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Docetaxel and carboplatin as first-line chemotherapy in patients with advanced gynecological tumors. A phase I/II trial of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO-OVAR) Ovarian Cancer Study Group

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Abstract

Objectives. We performed a phase I–II study in patients with ovarian and other gynecological cancers to determine the dose-limiting toxicities, maximum tolerated dose (MTD) and efficacy of docetaxel/carboplatin.

Methods. Thirty patients were treated in three cohorts with carboplatin (AUC 5) and escalating docetaxel (60, 75 and 90 mg/m^2), administered intravenously on day 1, repeated every 3 weeks. Premedication consisted of 16 mg dexamethasone per os on day −1, and +1 and 4 mg intravenously before docetaxel.

Results. A total of 6, 11 and 12 patients were eligible and treated on dose levels 1, 2 and 3, respectively. At docetaxel 90 mg/m^2, febrile and prolonged neutropenia were dose-limiting, and 75 mg/m^2 with carboplatin AUC 5 was considered the MTD. Prolonged neutropenia occurred in two, four and nine patients of dose levels 1–3, respectively, and febrile neutropenia in 2, 1, and 2 patients of dose level 1–3. Thrombocytopenia grade 4 was observed in one patient of dose level 1. Non-hematological toxicity including neuropathy was usually mild across all dose levels. Overall response rate was 73%. Median time to progression was 18.0 months, and median overall survival will exceed 24.4 months.

Conclusions. Docetaxel/carboplatin can be safely administered to patients with gynecological cancer despite substantial myelotoxicity and appears to be active in the treatment of ovarian cancer. Low neurotoxicity offers an option for comparison with paclitaxel-containing regimens.

Keywords: Chemotherapy; Ovarian cancer; Gynecological cancer; Docetaxel; Carboplatin

Introduction

Cisplatin and carboplatin are still considered to be the most active agents in the treatment of advanced ovarian cancer. The introduction of paclitaxel into first-line chemotherapy regimens has significantly improved treatment results. This was demonstrated in two large randomized trials of cisplatin/paclitaxel versus cisplatin/cyclophosphamide [1,2]. Three other randomized trials compared cisplatin/paclitaxel with carboplatin/paclitaxel and the results demonstrate that the carboplatin combination is better tolerated and appears to be equieffective [3–5]. Two studies on both the response and survival rates from differing doses of carboplatin in randomized comparisons showed no difference in the effectiveness of AUC 6–12 or AUC 4–8 [6,7].

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So far, the dosage of carboplatin as a combining partner in the first-line treatment of ovarian cancer is asserted to be in a range of AUC 5–6 [8]. Docetaxel is another, more recently developed member of the taxane group which has shown significant clinical activity in several solid tumors including breast and non-small cell lung cancer [9,10]. In ovarian cancer, docetaxel has demonstrated promising single agent activity in advanced stage disease. An overview of four phase II trials including a total of 340 extensively pretreated patients reported an overall response rate of 30% among 315 evaluable patients and of 28% among 155 patients with platinum-refractory disease (treatment-free interval <4 months) [11]. Recently reported preliminary results and preclinical data suggest that docetaxel may have activity even in paclitaxel-refractory ovarian cancer [12]. Additionally, preliminary data from a phase III trial indicate equiefficacy of docetaxel compared to paclitaxel as a combining partner of carboplatin in first-line treatment [13]. Toxicity data suggest that docetaxel/carboplatin induces less peripheral neurotoxicity and may improve quality of life but has a disadvantage with regard to other non-hematological toxicities, hematotoxicity and neutropenic complications. Present experiences with docetaxel warrant the systematic evaluation of docetaxel–platinum combinations in previously untreated patients with advanced ovarian cancer.

We conducted a phase I/II study to identify a clinically feasible regimen to combine docetaxel with carboplatin in the standard dosage of AUC 5 for the first-line treatment of patients with advanced ovarian cancer or other gynecological malignancies.

Patients and methods

Study design

The study was a conventional cohort dose escalation trial to determine the maximum tolerated dose (MTD) and to evaluate the dose-limiting toxicities (DLT) of the docetaxel–carboplatin combination. Additional patients were then treated at the recommended MTD to confirm the safety profile and to obtain preliminary information about the activity of the combination.

Eligibility

Patients were required to have a histologically or cytologically confirmed advanced gynecological malignancy excluding squamous cell carcinoma of the cervix uteri. Previous chemotherapy was not allowed but patients could have received previous immunotherapy until at least 4 weeks before study entry or hormonal therapy that had to be discontinued immediately before the first administration of the study drugs. Eligibility criteria were also: a performance status of 0–2 according to Eastern Cooperative Oncology Group (ECOG) or World Health Organization (WHO), or of ≥60% according to Karnofsky; age ≥18 years; minimum life expectancy of 12 weeks; normal cardiac function; adequate hematological, renal and hepatic function, defined as hemoglobin ≥10 mg/dl, absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, total serum bilirubin ≤1.25 times the upper limit of normal (ULN), and serum creatinine ≤1.25 times ULN. All women of childbearing potential were required to have a negative pregnancy test and to use an adequate contraceptive method throughout the study period. Patients were ineligible for study entry if they had clinical evidence of brain metastases; prior radiation therapy that extended beyond true pelvis; motor or sensory neurotoxicity ≥grade 2 according to NCI CTC criteria at baseline; active infection or any other medical condition making implementation of the study protocol or interpretation of study results difficult. The study was approved by the local Ethics Committees and informed consent was obtained from all patients before enrollment.

Treatment

Docetaxel was infused intravenously over 1 h on day 1 of each 3-weekly cycle. The docetaxel infusion solution

Table 1
Patient characteristics

		Patients	
		n	%
Level 1		6	20
Level 2		12[a]	40
Level 3		12	40
Total		30	100
Median age (range)		59 years (26–78)	
Performance status	0	21	70
	1	6	20
	2	2	7
	unknown	1	3
FIGO stage (only ovarian cancer)	Ia	1	4
	IIb	2	7
	IIc	1	4
	IIIb	2	8
	IIIc	16	64
	IV	3	12
Primary tumor	ovary	25	83
	fallopian tube	2	7
	others[a]	3	10
Histology	serous/papillary	16	53
	endometrioid	3	10
	mixed	2	7
	undifferentiated	1	3
	others	8	27
Grading	G 1	2	7
	G 2	15	50
	G 3	12	40
	unknown	1	3
Residual tumor after surgery	measurable	13	43
	not measurable	17	57

[a] One patient ineligible due to early disease progression.

Table 2
Dose levels

	Level 1	Level 2	Level 3
Docetaxel	60 mg/m^2	75 mg/m^2	90 mg/m^2
Carboplatin	AUC 5	AUC 5	AUC 5
Cycles	32	66	72

was prepared as follows: the concentrate was first diluted with the supplied solvent, and the required amount was subsequently reconstituted with 0.9% sodium chloride or 5% glucose solution. Carboplatin doses were individualized to a target area under the serum concentration versus time curve (AUC) based on renal function, using the Calvert formula (total dose in mg = target AUC × [glomerular filtration rate + 25]) [14]. Glomerular filtration rate was calculated from estimates of the creatinine clearance utilizing the Jelliffe formula [15,16]. Carboplatin was given via intravenous infusion over 30 min following docetaxel.

A short course of corticosteroid premedication of two oral doses of 8 mg dexamethasone was routinely given the day preceding the docetaxel infusion, 4 mg were administered intravenously 30 min before, and two additional oral 8-mg doses the day after docetaxel administration. Antiemetic prophylaxis consisted of a 5-HT_3 antagonist given 15 min before carboplatin. Growth factor support was not given routinely, but G-CSF could be added if considered appropriate by the investigator.

Treatment was continued for a maximum of six cycles or until tumor progression or unacceptable toxicity occurred.

Dose escalation

Dose limiting toxicity (DLT) was defined as the occurrence of at least one of the following adverse events during the first treatment cycle: neutropenia $\leq 0.5 \times 10^9$/l for 7 or more days or no recovery to 1.5×10^9/l or platelet count $\leq 25 \times 10^9$/l or no recovery to 100×10^9/l before the start of the next treatment cycle; neutropenic fever or infection (absolute neutrophil count $\leq 0.5 \times 10^9$/l with fever and hospitalization and/or the need for intravenous antibiotics); or any clinically relevant non-hematological grades 3 or 4 toxicity or persisting toxicity that requires hospitalization, drug therapy or treatment withdrawal.

Carboplatin was given at a fixed dose of AUC 5 throughout subsequent cycles. In the phase I portion of the trial, we planned to escalate docetaxel stepwise from an initial dose of 60 mg/m^2 to 75 and 90 mg/m^2. Three to six patients were planned to be treated on each dose level. Individual dose escalation was not allowed. If none of the first three patients developed DLT at a specific dose level, we proceeded to the next dose level. If one or two out of three patients experienced DLT, three additional patients were recruited on this dose level, and further dose escalation was allowed only as long as DLT occurred in no more than two out of six patients. Dose escalation was discontinued if three or more out of six patients developed DLT, and the previous dose level was defined as the MTD. Additional six patients were planned to be treated with the recommended MTD to confirm its safety profile. Additionally, the frequent appearance of DLT-like toxicity in subsequent cycles required the recruitment of six additional patients in the respective dose level if applicable.

Patient evaluation

Patients were evaluated on a regular basis during treatment. Twice weekly full hematology including differential blood counts was performed. Patients completing at least one treatment course were considered evaluable for toxicity. All patients with measurable disease at baseline who completed three cycles of protocol treatment or those with early disease progression were evaluable for response. Toxicity was graded according to the Common Toxicity Criteria (CTC) of the National Cancer Institute

Table 3
Dose limiting toxicity (DLT) in cycle 1 (top) and DLT-like toxicity in subsequent treatment cycles (bottom)

	Level 1		Level 2		Level 3	
	Patients	Toxicity	Patients	Toxicity	Patients	Toxicity
DLT in cycle 1	1/6	febrile neutropenia	1/11	neutropenia °4 ≥ 7 days	3/12	2× neutropenia ×°4 ≥ 7 days febrile neutropenia
	Patients (n = 6)	Cycles (%) (n = 32)	Patients (n = 12[a])	Cycles (%) (n = 66)	Patients (n = 12)	Cycles (%) (n = 72)
DLT-like toxicity in subsequent cycles	2[b]	8 (25%)	5	10 (15%)	9[b]	24 (33%)
Neutropenia °4 ≥ 7 days	2	6 (19%)	4	8 (12%)	9	24 (33%)
Febrile neutropenia	1	1 (3%)	1	2 (3)	1	1 (2%)
Thrombocytopenia °4	1	1 (3%)	–	–	–	–

[a] One patient ineligible.
[b] One patient with multiple DLT-like toxicities.

Table 4
Dose reductions and reasons

	Level 1	Level 2	Level 3	Total
	Patients ($n = 6$)	Patients ($n = 12$[a])	Patients ($n = 12$)	Patients ($n = 30$[a])
Dose reduction	2	4	8	14
Reasons				
Hematological toxicity	1	3	8	12
Non-hematological Toxicity	1[b]	1[c]	–	2

[a] One patient ineligible.
[b] Grade 4 hypersensitivity against docetaxel.
[c] Nephrotoxicity.

(NCI), and treatment response was assessed according to WHO criteria, using gynecological assessment, imaging techniques (X-ray, ultrasound, computerized tomography and/or magnetic resonance imaging), laparoscopy and CA 125 assessment.

Results

Dose escalation

Five centers recruited 30 patients into the study. The patient characteristics are shown in Table 1. Six patients were treated in dose level 1, 12 patients in dose level 2 and 12 patients in dose level 3 (Table 2). One patient in dose level 2 was ineligible for evaluation due to early disease progression.

Only one out of six patients treated on dose level 1 experienced DLT (febrile neutropenia) in the first treatment cycle (Table 3). On dose level 2, DLT again occurred in one of the first three patients (neutropenia grade 4 lasting 7 days) but when the dose cohort was extended to six patients, no further DLT occurred. Thus, dose level 3 was opened and two of the first six patients developed dose-limiting grade 4 neutropenia (of 8 and 9 days' duration, respectively) in this level. However, since five out of six patients experienced prolonged neutropenia in subsequent treatment cycles, it was decided to extend the dose level 3 to a total of 12 patients. As one more patient experienc dose-limiting febrile neutropenia in cycle 1, and four ot women of the six additionally recruited patients had p longed grade 4 neutropenia in subsequent treatment cycl dose level 2 (docetaxel 75 mg/m^2 with carboplatin AUC was considered the MTD. Six additional patients w recruited for dose level 2 to confirm its safety prof None of the six additional patients treated on this dose le developed DLT. Toxicities, which fulfilled the forr criteria for DLT but occurred in subsequent cycles, listed in Table 3. Prolonged grade 4 neutropenia for >7 d appeared in two (33%), four (36%) and nine (75%) patie of dose levels 1–3, respectively. In dose level 3, prolon grade 4 neutropenia >7 days occurred in 24 (33%) cycl

Toxicity

Twenty-seven (90%) patients completed a full six cy treatment course and a total of 170 cycles was evaluable toxicity.

Dose reductions were necessary in two (33%), f (36%) and eight (67%) patients in dose levels 1, 2 and respectively. Myelotoxicity was the leading cause for d reduction, followed by non-hematological toxicity (Table In dose level 3, all dose reductions were related to her tological toxicity.

Cycle delays >7 days occurred in one (17%), three (27 and four (33%) patients of dose levels 1–3, respectiv (Table 5). Myelotoxicity was the predominant cause cycle delays, followed by non-hematological toxicities a organizational reasons (Table 3). The mean cycle durat was 22 days with no significant differences within different dose levels.

G-CSF support was necessary in seven (64%) and f (33%) patients in dose levels 2 and 3, respectively, but n in dose level 1 (Table 6). Blood transfusions were given two (18%), three (27%) and three (25%) patients of d levels 1, 2 and 3, respectively. There was no need platelet transfusions in any of the dose levels and eminent differences concerning antibiotics or other sub tution therapies between the dose levels (table) could observed.

Table 5
Cycle delay >7 days and reasons

	Level 1		Level 2		Level 3		Total	
	Patients ($n = 6$)	Cycles (%) ($n = 32$)	Patients ($n = 12$[a])	Cycles (%) ($n = 66$)	Patients ($n = 12$)	Cycles (%) ($n = 72$)	Patients ($n = 29$)	Cycles ($n = 17$
Cycle delay >7 days	1[b]	2 (8%)	3[b]	4 (8%)	4[b]	5 (8%)	8[b]	11 (7%
Reasons								
Hematological toxicity	1	2 (8%)	1	1 (2%)	2	3 (5%)	4	6 (4%
Non-hematological toxicity	1	1 (4%)	2	2 (3%)	–	–	3	3 (2%
Others/organizational	–	–	1	1 (2%)	2	2 (3%)	3	3 (2%

[a] One patient ineligible.
[b] One patient with multiple delay >7 days.

Table 6
Substitution therapy

Supportives	Level 1		Level 2		Level 3		Total	
	Patients (n = 6)	Cycles (%) (n = 32)	Patients (n = 12[a])	Cycles (%) (n = 66)	Patients (n = 12)	Cycles (%) (n = 72)	Patients (n = 29)	Cycles (%) (n = 170)
G-CSF	–	–	7	18 (27)	4	8 (11)	11	26 (15)
Blood transfusions	2	3 (9)	3	6 (9)	3	4 (6)	8	13 (8)
Antibiotics	1	3 (9)	3	5 (8)	4	7 (10)	8	15 (9)
Others[b]	1	1 (3)	–	–	–	–	1	1 (1)

[a] One patient ineligible.
[b] Iron substitution therapy.

The hematological toxicity results are shown in Table 7. Grades 3/4 neutropenia occurred in 5 (83%), 10 (91%) and 10 (83%) patients of dose levels 1–3, respectively. Seven (4% of all cycles) episodes of neutropenic fever occurred, distributed to two patients in dose level 1, one patient in dose level 2 and two patients in dose level 3. One patient in dose level 1 experienced thrombocytopenia °4 in two cycles but none of the patients in dose levels 2 and 3. Grade 3/4 anemia occurred in one patient of dose level 1, and one patient dose level 2.

Treatment was withdrawn in one of the level-2 patients in cycle 1 because of grade 4 lung edema and grade 4 CNS toxicity (generalized seizures), which was not considered to be due to treatment. Three patients, each from dose levels 1–3, experienced grades 3/4 infections during treatment. One hypersensitivity reaction in dose level 1 and one case of nephrotoxicity in dose level 2 were responsible for a dose reduction in the respective dose level. Other non-hematological toxicities were usually mild to moderate and never dose-limiting (Table 8). Grade 1/2 peripheral neurotoxicity occurred in 21 patients (70%), 3 (50%) in dose level 1, and nine each in dose levels 2 and 3. Severe peripheral or motoric neurotoxicity was lacking across all dose levels. Myalgia/arthralgia grade 1/2 as attendant symptoms of sensory neuropathy were present in two (33%), five (45%) and four (33%) patients in dose levels 1–3, respectively. Grades 1–2 mucositis and stomatitis were rare and only one grade 3 episode in one patient of dose level 3 occurred. Nausea and emesis were common side effects but generally mild and of short duration. One patient in dose level 2 and one patient in dose level 3 experienced grade 3/4 diarrhea. Almost all patients developed a total alopecia. Two patients in dose level 2 which experienced grade 1 and one patient in dose level 1 which experienced grade 4 hypersensitivity reactions were encountered, all of them occurring in the first treatment cycle. Other non-hematological toxicities were mild to moderate in nearly all patients, with a frequency distribution similar to that seen in the total patient population.

Response and Survival

Nineteen (63%) patients had no evidence of disease (NED) at baseline. Eleven (37%) patients (one in level 1, seven in level 2 and four on level 3) had measurable disease. One (9%) patient in level 1 died during the second cycle due to progressive disease. Overall response rate within this group was 73% with three (27%) complete (CR) and five (46%) partial responses (PR). Two (18%) patients had stable disease (SD). Eight patients with ovarian cancer were evaluable for response. Seven (88%) achieved either a CR (two patients) or PR (five patients) and one had

Table 7
Hematological toxicities

CTC grade	Level 1		Level 2		Level 3		Total	
	Patients (n = 6)	Cycles (%) (n = 32)	Patients (n = 12[a])	Cycles (%) (n = 66)	Patients (n = 12)	Cycles (%) (n = 72)	Patients (n = 29)	Cycles (%) (n = 170)
Neutropenia								
1/2	1	2 (6)	1	18 (27)	1	5 (7)	3	25 (15)
3/4	5	22 (69)	10	32 (48)	10	48 (67)	25	102 (60)
Neutropenic fever	2	3 (9)	1	2 (3)	2	2 (3)	5	7 (4)
Thrombocytopenia								
1/2	3	6 (19)	7	12 (18)	8	20 (28)	18	38 (22)
3/4	1	2 (6)	–	–	–	–	1	2 (1)
Anemia								
1/2	5	26 (81)	9	50 (76)	12	67 (93)	26	143 (84)
3/4	1	1 (3)	1	3 (5)	–	–	2	4 (2)

[a] One patient ineligible.

Table 8
Non-hematological toxicities

CTC grade	Level 1		Level 2		Level 3		Total	
	Patients (n = 6)	Cycles (%) (n = 32)	Patients (n = 12[a])	Cycles (%) (n = 66)	Patients (n = 12)	Cycles (%) (n = 72)	Patients (n = 30[a])	Cycles (%) (n = 170)
Alopecia								
°2	5	18 (56)	11	59 (89)	12	57 (79)	28	134 (79)
Nausea								
1/2	5	22 (69)	8	45 (68)	11	39 (54)	24	106 (62)
3/4	–	–	2	2 (3)	–	–	2	2 (1)
Emesis								
1/2	1	7 (22)	7	22 (33)	8	20 (28)	16	49 (29)
3/4	–	–	1	2 (3)	–	–	1	2 (1)
Diarrhea								
1/2	4	8 (25)	5	21 (32)	4	8 (11)	13	37 (22)
3/4	–	–	1	2 (3)	1	1 (1)	2	3 (2)
Obstipation								
1/2	3	8 (25)	4	17 (26)	8	19 (26)	15	44 (26)
3/4	1	2 (6)	–	–	–	–	1	2 (1)
Sensory neurotoxicity								
1/2	3	6 (19)	9	36 (55)	9	30 (42)	21	72 (42)
3/4	–	–	–	–	–	–	–	–
Myalgia								
1/2	2	13 (41)	5	11 (17)	4	6 (8)	11	30 (18)
3/4	–	–	–	–	–	–	–	–
Stomatitis								
1/2	1	1 (3)	6	18 (27)	1	1 (1)	8	20 (12)
3/4	–	–	–	–	1	1 (1)	1	1 (1)
Mucositis								
1/2	1	2 (6)	4	13 (20)	9	21 (29)	14	36 (21)
3/4	–	–	–	–	–	–	–	–
Infections								
1/2	1	3 (9)	3	5 (8)	4	8 (11)	8	16 (9)
3/4	1	1 (3)	1	1 (2)	1	1 (1)	3	3 (2)

[a] One patient ineligible.

SD. None of the evaluable patients with ovarian cancer experienced disease progression while on study. Median time to progression was 18.0 months. Twelve months after randomization of the last patient, 19 patients (63%) were still alive and nine (30%) remained disease-free or had stable residual disease. Median overall survival has not yet been reached.

Discussion

The combination of carboplatin/paclitaxel (Carbo/Pac) is the recommended standard therapy for first-line treatment of ovarian cancer. However, approximately 75% of all patients recur on disease and progression-free and overall survival seems to be improvable. Furthermore, treatment, although not curative in the majority of patients, causes toxicity with relevant impact on quality of life. Hence, optimization of first line treatment is necessary. Docetaxel is one promising agent from the taxane group since it is considered to be equiefficient and may be less neurotoxic. However, other toxicities like myelosuppression might impair the potential advantage of lower neurotoxicity.

In this study, neutropenia was the major toxicity, occurring with grade 3/4 in 60% of all cycles and within a range of 83–90% of the patients across the three dose levels in our study. Nevertheless, treatment was rarely complicated by neutropenic fever or severe infections, and there was no treatment-related death. This may be due to the relatively short duration of the neutropenic phase and the low incidence of mucosal lesions (stomatitis, diarrhea). Based on the increasing occurrence of prolonged neutropenia at a docetaxel dose of 90 mg/m^2, particularly in cycles 3–5, we considered this dose level too toxic for routine clinical use

ven though the formal criteria for dose-limiting toxicity ere not fulfilled. On the other hand, G-CSF support was ıore frequent in the recommended MTD of 75 mg/m^2 ocetaxel combined with carboplatin AUC 5 than in dose evel 3. This might be attributed to the protocol, which llowed G-CSF support if considered appropriate by the ıvestigator, but not routinely in case of specified clinical or ıboratory findings. However, our recommended MTD of 5 mg/m^2 docetaxel combined with carboplatin AUC 5 orresponds well with the results of a large dose-finding udy conducted by the Scottish Gynecological Cancer rials Group (SCOTROC) [17]. The authors recommended carboplatin dose of AUC 5 or 6, depending on the method sed to determine glomerular filtration rate plus docetaxel 5 mg/m^2. A total of 139 chemo-naive patients with ovarian ncer was treated in this study on five dose levels, and 110 tients (79%) received all six planned cycles. In accor-nce with our study, sepsis was a rare complication despite gnificant myelosuppression, and the incidence of severe urotoxicity was very low. Preliminary results from a large ase III trial additionally confirm the hematotoxic potential this combination with a significant increase of grade 3/4 utropenia, neutropenic complications, G-CSF support and ophylactic antibiotics in comparison to standard treatment th CT [13].

In accordance with others, thrombocytopenia was infre-ent and usually mild in our trial. We observed only one ient in dose level 1 with thrombocytopenia grade 4. hough patients receiving combination carboplatin/pacli-el chemotherapy develop profound granulocytopenia, the quency of severe thrombocytopenia was shown to be all [5]. Thus, a platelet-sparing effect of paclitaxel has n proposed which is not related to changes in the rmacokinetics of carboplatin, but may be explained by anced detoxification of both drugs and induction of mbopoietin [18,19]. The lack of severe thrombocytope-in our study is in line with the findings of other stigators and indicates also a platelet-sparing effect for etaxel [13,20]. However, phase I/II results of the Carbo/ combination indicate that thrombocytopenia could also dose-limiting in taxane containing regimens, notably n the carboplatin dose exceeds AUC 5 [21].

Conclusively, myelotoxicity of the carboplatin–doce-l combination is most notably neutropenia and its plication.

eventy-two percent of our patients experienced symp-; like paraesthesia and decreased tendon reflex activity esting peripheral neuropathy grade 1/2. These were lly mild with no evidence of deterioration with increas-cumulative doses of docetaxel. However, docetaxel-ced onycholysis, which was recently reported to be to a neuropathic mechanism was also observed in our in some patients [22]. Vasey [13] already confirmed the neurotoxic potential of docetaxel/carboplatin in their scale phase III-study. The substitution of paclitaxel docetaxel lead to a significant decrease of sensory and motoric neuropathy during and following treatment. However, the study failed to show a significant improvement of quality of life as it could be expected due to less neurotoxicity of carboplatin/docetaxel.

Other non-hematological toxicities in our trial were usually mild and never dose-limiting. The most frequent non-hematological toxicity was a total alopecia. Actually, severe diarrhea, obstipation and mucositis or stomatitis were uncommon. Similarly, fluid retention and hypersensitivity reactions did not represent major problems, underlining the efficacy of a short course of dexamethasone before each administration of docetaxel.

The number of patients with measurable disease after primary debulking was small in our trial. Although we observed one death related to early disease progression, eight out of 11 patients with measurable disease responded to treatment, including three complete responses indicating appropriate antitumor efficacy. In our population, time to progression was 18 months, and median overall survival has not yet been reached at more than 2 years. Despite the low significance of our efficacy data, they are in line with the results from another phase I/II study and the preliminary data of the SCOTROC phase III trial [17,13].

Our phase I/II study has demonstrated that combination chemotherapy with docetaxel and carboplatin can be given safely in a dosage of 75 mg/m^2 and AUC 5, respectively, to previously untreated patients with advanced ovarian cancer or other gynecological malignancies. However, final results of ongoing phase III trials should be awaited to define the role for the carboplatin–docetaxel combination in ovarian cancer.

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