original article

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Ovarian cancer in elderly patients: carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in late relapse: a Gynecologic Cancer Intergroup (GCIG) CALYPSO sub-study

J. E. Kurtz[1]*, M. C. Kaminsky[2], A. Floquet[3], A. S. Veillard[4], R. Kimmig[5], A. Dorum[6], L. Elit[7], M. Buck[8], E. Petru[9], N. Reed[10], G. Scambia[11], N. Varsellona[12], C. Brown[4] & E. Pujade-Lauraine[13] on behalf of Gynecologic Cancer Intergroup

[1]Department of Hematology and Oncology, Hôpitaux Universitaires de Strasbourg, Strasbourg; [2]Department of Medical Oncology, Centre Alexis Vautrin, Vandoeuvre les Nancy; [3]Department of Medical Oncology, Institut Bergonié, Bordeaux, France; [4]National Health and Medical Research Council Clinical Trials Centre, Sydney, Australia; [5]Department of Gynecology and Obstetrics, University of Duisburg-Essen, Essen, Germany; [6]Department of Gynecologic Oncology, The Norwegian Radium Hospital, Oslo, Norway; [7]Department of Gynecologic Oncology, Juravinski Cancer Centre, Hamilton, Canada; [8]Department of Medical Oncology, Sir Charles Gairdner Hospital, Perth, Australia; [9]Department of Gynecology and Obstetrics, Medical University of Graz, Graz, Austria; [10]Beatson Oncology Centre, Gartnavel General Hospital, Glasgow, UK; [11]Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Rome; [12]Department of Gynecology and Obstetrics, AOR Villa Sofia-Cervello, Palermo, Italy; [13]University Paris Descartes, AP-HP, Hôpitaux Universitaires Paris Centre site Hôtel-Dieu, France

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Background: CALYPSO (CAeLYx in Platinum Sensitive Ovarian) patients compared carboplatin–pegylated liposomal doxorubicin (C–PLD) with carboplatin–paclitaxel (C–P) in patients with late-relapsing recurrent ovarian cancer (ROC). We analyzed outcomes in patients ≥70 years.

Patients and methods: Nine hundred and seventy-six patients with taxane-pretreated ROC relapsing >6 months after first- or second-line platinum-based therapy were randomly assigned to 4-weekly C area under the curve (AUC) 5 plus PLD 30 mg/m^2 or 3-weekly C AUC 5 plus P 175 mg/m^2 for six or more cycles.

Results: One hundred and fifty-seven (16%) patients ≥70 years (median: 74 years, C–PLD; 73 years, C–P; range 70–82 years) were included (n = 71, C–PLD; n = 86, C–P). In comparing elderly and younger, elderly patients experienced fewer grade ≥2 allergic reactions (P = 0.005) but more grade ≥2 sensory neuropathy (P = 0.007). Myelosuppression did not differ with age. Elderly patients completed planned treatment as frequently as younger (79%, C–PLD; 82%, C–P). In comparing arms within elderly patients, C–P was associated with more grade ≥2 alopecia, sensory neuropathy, arthralgia/myalgia (P < 0.001 for all), severe leukopenia plus febrile neutropenia; C–PLD was associated with more grade ≥2 hand–foot syndrome (P = 0.005). Median progression-free survival was 11.6 months (C–PLD) and 10.3 months (C–P; P = 0.44).

Conclusions: Patients ≥70 years experienced more neuropathy, with a higher incidence in the C–P arm. Similar to all study patients, C–PLD provided a better therapeutic index with less toxicity than C–P in elderly women with platinum-sensitive ROC.

Key words: carboplatin, elderly, ovarian cancer, paclitaxel, pegylated liposomal doxorubicin, relapse

introduction

The incidence of epithelial ovarian cancer peaks in the seventh decade of life, and there is evidence from the literature that elderly patients with ovarian cancer have a poorer prognosis, even after adjustment for stage, residual disease, and performance status (PS) [1–4]. Retrospective data suggest that patients >70 years may benefit as well as younger patients from optimal therapy [5]. Indeed, in a cohort study of 292 stage IIIC–IV ovarian cancer patients aged ≥65 years old, Eisenhauer et al. [6] showed that similar response rates to primary chemotherapy and survival could be achieved when compared with younger patients and that age was not independently associated with poorer survival. In that study, elderly patients receiving paclitaxel did not experience more side-effects, notably neuropathy, than patients <65 years old. Still, the boundary of 65 years for 'old age' is questionable in this work as more recent reports consider 70 years to be the lower age limit for the elderly population. Although a debate still exists with respect to the use of frontline paclitaxel–platinum in the

*Correspondence to: Prof. J. E. Kurtz, Department of Hematology and Oncology, Hôpitaux Universitaires de Strasbourg, 1 Avenue Molière, 67098 Strasbourg, France. Tel: +33-3-88-12-84-36; Fax: +33-3-88-12-76-81; E-mail: j-emmanuel.kurtz@chru-strasbourg.fr

elderly patient population [1, 7–12], there are only scarce data in the literature regarding salvage chemotherapy for these patients. A large retrospective Italian study recently investigated patterns of care in elderly patients with platinum-sensitive recurrent ovarian cancer (ROC) [13]. In this study, elderly patients were predominantly treated with single-agent platinum therapy and received a median number of 2.5 lines of therapy for recurrence as compared with 2.7 lines in younger patients. The response rate among younger patients was higher and overall survival was longer. Conversely, results of a retrospective study carried out in Denmark suggested that PS was more important than age in the outcome of ovarian cancer patients treated with second-line therapy [14].

The CALYPSO (CAeLYx in Platinum Sensitive Ovarian patients) phase III study compared the standard carboplatin–paclitaxel (C–P) to carboplatin–pegylated liposomal doxorubicin (C–PLD) as second- or third-line treatment for women with platinum-sensitive ROC [15]. The incorporation of PLD with carboplatin was hypothesized to decrease side-effects such as alopecia and cumulative neuropathy [16]. Findings of the CALYPSO landmark study demonstrated that C–PLD increased progression-free survival (PFS) and had a more favorable toxicity profile than C–P, thus establishing C–PLD as a new standard treatment option for platinum-sensitive ovarian cancer relapse [15]. The CALYPSO trial did not employ an upper age limit for enrollment, thus we undertook a sub-study to describe treatment tolerability and efficacy in the elderly subpopulation, defined as being aged ≥70 years old.

patients and methods

The CALYPSO trial was an international cooperative group phase III trial of salvage chemotherapy for late relapse (platinum-sensitive) ovarian cancer. The study is described in detail elsewhere [15]. A total of 976 patients with taxane-pretreated ovarian cancer that recurred >6 months after first- or second-line platinum-based therapy were randomly assigned to C–PLD (C AUC 5 plus PLD 30 mg/m^2 i.v. on day 1 every 4 weeks) or C–P (C AUC 5 plus P 175 mg/m^2 i.v. on day 1 every 3 weeks) for six cycles or until disease progression or unacceptable toxicity. Patients with disease stabilization or response were allowed to continue with additional cycles of chemotherapy. To assess the tolerability and the efficacy of both regimens in the elderly population, we analyzed data for patients ≥70 years old from the CALYPSO database. Along with standard disease characteristics [prior medical history, International Federation of Gynecology and Obstetrics stage, grade, left ventricular ejection fraction (LVEF) measurement], we analyzed data relevant to the elderly [Eastern Cooperative Oncology Group performance status (ECOG PS), body mass index (BMI), and number of comorbidities].

assessments

Safety data were analyzed according to the National Cancer Institute's Common Toxicity Criteria version 3.0. High toxicity was defined as any grade ≥3 toxicity. Severe toxicity (STox) was defined as the occurrence of at least one of the following events: febrile (>38.5°C) neutropenia, grade 4 neutropenia or thrombocytopenia, early treatment withdrawal or hospitalization lasting ≥1 week due to grade 3–4 toxicity as described in a geriatric population by Freyer et al. [17]. Quality of life was analyzed via the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 Version 3.0 and EORTC QLQ-OV28, collected at baseline, 3, 6, 9 and 12 months.

statistical methods

The primary objective of this sub-study was to compare toxicity and efficacy of platinum combination regimens according to patient age (<70 versus ≥70 years). Secondary objectives included the following: determination of factors at study entry in elderly patients predicting STox, quality-of-life analysis in elderly patients, and comparison of safety for both treatment arms in the elderly.

Descriptive statistics was carried out. The Chi-square test (or the conditional binomial exact test if small numbers) was used to detect differences in toxic effects between the treatment groups in the elderly population as well as to compare elderly and younger patients. To identify predictors of high toxicity (grade ≥3), a logistic regression model was carried out. Variables included age, ECOG PS, stage, tumor cell type, grade, BMI, glomerular filtration rate (GFR), number of prior chemotherapy lines, and number of comorbidities. Several parameters as potential predictors for the onset of STox were analyzed including age, nutritional status, cognitive function, attitude toward disease (anxiety), PS, renal function, hematologic status, and presence of comorbidities. PFS was calculated according to the Kaplan–Meier method, and differences between arms were assessed with a log-rank test.

results

patient characteristics

One hundred and fifty-seven patients (16%) ≥70 years were enrolled, among whom 71 and 86 were randomly allocated to the C–PLD and C–P arms, respectively. Compared with younger patients (<70 years), elderly patients had a significantly higher number of comorbidities, including a lower calculated GFR (Table 1). Elderly patients were diagnosed more frequently with peritoneal or fallopian tube adenocarcinoma, but pathological subtype and tumor grade were similar. Elderly and younger patients received similar prior chemotherapy, but elderly patients underwent less secondary cytoreduction before study enrollment (Table 1). Finally, elderly patients had worse ECOG PS at study entry than younger patients.

In the elderly subpopulation alone, characteristics were well balanced between the C–PLD and C–P arms. In particular, geriatric parameters, including age, PS, BMI (as a surrogate of nutritional status), number of comorbidities (including respiratory, endocrine, diabetes, hypertension, depression, vascular and cardiovascular and digestive conditions) and renal function, were similar. Additionally, the duration of prior chemotherapy was similar between the two arms. With respect to cardiac function, baseline LVEF data were available for 65 patients (92%) on C–PLD and for 53 patients (62%) on C–P. Of these patients, LVEF was normal in 98% of patients on the C–PLD arm and in 96% on the C–P arm at study entry.

treatment administration

Among all elderly randomized patients, 70 in the C–PLD arm and 85 in the C–P arm received chemotherapy. The median number of cycles was six in both arms, with 78.6% in the C–PLD arm and 82.4% in the C–P arm receiving six or more cycles and 8.6% in the C–PLD arm and 7.1% in the C–P arm receiving nine or more cycles. Carboplatin dose was reduced for hematologic toxicity in 2.6% of C–PLD cycles and 1.6% of C–P cycles. Treatment was delayed for hematologic toxicity in 9.5% of C–PLD cycles and 5.3% of C–P cycles.

Table 1. Patient characteristics

	Whole population, %			Elderly population, %	
	<70 years, $n = 817$	≥70 years, $n = 157$	P value	C–PLD, $n = 71$	C–P, $n = 86$
Median age (range), years	58.8 (24–70)	73.4 (70.1–82.5)	<0.05	74 (70.1–82.5)	73 (70.2–82)
Median BMI (range), kg/m^2	25.3 (16.1–49.1)	26.0 (15.4–40.2)	NS	25.2 (15.4–40.2)	26.3 (15.8–35.9)
No of comorbidities					
0–1	70.5	59.6	<0.05	56.3	62.4
2–3	22.8	23.7		26.8	21.2
>3	6.7	16.7		16.9	16.5
Median GFR (range), ml/min	82 (9–968)	59 (29–968)	<0.05	57 (29–968)	60 (38–708)
Primary site					
Ovary	90.8	80.8	<0.05	83.1	78.8
Peritoneal	5.9	12.8		7	17.6
Fallopian	3.3	6.4		9.9	3.5
Pathological subtype					
Serous	72.3	69.9	NS	70.4	69.4
Mucinous	1.7	1.9		2.8	1.2
Endometrioid	8.3	3.2		4.2	2.4
Clear cell	2.7	3.2		4.2	2.4
Mixed epithelial	2.7	1.9		0	3.5
Other/unspecified	12.2	19.9		18.3	21.2
Tumor grade					
1	5.3	5.8	NS	7	4.7
2	23.7	21.8		21.1	22.4
3	54.5	52.6		56.3	49.4
Unknown	16.5	19.9		15.5	23.5
Number of prior chemotherapy lines					
1	85.1	84.0	NS	85.9	82.4
2	14.9	15.4		14.1	16.5
Unknown	0	0.6		0	1.2
Prior surgery at relapse	20.3	13.5	<0.05	12.7	14.1
ECOG PS					
0	64.3	50.0	<0.05	49.3	50.6
1	31.1	43.6		43.7	43.5
2	2.6	4.5		4.2	4.7
3	0	0.6		0	1.2
Unknown	2.1	1.3		2.8	0

C–PLD, carboplatin–pegylated liposomal doxorubicin; C–P, carboplatin–paclitaxel; BMI, body mass index; NS, nonsignificant; GFR, glomerular filtration rate; ECOG PS, Eastern Cooperative Oncology Group performance status.

comparison of toxicity according to patients' age

In order to test whether age impacted treatment tolerability, safety profile between elderly and younger patients (<70 versus ≥70 years) in both arms of the entire study population was compared, focusing on the proportion of patients with grade ≥3 hematologic and grade ≥2 non-hematologic events. The incidence of grade ≥3 toxicity was similar between elderly and younger patients ($P = 0.434$). Additionally, STox did not differ between older and younger patients ($P = 0.348$).

There was no significant difference for hematologic toxicity between older and younger patients (Table 2). Moreover, elderly patients did not develop more febrile neutropenia ($P = 0.88$). With regard to non-hematologic toxicity, elderly patients experienced more grade ≥2 sensory neuropathy (24.4% versus 15.5%, $P = 0.007$; Table 2). Conversely, younger patients developed more grade ≥2 allergic reactions, including drug fever (13.9% versus 5.8%, $P = 0.005$). Other side-effects such as arthralgias/myalgias ($P = 0.57$) or hand–foot syndrome ($P = 0.73$) did not vary according to age.

predictors of grade ≥3 toxicity in the elderly population

Univariate logistic regression models used to identify baseline variables that predicted for high toxicity in the elderly population identified only number of prior chemotherapy lines to be significantly associated with development of high toxicity in the C–P arm. In the C–P arm, two lines of prior chemotherapy were associated with an odds ratio (OR) of 4.50 [95% confidence interval (CI) 1.28–15.8, $P = 0.019$]. This finding was not observed in the C–PLD arm (OR = 0.25, 95% CI 0.03–2.1, $P = 0.20$). The P value for the interaction calculated with the Wald test was significant ($P = 0.022$). However, these values should be interpreted with caution due to the small numbers of patients who received two prior lines of chemotherapy ($n = 14$ in the C–P

Table 2. Toxicity

	Whole population, % of patients			Elderly population, % of patients		
	<70 years	≥70 years	*P* value	C–PLD	C–P	*P* value
Hematologic						
Anemia						
Grade 0–2	93	97	0.06	97	96	0.83
Grade 3–4	7	3		3	4	
Thrombocytopenia						
Grade 0–2	89	88	0.56	83	92	0.10
Grade 3–4	11	12		17	8	
Neutropenia						
Grade 0–2	60	58	0.78	58	59	0.89
Grade 3–4	40	42		42	41	
Febrile neutropenia						
None	97	97	0.88	100	94	0.038
Present	3	3		0	6	
Non-hematologic						
Alopecia						
None/partial	54	48	0.17	89	14	<0.001
Complete	46	52		11	86	
Sensory neuropathy						
Grade 0–1	84	76	0.007	90	64	<0.001
Grade 2–3	16	24		10	36	
Hand–foot syndrome						
Grade 0–1	93	92	0.73	86	98	0.005
Grade 2–3	7	8		14	2	
Arthralgia/myalgia						
Grade 0–1	88	87	0.57	97	78	<0.001
Grade 2–3	12	13		3	22	
Allergic reaction						
Grade 0–1	86	94	0.005	96	93	0.46
Grade 2–3	14	6		4	7	

C–PLD, carboplatin–pegylated liposomal doxorubicin; C–P, carboplatin–paclitaxel.

arm and $n = 10$ in the C–PLD arm). Of note, geriatric parameters, including PS, number of comorbidities, or BMI, did not predict for higher toxicity or STox.

safety profile in the elderly population according to treatment arm

The incidence of high-toxicity events (grade ≥3) tended to be higher in the C–P arm (42.4%) than in the C–PLD arm (28.2%, $P = 0.066$). Similarly, a higher proportion (although not statistically significant) of patients experienced STox in the C–P arm (25.9% versus 15.5% with C–PLD, $P = 0.11$).

Of hematologic toxic effects, grade 3–4 thrombocytopenia was more common in the C–PLD arm (17% versus 8% with C–P, $P = 0.099$). Severe leukopenia was more frequent in the C–P arm (21% versus 8% with C–PLD, $P = 0.028$) and patients in the C–P arm experienced a significantly higher rate of febrile neutropenia (6% versus 0% with C–PLD; $P = 0.04$). Significant grade ≥2 non-hematologic toxicity was as expected, with higher rates of sensory neuropathy, arthralgia and alopecia in the C–P arm and a higher rate of skin reactions in the C–PLD arm (Table 2). Other events were similar between groups, including grade ≥2 nausea ($P = 0.88$) and vomiting ($P = 0.07$), fatigue ($P = 0.49$), infection without neutropenia ($P = 0.83$) and allergic reactions ($P = 0.46$). Cardiovascular toxicity did not differ between the two treatment arms ($P = 0.82$).

quality of life in the elderly population

The EORTC QLQ-C30 analysis showed that treatment arm did not affect the global health status score from baseline to any time point (Table 3). Similarly, no differences were found with respect to functional or symptom scale scores. The QLQ-OV28 demonstrated that patients receiving the C–P combination experienced significant deterioration of quality of life with regard to neuropathy (Table 3). However, the attitude toward disease and treatment was not influenced by treatment arm. Finally, there was no change in body image according to treatment at 3, 6, or 9 months. No difference was found in the quality-of-life scores between elderly and younger patients at +3 months, whereas at +6 months, emotional functioning was better in younger patients and neuropathy score was poorer in elderly women, both differences having disappeared at +9 months. Taken together, these data indicate that quality of life does not significantly differ according to age.

Table 3. Change from baseline in QoL items or domains[a]

Item or domain	Mean change from baseline (SD): C–P, C–PLD; *t*-test *P* values[b]		
	+3 months	+6 months	+9 months
QLQ-C30			
Global health status/QoL	−1.3 (21.3), 0.2 (26.1); $P = 0.76$	2.9 (22.2), 1.4 (23.3); $P = 0.77$	5.0 (19.2), 10.2 (26.8); $P = 0.42$
QLQ-OV28			
Body image	9.7 (24.7), 3.6 (34.3); $P = 0.33$	7.9 (27.0), 2.6 (24.3); $P = 0.40$	4.2 (29.3), 7.9 (34.0); $P = 0.68$
Peripheral neuropathy	24.7 (25.0), 4.4 (23.9); $P \leq 0.001$	29.4 (33.0), 13.7 (24.1); $P = 0.03$	19.5 (27.2), 0.7 (21.0); $P = 0.008$
Attitude to disease and treatment	3.5 (25.6), −1.2 (23.7); $P = 0.37$	6.5 (35.7), −7.8 (18.8); $P = 0.06$	−5.2 (24.7), −14.0 (33.2); $P = 0.29$

[a]For global health status/QoL, higher scores reflect higher functioning. Positive change scores reflect improvement with time. For symptom scales, higher scores reflect more troublesome symptoms. Positive change scores reflect worst QoL over time.
[b]Comparing the change score between the treatment groups.
SD, standard deviation; C–P, carboplatin–paclitaxel; C–PLD, carboplatin–pegylated liposomal doxorubicin; QLQ, quality-of-life questionnaire; QoL, quality of life.

efficacy in the elderly population

PFS was not significantly different between the treatment arms in elderly patients [hazard ratio (HR) = 0.873, 95% CI 0.62–1.24, $P = 0.44$; Figure 1]. Median PFS times were 11.6 months in the C–PLD arm and 10.3 months in the C–P arm; both arms were well balanced with regard to major prognostic factors influencing survival, particularly for residual disease. Moreover, taken together, elderly patients had similar PFS than their younger counterparts (HR = 0.972, 95% CI 0.81–1.17, $P = 0.769$; Figure 2).

discussion

With a population of 157 elderly patients receiving second- or third-line therapy for platinum-sensitive ovarian cancer, this sub-study has no equivalent in the literature. With a median age of 73 and 74 years in the C–P and C–PLD arms, respectively, our population is justly to be considered elderly. The 70 years boundary that was chosen for this sub-study analysis might be, however, evolving in future trials from 70 to 75 years. However, we stated that 70 years was a reasonable compromise between old age and the analysis of a relevant study subpopulation in the CALYPSO trial. Moreover, the 70 years limit is currently accepted in the literature in many oncogeriatric studies.

We compared treatment tolerability between the elderly population and the remaining patients <70 years old from the CALYPSO trial and showed that elderly patients experienced less allergic reactions but were more prone to peripheral neuropathy, a well-known side-effect of paclitaxel. Paclitaxel induces peripheral neuropathy in a cumulative manner, an issue that has to be particularly considered in the elderly as it impairs mobility and might severely alter vulnerable patients' autonomy. Paclitaxel-induced arthralgias and myalgias may also negatively impact morbidity in elderly patients and must be considered particularly debilitating side-effects in this setting. Protecting elderly patients from these side-effects is therefore of importance, particularly if one considers that paclitaxel is currently often incorporated in the frontline ovarian cancer setting in these patients [8–10].

Of note, in our study, elderly patients receiving C–PLD had minimal arthralgias/myalgias and neuropathy, making this regimen particularly appropriate for older patients. In addition, in contrast to the C–P arm, no patient experienced febrile neutropenia in the C–PLD arm, a major concern in the elderly. Quality of life, as assessed with the EORTC QLQ-C30 from baseline, did not differ in a treatment-dependent manner at any time during the study. Conversely, the QLQ-OV28 scores identified neuropathy as an item that significantly deteriorated quality of life in the C–P arm, thus reinforcing the superior tolerability of C–PLD. Elderly patients in this study also experienced minimal alopecia. Curiously, despite the fact that alopecia was more pronounced in the C–P arm, there was no disadvantage of this regimen in terms of body image. This finding supports acceptance of chemotherapy in this elderly population.

This sub-study was not sufficiently powered to detect survival differences in the subgroup of elderly patients. Despite the absence of a difference in PFS between the treatment arms, PFS curves were compared with respect to age (<70 versus ≥70 years), showing no evidence of an interaction effect between the elderly and the younger population (test for interaction $P = 0.50$). Hence, the treatment effects in both groups are consistent with the overall results. Nevertheless, the C–PLD regimen would be the preferable regimen due to tolerability issues.

There is no doubt that elderly patients that were enrolled in the CALYPSO trial were selected patients, as in any phase III trial. However, in current practice, comprehensive geriatric assessment distinguishes 'fit', 'vulnerable', and 'frail' patients to help medical oncologists base their treatment decisions on the patients' medical condition rather than solely on their chronological age [17, 18]. As the CALYPSO study did not specifically focus on elderly patients, no one benefited from an oncogeriatric assessment. However, among the analyzed baseline variables, we focused on ECOG PS, comorbidities, and BMI as a surrogate of nutritional assessment. Given our patients' characteristics, we presume that they would have fallen into the fit and perhaps in some cases in the vulnerable categories. Hence, we suggest that in routine practice, if not every platinum-sensitive relapsed ovarian cancer elderly patient can be treated with a platinum-based doublet

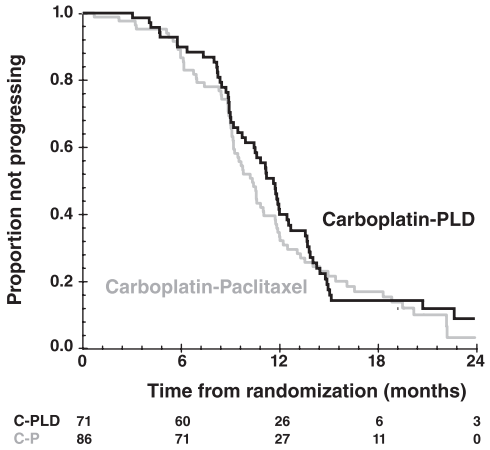

Figure 1. Progression-free survival in patients ≥70 years old treated with carboplatin–paclitaxel or carboplatin–pegylated liposomal doxorubicin (PLD) for platinum-sensitive recurrent ovarian cancer in late relapse (>6 months).

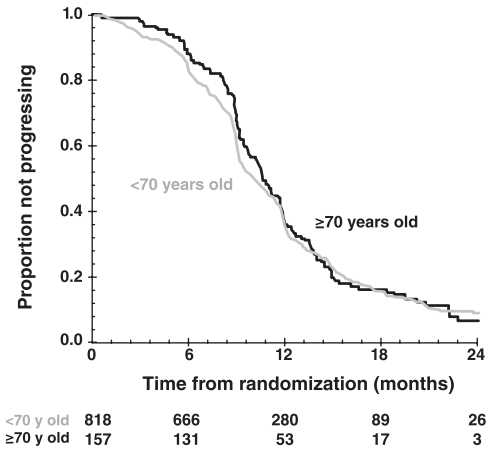

Figure 2. Progression-free survival in young (<70 years old) and elderly (≥70 years old), both arms (carboplatin–pegylated liposomal doxorubicin and carboplatin–paclitaxel combined) for each age category.

(particularly in the vulnerable category), selected women after oncogeriatric assessment may nowadays benefit more from C–PLD than from C–P.

conclusions

From our data, we conclude that carboplatin combination chemotherapy regimens are tolerable and effective in patients ≥70 years old who have platinum-sensitive ROC. Compared with younger patients, older patients experienced a higher incidence of neuropathy and a lower incidence of allergic reactions. In older patients, the C–PLD regimen is safe and showed a better tolerability profile than C–P, especially for sensory neuropathy and alopecia, two issues of outstanding importance in the care of elderly patients. Although definite conclusions with respect to increased PFS cannot be drawn from this subset of patients, our study presents a body of evidence that maintains consistency with the general CALYPSO study population that C–PLD offers a more favorable therapeutic index compared with C–P for elderly patients with late ovarian cancer relapse.

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disclosure

The following authors of this paper declare that there is no conflict of interest involved in this paper: JEK, MCK, AF, ASV, AD, LE, MB, EP, GS, NV, CB, EP-L. The following authors declared a conflict of interest: RK received honoraria from Essex in 2010 for a scientific presentation. NR has conducted clinical trials in the past for Schering-Plough and has participated in Schering-Plough advisory boards.

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