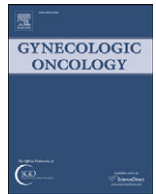




Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/gygno

Decreased hypersensitivity reactions with carboplatin-pegylated liposomal doxorubicin compared to carboplatin-paclitaxel combination: Analysis from the GCIG CALYPSO relapsing ovarian cancer trial[☆]

Florence Joly ^{a,*,1}, Isabelle Ray-Coquard ^{b,1}, Michel Fabbro ^{c,1}, Mark Donoghoe ^{d,1}, Karin Boman ^{e,1}, Akira Sugimoto ^{f,1}, Michelle Vaughan ^{g,1}, Alexander Reinthaller ^{h,1}, Ignace Vergote ^{i,1}, Gabriella Ferrandina ^{j,1}, Tiziana Dell'Anna ^{k,1}, Jens Huober ^{l,1}, Eric Pujade-Lauraine ^{m,1}

^a Centre François Baclesse, Medical Oncology Department, Caen, France

^b Centre Leon Bérard, Lyon, France

^c CRLC Val d'Aurelle, Montpellier, France

^d NHMRC Clinical Trials Centre, Sydney, Australia

^e Norrlands University Hospital, Department of Gynecological Oncology, Umeå, Sweden

^f London Regional Cancer Centre, London, UK

^g Christchurch Hospital, Christchurch, New Zealand

^h Medical University Vienna, Department of Obstetrics and Gynecology, Vienna, Austria

ⁱ University Hospital Leuven, Department of Obstetrics and Gynecology, Leuven, Belgium

^j Università Cattolica del Sacro Cuore, Campobasso, Italy

^k San Gerardo Hospital, Gynecology Department, Monza, Italy

^l University Hospital of Tübingen, Department of Gynecology, Tübingen, Germany

^m Université Paris Descartes, AP-HP, Hôpitaux Universitaires Paris Centre site Hôtel-Dieu, France

ARTICLE INFO

Article history:

Received 9 December 2010

Accepted 16 April 2011

Available online xxxx

Keywords:

Allergy

Carboplatin

Hypersensitivity reaction(s)

Ovarian cancer

Pegylated liposomal doxorubicin

ABSTRACT

Objective. To describe and analyze observed hypersensitivity reactions (HSR) from the randomized, multicenter phase III CALYPSO trial that evaluated the efficacy and safety of the combination of carboplatin and pegylated liposomal doxorubicin (CD) compared with standard carboplatin–paclitaxel (CP) in patients with platinum-sensitive relapsed ovarian cancer (ROC).

Methods. HSR documented within case report forms and SAE reports were specifically analyzed. Analyses were based on the population with allergy of any grade and for grade >2 allergy.

Results. Overall 976 patients were recruited to this phase III trial, with toxicity data available for 466 and 502 on the CD and CP arms, respectively. There was a 15.5% HSR rate associated with CD (2.4% grade >2) versus 33.1% with CP (8.8% grade >2), $p < 0.001$. HSRs occurred more often during first cycle in the CD (46%) arm than in the CP arm (16%). Multivariate predictors of allergy were chemotherapy regimen and age; patients randomized to CD and patients ≥ 70 years old on CP had less allergy. Few patients (<6%) stopped treatment due to allergy. Allergy rates were higher in patients who did not receive prior supportive treatment; however there was no relationship between allergy and the type of carboplatin product received, or response rate.

Conclusions. Use of PLD with carboplatin instead of paclitaxel and older age were the only 2 factors predicting a low rate of HSRs in patients with ROC. CD has previously demonstrated superior progression-free survival and therapeutic index than CP. Taken together these data support the use of CD as a safe and effective therapeutic option for platinum-sensitive ROC.

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Introduction

Evidence-based data and extensive clinical experience have established the platinum agents as the most biologically active cytotoxic agents in ovarian cancer [1–3]. Carboplatin, in particular, has become a standard first-line agent for ovarian cancer. Importantly, patients who have a late recurrence after initial treatment with carboplatin often respond to it a second time [1,4]. However, as a result of this expanded and extensive use, an increased incidence of

[☆] Research support: This research was supported by a research grant from Merck, formerly Schering Plough Corp.

* Corresponding author at: Medical Oncology Department, Centre François Baclesse-CHU Côte de Nacre, 3 avenue Général Harris-BP 5026, 14076 Caen Cedex 05, France. Fax: +33 2 31 45 50 97.

E-mail address: f.joly@baclesse.fr (F. Joly).

¹ On behalf of the Gynecologic Cancer Intergroup of GINECO, AGO-OVAR, NSGO, ANZGOG, NCIC-CTG, AGO-Austria, EORTC, MITO, and MaNGO.

carboplatin-associated hypersensitivity reactions (HSRs) has been observed [5–10].

When carboplatin HSRs occur, >50% of patients develop at least moderately severe symptoms, including diffuse erythroderma, tachycardia, angina, wheezing, edema, facial swelling, dyspnea, hypertension, or hypotension [7]. The likelihood for an even more severe consequence is evidenced by the growing number of reports that describe life-threatening reactions (respiratory arrest, anaphylaxis, and seizure) and even death as a result of the HSR [5,11–14].

Managing carboplatin allergy is an important challenge as up to 50% of patients who experience even a mild to moderate HSR will have their platinum therapy discontinued prematurely, even despite the use of platinum re-challenge protocols [6–8,10,15–18]. Most of the data reported to date are from limited retrospective series CALYPSO is a Gynecologic Cancer Inter Group (GCIg) trial including 976 ovarian cancer patients with platinum-sensitive relapse who were randomly assigned to carboplatin plus paclitaxel (CP) or to carboplatin plus pegylated liposomal doxorubicin (PLD; CD) [18]. This large study provides a unique opportunity to describe and analyze the observed HSR rate between the different carboplatin-based regimens; to identify predictive factors for developing allergy; to explore correlations between carboplatin HSRs and tumor response, development of hand–foot syndrome (HFS), use of supportive treatment as well as type of carboplatin administered (brand name versus generic); and, to determine if guidelines for rechallenge in case of allergy, such as those utilized in this trial, had an impact on carboplatin tolerance in patients with platinum-sensitive recurrent ovarian cancer (ROC).

Materials and methods

Design

The objective of the report was to describe and analyze observed HSRs of carboplatin based chemotherapy from the randomized, two-arm parallel non-inferiority multicenter phase III CALYPSO trial that evaluated the efficacy and safety of the combination of CD compared with standard CP in patients with platinum-sensitive ROC.

Eligibility

Patients randomized in the CALYPSO trial had a histologically confirmed diagnosis of cancer of the ovary, fallopian tube, or extra-ovarian papillary serous tumor and had disease progression >6 months after first- or second-line platinum-based chemotherapy; previous taxane therapy was required. Patients had to have measurable disease according to RECIST criteria or CA-125 assessable disease according to GCIg criteria or histological proven diagnosis of relapse. Other key eligibility criteria of the CALYPSO trial included an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 ; life-expectancy of at least 12 weeks; and adequate bone marrow, renal, and hepatic function. To be included, patients should have had no allergy to taxanes. Analysis of HSR was a secondary endpoint of the trial.

Treatment

Patients were randomized to 6 courses (or until disease progression) of PLD 30 mg/m² and carboplatin AUC of 5 (based on the Calvert formula) each administered on day 1 of a 4-week cycle or of paclitaxel 175 mg/m² and carboplatin AUC 5 on day 1 of a 3-week cycle. PLD was administered as a 1-h infusion followed by a 30-min infusion of carboplatin. Paclitaxel was administered as a 3-h infusion followed by a 30-min infusion of carboplatin.

All patients, regardless of assigned treatment, received dexamethasone 20 mg intravenously (IV) together with a single-dose IV 5HT3

antagonist 30 min prior to PLD or paclitaxel administration. Additionally, all patients randomized to CP received premedication to prevent paclitaxel HSRs, consisting of clemastine (anti-histamine) 2 mg IV and a H2-blocker (such as ranitidine 50 mg IV). Reintroduction of paclitaxel or carboplatin was conducted according to EORTC guidelines for rechallenge after an HSR. This includes dexamethasone 10–20 mg IV with ranitidine 50 mg IV 30 min prior to paclitaxel or PLD followed by clemastine 2 mg IV 15 min prior to paclitaxel or PLD. A 5HT3 antagonist is administered 30 min before carboplatin followed by clemastine 2 mg IV 15 min prior to the start of carboplatin diluted in 500 ml NaCl 0.9%. Carboplatin is administered with clemastine 2 mg IV at 15 ml/h during the first 30 min. If no reaction occurs, the infusion rate is increased to 84 ml/h during the next 30 min and continued at a rate of 500 ml/h if no reaction. Duration of the carboplatin infusion should not be <1 h 30 min. If retreatment is successful with this procedure, the same treatment procedure is repeated in all subsequent carboplatin administrations, which occurs after premedication with two 10 mg dexamethasone orally the evening before the infusion.

Sub-study and statistical analyses

In the whole population, any grade of allergy and allergy grade >2 were evaluated in the two treatment arms. Allergy, consistent with other adverse events observed in the CALYPSO trial, was graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTCAE version 3.0 [19]) as the following: grade 1: transient flushing or rash, drug fever <38 °C (<100.4 °F); grade 2: rash, flushing, urticaria, dyspnea, drug fever ≥ 38 °C (≥ 100.4 °F); grade 3: symptomatic bronchospasm with or without urticaria, parenteral medication(s) indicated, allergy-related edema/angioedema, hypotension; grade 4: anaphylaxis; grade 5: death. Descriptive statistics was used to summarize the data for the comparison of baseline characteristics for the two treatment arms experiencing allergy of any grade and grade >2, as well as in the depiction of the allergic event (e.g., severity) and resultant effects (e.g., drug discontinuation). Only allergy reported as an SAE was related by the investigator to a particular drug.

Predictive factors were analyzed in univariate and multivariate logistic regression models. These analyses were based on the whole study population with allergy of any grade and grade >2 and included the following variables: previous history of allergy (asthma, allergy, urticaria, eczema, hyper-sensitivity, lactose intolerance), age, ECOG performance status, histology, platinum-free interval, grade, stage at diagnosis, primary site, number of previous lines of chemotherapy, type of previous chemotherapy, number of previous cycles and lines of carboplatin prior to study entry, initial leukocyte count, absolute neutrophil count (ANC), lymphocyte count, body surface area, body mass index, creatinine, and treatment arms. An adjustment for treatment arm was incorporated into each univariate model. For the multivariate models, all predictors were entered into the model at the start and removed if their effect was not significant. Kendall tau-b rank correlation coefficients were calculated between allergy grade and best tumor response, as well as between allergy grade and HFS grade.

There were two separate analyses evaluating the association between allergy and supportive treatment (e.g., hematological growth factors, G-CSF, erythropoietin, antibiotics): the first analyzed supportive treatment at any time prior to the patient's first allergic reaction, and the second assessed whether supportive treatment was administered at the cycle immediately prior to the patient's first allergic reaction. In the analysis for correlation between risk of allergy and type of carboplatin received (generic versus brand name or type of generic administered), if a patient received more than one type of generic drug and did not experience an adverse event while receiving the drugs, they were included in the denominator of each type of drug received. If, however, a patient experienced an adverse event from

one type of generic received, the event would be attributed to this specific generic product, even if the patient went on with other brands. Statistical inferences were drawn at a two-sided significance level of 5%, with no adjustment for multiple comparisons.

Results

Description of allergy

Toxicity data were available for 99.1% of the 976 patients recruited to the trial: 502 of 509 patients included in the CP arm and 466 of 467 in the CD arm. From the beginning of the study, 238 patients (24.6%) had an allergic reaction: 166 patients (33.1%) in CP arm versus 72 (15.5%) in CD arm ($p < 0.001$; Table 1). Of these, 44 (8.8%) and 11 (2.4%) were grade >2 , respectively. A total of 56 patients (5.7%) stopped treatment due to allergy, 8 (1.7%) in the CD arm and 48 (9.4%) in the CP arm.

Allergic reactions reported as severe adverse events (SAE) were analyzed in order to obtain detailed information on the contribution of each specific drug to allergy that was not available in the global toxicity reports. Allergic reaction (most often grade >2) was defined as an SAE when it was considered medically significant by the investigator or required prolonged hospitalization. Allergic reaction SAEs were reported in 50 cases. Most of the allergic reactions (46/50; 92%) were attributed to carboplatin alone (38/50) or in combination (6 due to CP and 2 to CD), while 2% of allergies (1/50) were specifically related to paclitaxel and 6% (3/50) to PLD (Table 2). Within the 43 cases declared as SAEs occurring in the CP arm, carboplatin was reintroduced in 14 cases. Treatment could be completed without major allergic complication in 7/14 cases. In the additional 7 cases, the allergic reaction reappeared with retreatment despite rechallenge protocol, and required discontinuation of study drug(s). In total and counting the 7 allergic reappearances after reintroduction; allergic reaction led to drug(s) discontinuation in 36 of the 43 cases in the CP arm. In the CD arm, 7 SAE allergic reactions were reported, which all led to drug discontinuation. No drug reintroduction was performed.

In nearly half of the cases in the CD arm, the allergic reaction occurred in cycle 1 (33/72 or 45.8% any grade), with a median cycle of occurrence of 2 (Table 1). In the CP arm, 15.7% (26/166) of all allergic reactions (any grade) occurred in cycle 1; median cycle of occurrence was 2. For grade >2 allergy, 82% (9/11) of cases in the CD arm occurred in cycle 1 (median 1), whereas no cases of grade >2 occurred in cycle 1 for the CP arm; however, 50% of cases in the CP arm occurred in cycle 2 (median 2.5). This difference between cycles of first occurrence reached statistical significance ($p < 0.001$).

As recently reported, treatment arms were balanced for baseline characteristics in the intent-to-treat analysis of the CALYPSO trial [18]. Baseline characteristics of patients experiencing an HSR of any grade are depicted in Table 3. Few patients (57/968) had previous medical history of allergy before the ovarian cancer (6%).

Table 1
Descriptive analyses for allergy (any grade and grade >2).^a

Allergy	Carboplatin/PLD (n = 466)	Carboplatin/paclitaxel (n = 502)	p-value
Any grade	72 (15.5%)	166 (33.1%)	<0.001
Median cycle of first	2	2	0.001
Occurrence at cycle 1	33 (45.8%)	26 (15.7%)	<0.001
Grade >2	11 (2.4%)	44 (8.8%)	<0.001
Median cycle of first occurrence	1	2.5	<0.001
Occurrence at cycle 1	9 (81.8%)	0	<0.001

PLD, pegylated liposomal doxorubicin.

^a Data from the global analysis.

Four patients were previously treated with immunotherapy. There was no relationship between HSR and primary site, stage at diagnosis, grade, previous immunotherapy or body-mass-index.

Predictive factors for allergy

The candidate variables for predictors of allergy (any grade) are listed in Table 4. There was a significant treatment interaction ($p = 0.040$) with age (≥ 70 years vs. <70) in the prediction of allergy of any grade. Age was a significant predictor in the CP arm, with older patients having lower rates of allergy (odds ratio (OR) 0.450, $p = 0.006$); however, there was no relationship in the CD arm. As a result, there was a strong treatment effect (CD vs. CP) in patients <70 years old (OR 0.322, $p < 0.001$), but no difference between the treatments in older patients (OR 0.813, $p = 0.62$). There were no additional predictive variables for allergy in multivariate analysis (Table 5). For prediction of allergy grade >2 , treatment arm (CD vs. CP) was the only significant variable in univariate analyses (OR 0.252, $p < 0.001$). When exploratory analysis was performed separately within the CP arm, results were consistent with prior data presented, with age ≥ 70 years as the only significant predictor of allergy (less allergy after age 70) in both models (any grade, OR 0.450, $p = 0.006$; grade >2 , OR 0.215, $p = 0.036$).

Association of allergy and supportive treatment, HFS, type of carboplatin, or response

There was a correlation between the administration of supportive treatment (e.g., G-CSF or erythropoietin) and the incidence of allergy, either of any grade or grade >2 . In both treatment arms, there were higher rates of allergy in patients who had not received prior supportive treatment (43% vs. 18% in the CP arm, and 24% vs. 6% in the CD arm; $p < 0.001$, stratified by treatment arm). This pattern was consistent for allergy of grade >2 (12% vs. 5% CP, 5% vs. 0% CD; $p < 0.001$), and also when examining G-CSF and erythropoietin separately. Additionally, there was no evidence of a strong correlation between allergy and the development of HFS in the CD arm (correlation between worst allergy and worst HFS grade was 0.118). The association between drug product administered (brand name versus generic as well as brand of generic carboplatin administered) and allergy was also evaluated. The test for interaction in the rate of grade >2 allergic reaction for brand name (Bristol Myers Squibb) versus generic was not significant (Mantel-Haenszel test, stratified for treatment excluding unknown, was $p = 0.602$). There was no correlation between allergy and response to treatment ($p = 0.759$).

Discussion

The results of this analysis from the randomized phase III CALYPSO study, conducted in relapsed/recurrent ovarian cancer, confirm that reintroduction of carboplatin-based chemotherapy in patients with platinum-sensitive ovarian cancer is associated with a high rate of hypersensitivity (23.6%). Patients on both arms of the study experienced allergic reactions; however, patients randomized to the PLD-containing arm had significantly less allergy associated with their treatment than those randomized to receive CP: 15.5% versus 33.1%, respectively ($p < 0.001$). Additionally, significantly fewer severe allergic reactions ($>grade 2$) were observed in patients in the CD arm than in the standard CP arm: 2.4% versus 8.8%, respectively ($p < 0.001$). The higher HSR rate in the CP arm occurred despite intensive anti-allergic premedication given with paclitaxel, whose administration preceded that of carboplatin. Allergy that was declared as an SAE in the CP arm was mainly due to carboplatin, whereas SAE allergy in the CD arm was likely related to PLD. Though we were unable to delineate which agent contributed toward allergy for allergies that were not considered SAEs, a limitation to this analysis,

Table 2
Descriptive analysis of allergy (from SAE).^a

SAE (n = 50)	Chemotherapy relationship	Allergy incidence	Treatment stopped	Treatment rechallenged	Treatment completion after rechallenge	Allergic reappearance after rechallenge
Arm 1 (n = 43)	Carboplatin	36	24	12	6	6
	Carboplatin–paclitaxel	6	4	2	1	1
	Paclitaxel	1	1	0	–	–
Arm 2 (n = 7)	Carboplatin	2	2	0	–	–
	Carboplatin–PLD	2	2	0	–	–
	PLD	3	3	0	–	–

PLD, pegylated liposomal doxorubicin.

^a Data available for 50 patients.

allergies rated as an SAE reflected the important allergy that had an impact on the continuation of chemotherapy.

This is the largest prospective series reporting allergy after carboplatin rechallenge in ovarian cancer; other series have been either chart reviews or retrospective analyses with limited numbers of patients [5–9,11,20,21]. The global rate of hypersensitivity (24.6%) observed in the CALYPSO trial is consistent with that reported in the literature for the combinations as well as with that observed in studies of retreatment with single-agent carboplatin [22–26]. In the rechallenge setting, the incidence of carboplatin HSRs can exceed 20% [20,27].

Hence, a number of researchers have attempted to investigate predictive factors to identify patients who are likely to develop hypersensitivity [7,9,16,20,21,28–30]. Usual predictive factors studied include previous medical history of allergy, platinum-free interval,

previous number of cycles, and cumulative carboplatin dose. None of these factors studied were found to have predictive value in the CALYPSO trial. Few of our patients, however, experienced previous medical history of allergy, and patients with prior carboplatin HSRs were excluded from the trial. All the patients included had platinum-sensitive disease preventing the comparison of HSR rates between this subset of patients and patients relapsing within 6 months from last carboplatin dose (platinum-resistant disease). The allergic reaction to carboplatin is often said to mainly occur after a median number of 6–8 courses, i.e., commonly the second cycle of the first course administered in the second-line setting [6,7,9,15,20,31].

The two main predictive factors for allergic reaction within the large CALYPSO trial were treatment arm and age. Age was not surprising, as a decline in immune function that is a common phenomenon in the elderly and consistent with the observation that

Table 3
Baseline characteristics for patients randomized to CD, CP, and all patients with any grade allergy. ANC, absolute neutrophil count; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; PLD, pegylated liposomal doxorubicin; WBC, white blood cell count.

		Carboplatin/PLD (N = 466)		Carboplatin/paclitaxel (N = 502)	
		Any allergy (n = 72)		Any allergy (n = 166)	
		n/N	% ^a	n/N	% ^a
Prior allergy	No	63/433	14.5%	157/477	32.9%
	Yes	9/33	27.3%	9/24	37.5%
Age (years)	<55	19/139	13.7%	59/139	42.4%
	55–70	41/256	16.0%	90/278	32.4%
	70+	12/71	16.9%	17/85	20.0%
ECOG status	0	44/286	15.4%	104/314	33.1%
	1	23/158	14.6%	56/161	34.8%
	2	2/13	15.4%	3/15	20.0%
	3	0/0	0.0%	0/1	0.0%
	Unknown	3/9	33.3%	3/11	27.3%
WBC (x10 ⁹) ^b	≤7.0	41/270	15.2%	104/295	35.3%
	>7.0	31/192	16.1%	62/204	30.4%
WBC–ANC (x 10 ⁹) ^c	≤2.3	31/224	13.8%	77/222	34.7%
	>2.3	34/196	17.3%	77/235	32.8%
Number of previous lines of CT	1	63/408	15.4%	138/415	33.3%
	2	9/58	15.5%	28/86	32.6%
First line: Taxane-based	No	2/14	14.3%	6/16	37.5%
	Yes	70/452	15.5%	160/485	33.0%
First line: Platinum-based	No	0/1	0.0%	1/2	50.0%
	Yes	72/465	15.5%	165/499	33.1%
Second line: Taxane	No	67/421	15.9%	142/432	32.9%
	Yes	5/45	11.1%	24/69	34.8%
Second line: Platinum-based	No	63/409	15.4%	138/420	32.9%
	Yes	9/57	15.8%	28/81	34.6%
Platinum-free interval	6–12 months	24/152	15.8%	55/171	32.2%
	>12 months	46/302	15.2%	106/316	33.5%
Number of prior cycles of carboplatin	0	3/24	12.5%	11/26	42.3%
	1–6	28/220	12.7%	75/214	35.0%
	7–9	24/129	18.6%	44/150	29.3%
	>9	17/91	18.7%	35/109	32.1%

^a % represents the percentage of patients who experienced allergy among those with the given characteristic.

^b The median of WBC was 7.

^c The median of ANC was 2.3.

Table 4
Univariate predictors of allergy (any grade).

	Parameter	Odds ratio (95% CI)	p-value
Model	Treatment	Carbo–PLD vs. Carbo–Paclitaxel	0.370 (0.271–0.506)
	Prior allergy	Yes vs. No	1.643 (0.905–2.983)
	ECOG status	≥ 2 vs. 0	0.609 (0.225–1.649)
	Histological grade	3 vs. 1	0.712 (0.371–1.363)
	Stage at diagnosis	Advanced vs. Early	1.137 (0.477–2.706)
	Primary site	Ovary vs. Fallopian	0.884 (0.414–1.888)
	Prior taxane treatment	Yes vs. No	0.679 (0.197–2.344)
	Age group	≥ 70 vs. <70 [CP arm]	0.450 (0.255–0.794)
		≥ 70 vs. <70 [CD arm]	1.136 (0.576–2.239)
	Platinum-free interval	>12 vs. ≤12 months	1.034 (0.752–1.424)
	Prior cycles of carboplatin	7–9 vs. <7	0.795 (0.398–1.590)
	BMI group	>30.0 vs. ≤30.0	1.099 (0.763–1.584)
	Previous lines of CT	2 vs. 1	0.980 (0.647–1.484)
	WBC	cts (per 1 × 10 ⁹)	1.053 (0.988–1.123)
	ANC	cts (per 1 × 10 ⁹)	1.038 (0.961–1.120)
	WBC–ANC	cts (per 1 × 10 ⁹)	1.107 (0.933–1.313)
	Creatinine	cts (per 1 mg/l)	1.011 (0.975–1.047)

ANC, absolute neutrophil count; BMI, body mass index; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; PLD, pegylated liposomal doxorubicin; WBC, white blood cell count.

women in this study >70 years old had less treatment-induced allergy. Treatment arm was the strongest predictive factor for development of allergy. The incidence and severity of allergy (that induces an SAE) in the PLD-containing arm was significantly less than observed in the CP arm. Indeed, results from our trial mirror those of the recently reported randomized phase II trial from the Hellenic Cooperative Oncology Group in which 31% of patients randomized to CP experienced an allergic event compared with only 8% in the CD arm [23]. In a phase II trial of 104 patients with advanced ovarian cancer in late relapse treated with CD, only 2% of HSRs was observed [25]. This low rate of HSRs (3.4%) was also observed with CD in another phase II trial in patients recurring 6 to 12 months after treatment with CP [26]. In another phase II trial in relapsed gynecologic cancer, treatment with CD was associated with a 14% incidence of allergy of any grade and 2% grade >2 among 136 evaluable patients [32].

The exact mechanism by which carboplatin induces hypersensitivity remains unknown. Historical evidence suggests the main mechanism to be a type I immunoglobulin E-mediated reaction, with a clinical presentation characterized by symptoms consistent with the release of mast cell mediators [9–11,20,28,31]. In this scenario, carboplatin is thought to act as a hapten, binding to serum proteins [33]. It has already been suggested that IgE antibody-specific allergic activity is age-dependent, which is consistent with the observation of the influence of age in the CALYPSO trial [34]. Recent findings suggest that T-cell subpopulations may also be involved, giving evidence to support the mixed clinical presentation often associated with a carboplatin-induced allergic event [35]. These type IV delayed hypersensitivity reactions are observed when antigen-sensitized cells release cytokines after subsequent contact [36]. These reactions may occur at or near the completion of the intravenous infusion, hours to even days after administration, and with repeated exposure [6–10,20,31]. Thus, the greatest probability of reduced HSR in the CD arm is a proposed protective immune effect induced by PLD. Pegylation appears to lower the immunologic response by steric masking of antigenic sites, thereby preventing immune recognition of the therapeutic protein as foreign [37]. The PEG moiety stabilizes liposomes by providing a steric barrier against interactions with plasma proteins and opsonins and reduces liposome uptake by mononuclear cells of the reticulo-endothelial system [38]. By minimizing the exposure of antigenic determinants, pegylation reduces or prevents the generation of neutralizing antibodies [39]. Experimental data suggest that Immune T-cells responsible for the ABC phenomenon (accelerated blood clearance) that is implicated in immediate immune response might be selectively damaged by the

doxorubicin encapsulated in PEGylated liposomes but not by pegylated liposomes or doxorubicin alone [40]. Taken together, these data support the proposed protective effect induced by PLD.

We have also excluded the role of generics compared to brand of either carboplatin or paclitaxel, where the incidence of HSR was found similar [41]. Data had suggested that the high incidence of observed HSR with CP may be due to potentiation secondary to paclitaxel co-administration [6]. O'Cearbhaill et al., however, demonstrated that the majority of the 707 patients that experienced a carboplatin HSR during second-line or greater carboplatin-based treatment received non-paclitaxel-containing regimens (44% HSR rate with carboplatin–gemcitabine and 35% with carboplatin alone) [42]. Additionally, a phase III SWOG (S0200) trial that compared carboplatin with CD in recurrent ovarian cancer showed no carboplatin HSR among 61 patients in the PLD-containing arm versus 30% in the carboplatin alone arm.

Not only is the incidence of HSR important, but also the ability to safely rechallenge the patient after an allergic event. It has been reported that up to 50% of patients who experience a carboplatin HSR will have their platinum therapy permanently discontinued [8,15–18]. From the data from SAE of the CALYPSO trial, we confirmed that few patients continued carboplatin despite implementation of a rechallenge protocol and when rechallenged with carboplatin, half experienced another event requiring drug discontinuation. Many experiences and strategies of carboplatin re-introduction have been proposed with limited success, including desensitization, premedication with corticosteroids or antihistamines, prolonged infusions, and substitution with cisplatin [6–8,10,15–18,28,42–45]. Though successful, these programs can be complicated and time consuming,

Table 5
Multivariate predictors of allergy.

Parameter	Odds ratio (95% CI)	p-value
<i>Any grade</i>		
Treatment: CD vs. CP [Age<70]	0.322 (0.229–0.453)	<.001
Age ≥ 70 [CP arm]	0.450 (0.255–0.794)	0.006
Age ≥ 70 [CD arm]	1.136 (0.576–2.239)	0.713
<i>Grade >2</i>		
Treatment: Carboplatin–PLD vs. carboplatin–paclitaxel	0.252 (0.128–0.495)	<.001

CD, carboplatin–pegylated liposomal doxorubicin treatment arm; CP, carboplatin–paclitaxel treatment arm; PLD, pegylated liposomal doxorubicin; WBC, white blood cell count.

frequently requiring hospitalization, as well as stressful to both patient and healthcare staff. In order to minimize the risk of the development of a carboplatin HSR, a number of predictive factors have been investigated, including skin testing [30,43,46]. Despite its high negative predictive value, carboplatin skin testing is not widely utilized because of the time, effort, and necessary training.

In summary, based on the efficacy data reported from the CALYPSO trial, the combination of CD offers an evidence-based therapeutic option for the treatment of platinum-sensitive recurrent ovarian cancer. Additionally, based on this sub-study, the combination of CD provides an additional attractive benefit over CP by minimizing and/or diminishing the risk of carboplatin based regimen HSR.

Conflict of interest statement

The authors have no conflicts to disclose except Dr. Jens Hueber who declares BMS advisory board consulting fee.

Acknowledgements

The authors would like to acknowledge Phillips Gilmore for technical assistance in the preparation of this manuscript and Nathalie Le Fur from GINECO for the sub-study coordination.

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