150 mg daily.^{26,27} Other toxicities, such as nausea and vomiting, were mild in most patients and easily reduced by using conventional antiemetic agents. Oxaliplatin-induced neuropathy grade 1 was reported only in 2 (12.5%) patients and was reversible after treatment without permanent impairment of sensory functions.

Thus, the combination of PLD/oxaliplatin has been demonstrated to be active and feasible in this group of bone marrow “frail” patients with either platinum-sensitive or platinum-resistant relapsed advanced ovarian cancer. It is noteworthy that the difference in median overall survival was not statistically significant among the 2 groups of platinum-sensitive and platinum-resistant patients. Obviously, the size of our group of patients does not permit us to draw any conclusion, but the results herein described are positive. Phase II studies of PLD and oxaliplatin have already shown a promising activity and a safe toxicity profile in heavily pretreated ovarian cancer patients.^{15,16} At our institution, this combination has demonstrated a response rate of 90%, when used directly as second line in long-progression free interval patients.²⁸ Therefore, these data indicate the need for larger phase III trials to further confirm these results.

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