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Efficacy of pegylated liposomal doxorubicin (PLD) plus carboplatin in ovarian cancer patients who recur within six to twelve months: A phase II study ☆

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ABSTRACT

Objectives. Pegylated liposomal doxorubicin is one of the preferred alternatives for ovarian cancer patients with early relapse (<6 months) and taxane/carboplatin for late relapse (>12 months), but the optimal therapy for the partially platinum-sensitive (6–12 months) population has not been defined. This single-arm phase II trial was designed to assess the efficacy of pegylated liposomal doxorubicin (PLD)/carboplatin in ovarian cancer patients who relapse between 6 and 12 months after initial treatment with platinum-based chemotherapy.

Methods. Ovarian cancer patients who previously completed a course of therapy with paclitaxel/carboplatin were administered PLD 30 mg/m^2 followed by carboplatin AUC 5 mg/mL/minute every 4 weeks.

Results. Fifty-eight patients were enrolled in the study and 54 were eligible for the efficacy analysis, of whom most (75%) received at least 6 cycles of PLD/carboplatin. The objective response rate was 46% (4% CR and 42% PR), with an additional 33% experiencing disease stabilization >6 months. For those patients with measurable CA-125, the response rate was 66% (28% CR and 38% PR), with an additional 18% experiencing disease stabilization >6 months. Median time-to-progression was 10 months (1.5–25). Median overall survival was 19.1 months (2.2–38.9). The most frequent adverse effects were neutropenia, thrombocytopenia, and constipation.

Conclusions. The combination of PLD/carboplatin is efficacious and well tolerated in women with partially platinum-sensitive ovarian cancer and represents a valuable alternative for patients who relapse within 6–12 months of completing paclitaxel/carboplatin chemotherapy.

Introduction

Despite maximal cytoreductive therapy, most ovarian cancer patients will relapse following first-line taxane/platinum therapy and further chemotherapy is often considered. Response to second-line therapy has been correlated with the interval between relapse and the end of the first-line treatment (treatment-free interval, TFI) [1]. For platinum-resistant tumors (relapse <6 months), pegylated liposomal doxorubicin (PLD) and topotecan are the most commonly used agents.

For platinum-sensitive tumors (response >12 months), taxane/platinum combination therapy is recommended based on the results of the ICON-4 study [2,3]. The ICON-4/AGO-OVAR-2.2 (International Collaborative Ovarian Neoplasm/Arbeitsgemeinschaft Gynaekologische Onkologie) trial demonstrated that a taxane/platinum combination is superior to conventional platinum chemotherapy in

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patients with recurrent platinum-sensitive ovarian cancer; platinum sensitivity was defined as a recurrence-free interval following platinum-based therapy >6 months [3]. In that study the 2-year progression-free survival was 57% with taxane/platinum versus 50% with conventional platinum chemotherapy; median survival was 29 versus 24 months, respectively. However, the majority of patients (75%) in the ICON-4 study relapsed >1 year after the initial chemotherapy. In the patient subgroup with a TFI between 6 and 12 months, there was no relapse-free or overall survival benefit of the combination compared to platinum monotherapy.

The optimal treatment approach for ovarian cancer patients who relapse between 6 and 12 months after completing chemotherapy has not been defined. Indeed, during the design of the present trial, platinum sensitivity was controversial, with some authors historically defining platinum-sensitive disease as TFI >6 months and others defining it as TFI >12 months.

In the recent years, the concept of sensitivity has been refined and patients who relapse between 6 and 12 months are now recognized as partially platinum-sensitive and considered as being at intermediate risk. Taxane/platinum combination therapy may not always be feasible in that subgroup of patient due to emergence of taxane-related neurotoxicity or other adverse effects. It was hypothesized that this patient group might respond to novel agents alone or in combination with platinum chemotherapy.

Two randomized controlled trials have previously compared PLD (Doxil/Caelyx) monotherapy to paclitaxel or topotecan in relapsing ovarian cancer. In a phase III trial comparing PLD 50 mg/m^2 q4 weeks versus paclitaxel 175 mg/m^2 q3 weeks, progression-free survival (PLD 21.7 vs. P 22.4 weeks, $p=0.15$), overall response (PLD 17.8% vs. P 22.4%, $p=0.34$) and median survival (PLD 45.7 vs. P 56.1 weeks, $p=0.44$) were similar [4]. However, toxicity profiles were different with more nausea/vomiting, stomatitis and palmar–plantar erythrodysesthesia (PPE) in the PLD group, while alopecia, myalgia, arthralgia and paresthesiae were more frequent with paclitaxel.

A trial comparing PLD 50 mg/m^2 q28 days versus topotecan 1.5 mg/m^2 × 5 days q21 days reported an 18% reduced risk of mortality with PLD (median survival 62.7 vs. T 59.7 weeks, $p=0.05$) [5]. This difference was primarily due to patients relapsing after 6 months, where a 30% reduction in the risk of mortality was observed with PLD versus topotecan (median survival 107.9 vs. 70.1 weeks, $p=0.017$). A separate comparison reported that PLD had comparable efficacy but was more cost-effective than topotecan [6].

Since PLD appeared to be active as monotherapy in relapsed ovarian cancer and has a favorable toxicity profile, it was a suitable candidate as an alternative to a taxane in combination therapy. The preliminary results of a GINECO phase II trial of PLD plus carboplatin indicated that this combination was active in patients with platinum-sensitive disease (relapse >6 months) [7]. A subsequent analysis reported an overall response rate of 63% (CR 38%), median PFS of 9.4 months and median overall survival of 32 months, results which compared favorably to those seen with the taxane/platinum combination used in the ICON-4 trial [8]. Hsiao et al. evaluated the combination of 40 mg/m^2 liposomal doxorubin and carboplatin AUC 6 in 32 platinum-sensitive patients and reported an overall objective response rate of 62% with a median progression-free survival and overall survival of 9.1 and 27.9 months, respectively. This trial reported little toxicity [16]. The Southwest Oncology Group randomly compared liposomal doxorubicin (30 mg/m^2) plus carboplatin (AUC 5) versus carboplatin (AUC 5) alone in platinum-sensitive patients. Although the trial closed early due to slow recruitment, 61 patients were evaluable. Response rates were 67% with combination treatment versus 32% in the carboplatin alone arm. Estimated median progression-free survival was 12 months for the combination group versus 8 months for the carboplatin group. Estimated overall survival was 26 and 18 months, respectively [17]. ARCADY/GINECO is currently comparing PLD/carboplatin versus paclitaxel/carboplatin in platinum-sensitive ovarian cancer in the phase III CALYPSO trial (NCT00189553).

Although nontaxol regimens in platinum-sensitive patients have reported reasonable response rates and little toxicity [18] no study to date has specifically addressed the partially sensitive population. This single-arm phase II trial was designed to specifically assess the efficacy of combined PLD/carboplatin in ovarian cancer patients who relapsed between 6–12 months after completion of first-line paclitaxel + carboplatin chemotherapy.

Methods

This was a multicenter single-arm phase II trial designed to assess the toxicity and efficacy of PLD 30 mg/m^2 in combination with carboplatin area-under-the-curve (AUC) 5 mg/mL/min every 4 weeks for patient at first recurrence following a platinum taxane combination. The main eligibility criteria included: histological diagnosis of epithelial ovarian cancer, ECOG performance status >2, measurable disease, prior taxane/platinum combination therapy with a TFI between 6 and 12 months, adequate liver, kidney and cardiac function, life expectancy >6 months and signed informed consent.

The primary outcome measure was response according to Response Evaluation Criteria in Solid Tumors (RECIST) [9] in patients receiving at least two cycles of chemotherapy. Secondary endpoints included toxicity, cancer antigen (CA)-125 response, PFS and OS.

CA-125 response was obtained in accordance with current Gynaecologic Cancer Intergroup (GCIG) recommendations [10]. Response was defined as a >50% decrease in serum CA-125 levels in accordance with the Rustin criteria [11,12].

The dose of PLD was set at 30 mg/m^2 every four weeks in combination with AUC 5 of carboplatin. The dose of PLD was lower than that used for monotherapy to maximize platinum exposure while minimizing potential marrow toxicity. These doses of PLD and carboplatin were used in the GINECO trial [8].

For the statistical analysis, base on the literature and the recommendation of the study steering committee, it was assumed that the PLD/carboplatin combination was active if the objective response rate (ORR) was >35%, and inactive if the ORR was <20%. Thus, 12 responders out of 60 patients were required to meet the primary endpoint. The trial was performed using a two-stage design: if at least 7 patients of the initial 30 showed response, the trial could move to the next stage and full enrolment. Patient accrual was between January 2004 and September 2006.

Results

Fifty-eight patients were enrolled in the study. Median age was 59.1 years (range 43.9 to 85.4 years) (Table 1). Subjects had received a median of six prior cycles (range 4–12) of paclitaxel/carboplatin. The median progression-free interval at study entry was 8.75 months (range 5.6–12 months). CA-125 levels were elevated in 70% of

Table 1
Patient demographics.

	Median	Range
Age (years)	59.1	43.9–85.4
ECOG Performance status (%)		
0	54%	
1	46%	
Prior cycles (carboplatin + paclitaxel)	6	4–12
Treatment-free interval prior to study entry (months)	8.65	5.6–12
CA125 (KU/L, baseline)	341.5	5–8093
Number of metastatic sites[a]	3	1–10

[a] Number of anatomic site where disease could be identified.