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ORIGINAL ARTICLE

Topotecan and carboplatin in patients with platinum-sensitive recurrent ovarian cancer. Results of a multicenter NOGGO: phase I/II study

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Abstract
Objective Second-line treatment with paclitaxel and carboplatin enhances survival of women with platinum-sensitive recurrent ovarian cancer (ROC). However, because of its cumulative neurotoxicity, there is a strong demand for platinum-combinations with better therapeutic index. Because of its pharmacological properties, topotecan is a good adjunct to carboplatin in this setting, but its safety and efficacy remains to be defined.

Methods Patients with platinum-sensitive ROC were eligible in this multicenter phase I/II study, stratified according to treatment-free interval (TFI). Dose level 0 consisted of topotecan 1 mg/m^2/d1–3/q21d plus carboplatin AUC5/d3/q21d. DLT was defined as grade $\geq$3 neutropenia or thrombocytopenia or grade $\geq$3 non-hematological toxicity excluding alopecia, nausea and vomiting, accompanied by a treatment delay >1 week.
Results From June 2004 to August 2005, 26 patients were enrolled, receiving a total of 145 cycles of chemotherapy. MTD was reached at topotecan 0.75 mg/m^2 and carboplatin AUC5. We observed a single grade 4 leucopenia. There were 3 (12%), 15 (58%) and 8 (31%) events of grade 3/4 hematological anaemia, leucopenia, and thrombocytopenia. Response rate was 67% (95% CI 43–85), median progression-free survival 9.5 months (95% CI 7.3–12.0), median overall survival 19.4 months (95% CI 12.3–26.9). None of the toxicity or efficacy endpoints were associated with TFI.
Conclusion Topotecan and carboplatin is a well tolerated novel doublet option for women with platinum sensitive ROC. We encourage further studies on this approach, but to limit the doses of topotecan to 0.75 mg/m^2/d1–3 and carboplatin AUC 5/d3.

Keywords Carboplatin · Chemotherapy · Platinum-based combination · Platinum-sensitive recurrent ovarian cancer · Topotecan

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Introduction

Epithelial ovarian cancer is the leading cause of death from all gynaecological malignancies world-wide [1]. Most patients present with advanced disease at initial diagnosis. Current standard management of primary ovarian cancer

includes radical surgery, followed by chemotherapy with carboplatin plus paclitaxel. Apart from marked improvements in short- and mid-term tumour control and health-related outcomes, more than 65% of all patients will relapse within two years and ultimately die of progressive disease [2].

Retrospective studies have identified two subgroups of patients with recurrent ovarian cancer, termed platinum-sensitive and platinum-resistant, according to the best response to platinum-based chemotherapy and according the treatment free interval [3, 4].

A large randomised trial (ICON4/AGO-Ovar 2.2) showed the superiority of a combined carboplatin and paclitaxel regimen over platinum monotherapy in platinum-sensitive patients [5]. However, the cumulative neurotoxicity of carboplatin and paclitaxel offsets the potential efficacy of this second-line approach, and precludes administration to patients with residual neurological deficits [6, 7].

Various study groups are currently exploring other platinum combinations to optimize the therapeutic index in patients with platinum-sensitive recurrent ovarian cancer [8, 9].

Topotecan (Hycamtin®, GlaxoSmithKline) is a topoisomerase I inhibitor that has demonstrated antitumor activity in relapsed ovarian cancer. Based on large phase-III trials, topotecan is as effective as paclitaxel and liposomal doxorubicin in the treatment of ovarian cancer [10, 11]. It lacks cross-resistance to both paclitaxel and platinum and pegylated liposomal doxorubicin [12] and shows almost no overlapping or cumulative toxicity [13]. Topotecan is associated with few non-hematological side effects as well as manageable and non-cumulative hematological toxicities [13]. In vitro data have demonstrated marked synergy of topotecan with platinum compounds [14–17].

Therefore topotecan may be a good candidate for developing a novel platinum-based combination chemotherapy.

A phase I/II study was initiated to evaluate the toxicity profile, maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of six cycles of the combination of topotecan (dose level 0: 1.00 mg/m^2, dose level −1: 0.75 mg/m^2) on days 1 to 3 plus carboplatin (AUC 5) on day 3, repeated every 21 days in patients with platinum-sensitive recurrent ovarian cancer. As it is unclear whether the treatment-free interval after first-line chemotherapy can affect the tolerability of a second-line chemotherapy, we prospectively stratified study participants according to the treatment-free interval of less and more than 12 months.

Patients and methods

Design

This was a prospective multi-institutional phase I/II study of the North-Eastern German Society of Gynaecologic Oncology (NOGGO) study group ovarian cancer. Patients were enrolled at seven German institutions (six hospitals and one outpatient facility). The Department of Gynaecology and Obstetrics of the Charité University Hospital, Berlin, was the coordinating centre. The study was performed in accordance with the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. Protocol approval was gained from the institutional review board or the local ethics committee of each participating institution. An independent monitoring institute was responsible for data control.

The primary objective of the study was to determine the toxicity profile, MTD and dose-limiting toxicity of the carboplatin/topotecan combination. Remission rate (RR) and progression-free survival (PFS) were defined as secondary endpoints.

Patients were stratified according to the platinum-free interval, defined as the period between completion of first-line chemotherapy with carboplatin and paclitaxel and time of recurrence (6–12 months vs. >12 months), to identify potential differences in tolerability between both cohorts.

Patients

Women ≥18 years of age with platinum-sensitive recurrent ovarian cancer, fallopian tube carcinoma or primary peritoneal cancer, relapsed at least 6 months after completion of primary standard therapy with surgery and first-line combination therapy with platinum and paclitaxel were eligible for study enrolment. Patients were required to have measurable or assessable lesions, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, normal hematological, liver and renal function with laboratory parameters within the normal range, including a glomerular filtration rate ≥ 60 ml/min, serum creatinine levels ≤ 1.5 mg/dl and an adequate bone marrow function (absolute neutrophil count, ANC ≥ 1.5 × 10^9/l and platelets ≥ 100 × 10^9/l). Patients suffering from a secondary malignancy or serious concomitant systemic disorders or psychiatric disease were excluded from the study, as were subjects receiving other cytotoxic, immunological, hormonal or targeted therapy. All patients provided written informed consent.

Treatment plan

Patients were to receive six cycles of topotecan (dose level 0: 1.00 mg/m^2, dose level −1: 0.75 mg/m^2) on days 1 to 3 plus carboplatin equating an area under the curve (AUC) of 5 on day 3 after infusion of topotecan, repeated every 21 days. Both study drugs were infused over 30 min in 250 ml of 0.9% saline solution.

A 5-HT3-antagonist was given intravenously 15 min prior to each course of chemotherapy.

Two dose-levels were defined:

- dose level 0: Topotecan 1.00 mg/m^2/d1–3 + Carboplatin AUC5/d3, q21d
- dose level −1: Topotecan 0.75 mg/m^2/d1–3 + Carboplatin AUC5/d3, q21d

In the phase I of this study, nine patients in each stratum (treatment-free interval 6–12 months and >12 months) were to be treated at dose level 0. In the absence of dose-limiting toxicity during the first four cycles of treatment, an additional nine patients in each stratum were to be treated at dose level 0. A dose reduction to dose level −1 was required in event of a single dose-limiting toxicity during any of the first four cycles of treatment. The protocol required all subsequent patients in a given stratum to be treated at dose level −1. Dose re-escalation was not allowed.

No primary prophylactic use of granulocyte colony-stimulating factor (G-CSF) was allowed. Darbepoetin alfa (2.25 μg/kg weekly or 6.75 μg/kg three-weekly) was applied in case of anaemia with hemoglobin concentrations ≤11.0 g/day.

It was at the investigator's discretion to continue treatment until disease progression.

Toxicity

Toxicity was assessed after each cycle, graded according to the NCI-Common Terminology Criteria for Adverse Events (CTCAE) v3.0, August 9, 2006 [18].

Dose-limiting toxicities were defined as:

- CTC grade ≥3 neutropenia or thrombocytopenia with a treatment delay of more than 1 week,
- CTC grade ≥3 non-hematological toxicity, excluding alopecia, nausea and vomiting (grade 3).

Blood samples for monitoring of hematology and blood chemistry were carried out regularly once a week.

Treatment was continued if leucocyte count was $\geq 2.0 \times 10^9$/l, absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l respectively, platelet count was $\geq 100 \times 10^9$/l and hemoglobin was ≥9g/dl.

During the first four cycles, treatment could be postponed up to 1 week in case of toxicity. A dose reduction was necessary, if no haematological recovery (ANC < 2.0×10^9/l, platelet count <100×10^9/l was seen after a treatment delay of more than 7 days. Patients were discontinued in absence of recovery of hematological and non-hematological toxicities longer than 2 weeks.

Efficacy

Patients were assessed before treatment, prior to each course during treatment and every 3 months after treatment for 2 years, then every 6 months for 3 years.

Physical examination, CA-125, and radiological evaluation of tumor lesions were performed as baseline assessment.

Evaluation of response was performed after completion of four cycles of chemotherapy, after every three cycles of treatment and in any case of suspected progression of disease. Clinical response was determined by physical examination and ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) scans. Response was measured according to the criteria of the International Union Against Cancer [19]. Response by assessment of CA-125 was evaluated according to the Recist-criteria established by Rustin et al. [20].

Duration of response was defined as from the date of first response to the date of disease progression or death from any cause. Progression-free survival was defined as the time from the date of enrollment to the date of disease progression or death from any cause.

Statistical analysis

All efficacy and safety analyses were conducted in an exploratory fashion. Results are presented as raw numbers, rates, medians with 95% CI or ranges, according to the underlying distribution. Binomial-exact 95% confidence intervals (CI) were computed for response rates and toxicity incidence rates, where appropriate. Survival and progression-free survival were analysed by the non-parametric Kaplan-Meier method. STATA 8.0 statistical software (STATA Corp., TX, USA) was employed for all analyses.

Results

From June 2004 to August 2005, 26 women with a median age of 62 years (range 28–75 years) were enrolled into this study. Most patients were primary diagnosed with advanced tumour stage and were at the time of study entry in good condition. The histological type consisted in the majority of the patients of a serous papillary carcinoma. Baseline demographics are displayed in Table 1. The median follow-up was 12.3 months (range 0.6–24.6 months).

In total 145 cycles of chemotherapy with a median of six courses (range 1–10) were administered. An overview about further details of therapy according the strata of the treatment free interval is given in Table 2.

Treatment delay

A treatment delay was defined as any delay of >7 days after the scheduled start of a course of chemotherapy. According to this definition, nine treatment delays (6.2% of all cycles)

Table 1 Baseline demographics

	Stratum		Total
	6–12 months	>12 months	
No. of patients	13	13	26
No. assessable for toxicity	13	13	26
No. assessable for response	9	11	20
No. assessable for progression-free survival	13	11	24
Median age, years (range)	60 (35–75)	63 (28–71)	62 (28–75)
ECOG performance status			
0	3	1	4
1	9	12	21
2	1	0	1
FIGO stage			
I	0	3	3
II	1	1	2
III	10	8	18
IV	2	1	3
Histology			
Serous-papillary	13	10	23
Endometroid	0	2	2
Clear cell	0	1	1
Ascites	6	5	11
Debulking surgery for recurrent disease	4	4	8

Table 2 Treatment profile

	Stratum		Total
	6–12 months	>12 months	
No. of cycles	72	73	145
Median no. of cycles	6 (2–8)	6 (1–10)	6 (1–10)
No. of patients at dose level 0	13	3	16
No. of patients at dose level −1	0	10	10
No. of patients receiving ≥6 cycles	9	9	18
No. of patients with treatment delay	6	3	9
Patients discontinuing treatment	4	4	8
No. of patients with dose-limiting toxicity	0	1	1

occurred among six patients during the course of the study, six treatment delays (8.2% of all cycles) in stratum 6–12 months and three treatment delays (4.2% of all cycles) in stratum >12 months, respectively. The median time of treatment delay was 13 days (range 8–15 days) for all patients, 13.5 days (range 9–15 days) in stratum 6–12 months and 9 days (range 8–14 days) in stratum >12 months, respectively.

Seven treatment delays were related to hematological toxicity: five patients in stratum 6–12 months and dose level 0; two patients in stratum >12 months, one in dose level 0 and one in dose level −1). Two treatment courses were postponed upon a patient's request (stratum 6–12 months: 1; stratum >12 months: 1) (Table 2).

The risk of a treatment delay with combined topotecan and carboplatin was estimated at 35% (95% CI 17–56%).

Treatment discontinuation

Eight patients discontinued treatment (31%, 95% CI 14–52%). Overall, four patients discontinued treatment due to hematological events (leucopenia, thrombocytopenia): two patients in stratum 6–12 months in dose level 0, both after receiving cycle 4, and two patients in stratum >12 months, one in dose level 0 after cycle 1 (DLT) and the second patient in dose level −1 after receiving cycle 4. One treatment discontinuation was related to progressive disease, in two patients tumor-related death occurred during the course of therapy. One patient stopped treatment on her own request (Table 2).

Dose-limiting toxicity

Dose-limiting toxicity was defined as treatment delay >7 days during the first four courses of chemotherapy because of CTC grade ≥3 neutropenia or thrombocytopenia or CTC grade ≥3 non-hematological toxicity, excluding alopecia, nausea and vomiting (grade 3).

We observed only one episode of dose-limiting myelotoxicity, for a risk of 4% (95% CI 1–20%) in one patient of stratum >12 months before cycle 2 (leucopenia grade 4). Therefore, a dose reduction to dose level −1 was performed. All following treatments in stratum >12 months were applied according to dose level −1. Patients in stratum 6–12 months received a median dose of topotecan of 1.0 mg/m^2 (range 0.75–1.0 mg/m^2) and carboplatin AUC5 (range AUC5–AUC5). The median dose given in stratum >12 months was topotecan 0.75 mg/m^2 (range 0.67–1.2) and carboplatin AUC5 (range AUC5–AUC5) (Table 2).

Toxicity

Hematological toxicity

There were no episodes of sepsis or chemotherapy-related deaths. Myelotoxicity, specifically leucopenia, was the leading adverse event (Table 3). The incidence for grade III/IV leucopenia was estimated at 58% (95% CI 37–77%) but was generally not complicated by fever events.

Table 3 Worst hematological and non-hematological toxicities (CTC-Grade III/IV)

	Stratum		Total
	6–12 months	>12 months	
Anemia	2	1	3
Leucopenia	10	5	15
Neutropenia	7	8	15
Thrombocytopenia	4	4	8
Hypersensitivity to carboplatin	0	1	1
Alopecia	0	0	0
Neurotoxicity	0	0	0
Diarrhea	0	2	2
Nausea	2	2	4
Emesis	1	1	2

Overall, hematological side effects were manageable and without clinical sequelae. The incidence of grade 3–4 hematological toxicities was comparable in both strata ($P = 0.26$) (see Table 3). Grade 4 neutropenia occurred in only 1 (6.2%) patient in dose level 0 and in 3 (30%) patients in dose level −1. One patient (stratum > 12 months) suffered from grade 4 anemia in dose level −1. No other grade 4 hematological toxicities were observed.

Blood transfusions, erythropoietin, and supportive G-CSF were given in 14 (9.79%), 72 (50.35%), and 21 (14.69%), respectively, of a total 145 cycles.

Blood transfusions (9 (6.29%) versus 5 (3.50%)), erythropoietin (40 (27.97%) versus 32 (22.38%)), and supportive G-CSF (15 (10.49%) versus 6 (4.20%)) was given in a lower number of cycles within dose level −1 in comparison to dose level 0.

Non-hematological toxicity

No unexpected non-hematological toxicity was observed. Generally, non-hematological side effects were generally mild. No grade 4 non-hematological side effects occurred. Of note, only few patients presented typical gastrointestinal side effects like diarrhea, nausea and emesis. Two patients suffered from grade 3 diarrhea, and two patients from grade 3 emesis. Seven patients (stratum > 12 months) experienced mild hypersensitivity to carboplatin, one patient from grade 1, and five patients from grade 2. Grade 3 hypersensitivity occurred in only one patient. Hypersensitivity did not require treatment discontinuation in any patient. Patients did not encounter severe alopecia or neurotoxicity. Alopecia grade 2 was observed in 5 patients, grade 1 in 14 patients.

Efficacy

Twenty patients could be assessed for response, seven of whom had a complete and another seven had a partial response. Overall response rate was estimated to be 54% (95% CI 33–73%) (Table 4). Accounting only for patients with measurable disease, the response rate was 67% (95% CI 43–85%).

The evaluation of response according to CA-125 was assessable for 19 patients, which showed an elevated CA-125 level (≥70 U/ml) before first cycle of chemotherapy. Overall, 12 (63%) patients had a complete response and another 4 (21%) had a partial response.

Overall, no significant difference in response rate was observed between both dose levels ($P = 0.351$) and strata ($P = 0.15$).

Figure 1 displays the survival curves. At the time of the analysis for survival 11 patients were still alive. The predicted median progression-free survival was 9.5 (95% CI 7.3–12.0) months. The median overall survival was predicted at 19.4 (95% CI 12.3–26.9) months.

Discussion

Re-induction treatment with a platinum-based combination therapy with paclitaxel or gemcitabine is now considered as standard second-line treatment for patients with platinum-sensitive ovarian cancer [5, 8]. However, the use in second-line treatment is limited because of cumulative neurotoxicity [21].

The incidence neurotoxicity in patients receiving conventional paclitaxel and carboplatin as first-line treatment is estimated at 54% of all patients [22], while approximately 13% suffer from grade 2 to 3 neurotoxicity.

Table 4 Summary of response status

	Stratum		Total
	6–12 months	>12 months	
Response, no. of points			
NED/N.E.	4	2	6
PD	1	1	2
SD	3	1	4
PR	3	4	7
CR	2	5	7
Overall response rate (CR + PR), % (95% CI)	38.5 (14–68)	69 (39–91)	54 (33–73)

* P value 0.15 for the comparison of response rate between the two strata

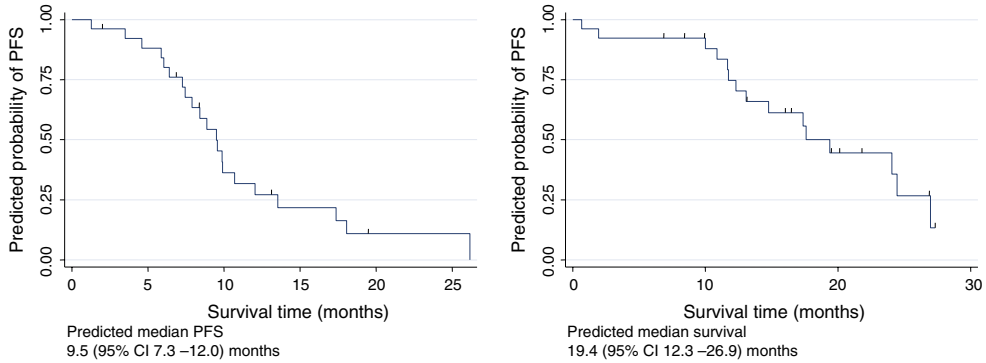


Fig. 1 Kaplan-Meier Plots of PFS and Survival

In the large phase-III of the ICON-AGO intergroup study evaluating treatment with carboplatin and paclitaxel as second-line therapy, a significantly higher incidence of grade 2 to 4 neurotoxicity (20%) was observed compared to conventional platinum-based chemotherapy (1%) [5]. This is notable because in this trial only 43% of recurrent ovarian cancer patients had received previous platinum- and taxane-based chemotherapy. Since currently most patients will be treated with carboplatin and paclitaxel as first-line therapy the incidence of neurotoxicity will be probably significantly higher.

Therefore, there is a high clinical need for alternative platinum-based combinations to improve the therapeutical index.

In this regard, topotecan is an attractive candidate as it has proven activity in relapsed ovarian cancer and it is associated with only few non-hematological side effects as well as manageable cumulative hematological toxicities [10, 11, 13]. Neurotoxicty is generally rare and in most cases due to prior taxane-based chemotherapy [10, 11, 13].

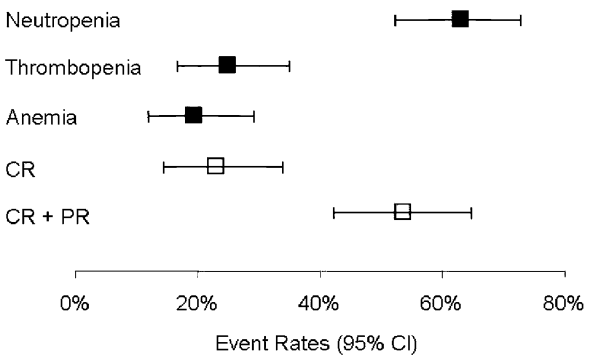
Currently, various study groups are exploring different schedules and doses of topotecan in combination with carboplatin [17, 23, 24, 28, 30–32] (Fig. 2).

Previous phase-I and II trials suggest that 5-day topotecan regimes with carboplatin are feasible [24–26], however, 3-day schedules may likely be more suitable and convincing for combination with other cytotoxic drugs [27–30]. Several phase I/II studies [24, 31, 32] suggest a better toxicity profile and equivalent efficacy of a 3-day schedule of topotecan 1.0 mg/m^2/d1–3 and carboplatin AUC5/d3 in pretreated ovarian cancer patients. Therefore, the 3-day schedule of topotecan was chosen.

The weekly schedule of topotecan plus carboplatin seems to results also in a decreased hematological toxicity profile and needs to be evaluated further [23].

So far there is only one other trial in relapsed ovarian cancer using this 3-day schedule. Bolis et al. [28] performed a phase I/II study in 39 patients of whom 21 (53.8%) had received prior taxane-based chemotherapy. In contrast, in our study all patients were pretreated with paclitaxel and carboplatin.

Fig. 2 Comparison of the results of various trials investigating topotecan plus carboplatin in relapsed ovarian cancer: event rates (95% CI) of haematological toxicities and response rates (95% CI)



Author	Year	n	Median age	Platinum-sensitive	Neutro-penia	Thrombo-penia	Anemia	CR	PR
Bowman	2001	20	58 (34 - 73)	5	6	1	1	0	5
Bolis	2001	29	56 (33 - 76)	22	23	12	10	8	4
Rose	2005	17	60 (38 - 81)	17	10	2	4	4	9
Sehouli	2007	26	62 (28 - 75)	13	19	8	3	7	7

Due to the high frequency of severe and prolonged thrombocytopenia and neutropenia, for the subsequent phase-II study (n = 19 patients) of Bolis et al. [28] a topotecan dose of 1.0 mg/m^2/d1–3 and carboplatin dose according AUC5 every 3 weeks was selected.

In the phase II study of Bolis et al. [28] neutropenia was the main hematological toxicity. Grade 3–4 neutropenia was observed in 58.9%, thrombocytopenia in 30.8% and grade 3 anemia in 25.6% of patients. Dose reductions were necessary in 38.5% of all patients. Hematological toxicity caused dose delays of more than 7 days in 10.2% of patients. The non-hematological toxicity observed was generally mild. The overall response rate in phase II was 63.2%.

In comparison to our study similar results with regard to toxicity and response were observed by Bolis et al. [28]. In the present study, grade 3–4 neutropenia was documented in 57.7% and thrombocytopenia in 30.8% of patients. Grade 4 neutropenia occurred in only one patient in the dose level with topotecan 1.0 mg/m^2 plus carboplatin (AUC 5) and in three (30%) patients in the dose level with topotecan of a dose of 0.75 mg/m^2 plus carbolatin (AUC 5), but without clinical sequelae. With the exception of one patient suffering from grade 4 anemia, there were no other grade 4 hematological toxicities at this dose level. Non-hematological side effects were mild. Despite the fact that all patients in our study were were pretreated with paclitaxel and carboplatin as first-line chemotherapy severe neurotoxicty was not observed.

Overall response rate was 54% (95% CI 33–73%) and was in line with the result of Bolis collegues.

There were no statistically significant differences observed for response rates between both dose levels and TFI stratums in our trial. Therefore the lower dose level with topotecan of 0.75 mg/m^2 plus carboplatin according AUC 5 every 3 weeks seems to be as effective but less toxic than the higher dose.

It could be speculated that patients with a shorter treatment-free interval are in poorer general condition (e.g., a higher rate of fatigue or neurotoxicity) and, consequently, chemotherapy will induce higher toxicity in this patient group. In contrast to the study of Bolis and co-workers, we prospectively stratified our dose-finding study according to the treatment-free interval (6–12 vs. >12 months).

Interestingly, however no significant differences in the incidence of hematological or non-hematological toxicities were observed between both strata, which suggest that tolerability of this regimen is not associated with the treatment-free interval. Hence, primary dose modification for future trials is not required.

In summary, the present data demonstrate that a combination therapy with topotecan and carboplatin is a tolerable and an effective chemotherapy regimen. Therefore this combination warrants further investigation in platinum-sensitive recurrent ovarian cancer. Based on these encouraging data we now have designed a randomized phase III trial comparing topotecan 0.75 mg/m^2 plus carboplatin AUC 5 to the current standard of care. In this concept patients will receive carboplatin (AUC 5) plus paclitaxel (175 mg/m^2/q21d) or carboplatin (AUC 4) plus gemcitabine (1,000 mg/m^{2}d1, d8/q21d according to the individual patient's preference in order to more accurately reflect clinical reality (*HECTOR*-trial)[1]. Progression-free survival is defined as primary objective; and quality of life, response rate and overall survival are secondary objectives. Enrollment is expected to start internationally in April 2007.

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