Topotecan plus carboplatin versus standard therapy with paclitaxel plus carboplatin (PC) or gemcitabine plus carboplatin (GC) or pegylated liposomal doxorubicin plus carboplatin (PLDC): a randomized phase III trial of the NOGGO-AGO-Study Group-AGO Austria and GEICO-ENGOT-GCIG intergroup study (HECTOR)


1. Department of Gynecology, European Competence Center for Ovarian Cancer, Charité University Hospital of Berlin, Berlin, Germany; 2. Department of Gynecology and Gynecologic Oncology, Medical University of Vienna, Vienna, Austria; 3. Department of Medical Oncology, MD Anderson Cancer Center Spain, Madrid, Spain; 4. Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, Essen, Germany; 5. Department of Obstetrics and Otorhinolaryngology, University Hospital of Graz, Austria; 6. Department of Obstetrics and Gynecology, Johann Wolfgang Goethe-University Frankfurt am Main; 7. Department of Gynecology, Park Clinic Weißensee, Berlin; 8. Department of Gynecology and Obstetrics, Carl Gustav Carus University, Dresden; 9. Gynecological Practice for Gynecologic Oncology, Medical University of Vienna, Vienna, Austria; 10. E-mail: jalid.sehouli@charite.de

Background: Randomized, phase III trial to evaluate safety and efficacy of topotecan and carboplatin (TC) compared with standard platinum-based combinations in platinum-sensitive recurrent ovarian cancer (ROC).

Patients and methods: Patients were randomly assigned in a 1:1 ratio to the experimental TC arm (topotecan 0.75 mg/m²/ days 1–3 and carboplatin AUC 5 on day 3 every 3 weeks) or to one of the standard regimes [PC] paclitaxel plus carboplatin; [GC] gemcitabine plus carboplatin; [PLDC] pegylated liposomal doxorubicin and carboplatin] which could be chosen by individual preference but before randomization. The primary end point was progression-free survival (PFS).

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*Correspondence to: Prof. Jalid Sehouli, Charité University Medicine Berlin, Department of Gynecology, European Competence Center for Ovarian Cancer, Augustenburger Paltz 1, 13353 Berlin, Germany. Tel: +49-30-430-564-002; Fax: +49-30-430564-900; E-mail: jalid.sehouli@charite.de
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after 12 months. Overall survival (OS), response rate, toxicity, quality of life and treatment preference regarding standard treatment were defined as secondary end points.

Results: A total of 550 patients were recruited. The PFS rate after 12 months was 37.0% for TC compared with 40.2% in the standard combinations ($P = 0.470$). The overall response rate was 73.1% for TC versus 75.1% for standard combinations ($P = 0.149$). After a median follow-up of 20 months, the median PFS was 10 months [95% confidence interval (CI) 9.4–10.6] and did not differ between both arms ($P = 0.414$). The median OS was 25 months in the TC arm versus 31 months in the standard arm (95% Cl: 22.4–27.6 resp. 26.0–36.0; $P = 0.163$). Severe hematologic toxicities (grade 3/4) were rare in the experimental arm ($P < 0.001$), with 17.4% leucopenia, 27.8% neutropenia and 15.9% thrombopenia.

Conclusion: The combination of carboplatin and topotecan was well tolerated with significant lower rates of severe hematological toxicities but did not improve PFS or OS in platinum-sensitive relapsed ovarian cancer compared with established standard regimens.

Key words: ovarian cancer, platinum-sensitive, topotecan

introduction

Ovarian cancer is the third frequent gynecological cancer entity and ranks fifth among cancer-related deaths in women [1]. Despite improved surgical techniques to achieve maximal cytoreduction and effective cytostatic first-line treatment, the majority of the patients experience recurrence and die due to tumor progression. Depending on the disease-free interval, recurrent ovarian cancer (ROC) ≥6 months after first-line platinum-based chemotherapy is defined as platinum-sensitive disease [2, 3]. Modern clinical strategies indicate a potential role of surgery, but chemotherapy remains the cornerstone of treatment in this situation.

Based on various phase III trials, different platinum-based combinations are currently recommended for patients with platinum-sensitive ROC [4–7]. Large randomized trials (ICON4/AGO-Ovar 2.2 and AGO-Ovar 2.5/NCIC/EORTC) have demonstrated the superiority of a combination of carboplatin with paclitaxel (PC) or gemcitabine (GC) regimen over platinum monotherapy in platinum-sensitive patients [4, 6]. However, cumulative neurotoxicity of paclitaxel confines the potential efficacy, and precludes administration to patients with residual neurological deficits [8]. The GC regimen seems to induce higher hematological toxicity, leading to dose modifications and treatment discontinuation. The combination of carboplatin with pegylated liposomal doxorubicin (PLDC) allowed further improvement in systemic recurrent treatment demonstrating PFS-superiority and better therapeutic index over the PC regimen in platinum-sensitive ROC patients [7]. Thus, further optimization of the toxicity profiles remains a key requirement for further treatment innovations in patients with ROC.

The topoisomerase I inhibitor topotecan is well established in palliative therapy of ROC and was proven to be similarly effective as paclitaxel and PLDC in platinum-resistant ovarian cancer [9, 10]. In a subgroup analysis, pegylated doxorubicin demonstrated superiority over topotecan in overall survival (OS) in platinum-sensitive ROC patients but without significant differences in the overall population [11].

In vitro analyses have shown marked synergy of topotecan with platinum compounds and high activity [12–14]. The North-Eastern German Society of Gynecological Oncology (NOGGO) has carried out a multicenter phase I/II trial with a 3-day schedule of topotecan in combination with carboplatin which demonstrated the feasibility of this combination and reported promising response rate of 67%, with a median of 9.5 months progression-free survival (PFS) and 19.4 months OS, and acceptable hematological profile [15].

The aim of this multicenter randomized phase III trial was to compare the efficacy and the clinical outcome of topotecan and carboplatin (TC) compared with established standard platinum-based combinations.

methods

patients

Patients with histologically or cytologically confirmed ovarian carcinoma, peritoneal carcinoma or fallopian tube carcinoma and relapse/progression ≥6 months after the end of platinum-containing primary or secondary therapy were eligible. Further inclusion criteria were: previous treatment with taxane, age ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, sufficient bone marrow, renal and hepatic function. This study was approved by the local ethics committee and carried out in accordance with local laws and regulations, and the guidelines on Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all patients before study entry. This trial was registered in the clinical trial register with the number NCT00170677.

study design and treatment

This multicenter trial was conducted at 62 centers in Germany (coordinated by NOGGO and AGO Study Group), 12 centers in Spain (coordinated by Grupo Español de Investigacion en Cancer de Ovario—GEICO) and 9 institutions in Austria (coordinated by Arbeitsgemeinschaft Gynäkologische Onkologie, Austria—AGO Austria). All centers had to indicate their preferred standard treatment arm for each individual patient before randomization. Patients were randomly assigned to the experimental and the standard treatment arm in a 1:1 ratio. Treatment in the experimental arm consisted of topotecan 0.75 mg/m²/day on days 1–3 and carboplatin AUC 5 on day 3 after topotecan, every 3 weeks. There were three different treatment possibilities in the standard arm: (PC) paclitaxel 175 mg/m²/day on day 1,
and carboplatin AUC 5 on day 1, every 3 weeks; (GC) gemcitabine 1000 mg/m²/day on day 1 and 8 and carboplatin AUC 4 on day 1, every 3 weeks. At study initiation, the ongoing CALYPSO trial was not finished, so that the study protocol approve the PLDC-combination in the case of positive results as third additional standard treatment option: pegylated doxorubicin 30 mg/m² on day 1 and carboplatin AUC 5 on day 1, every 4 weeks [16].

**study end points**

The primary study end point was the comparison of PFS rate (PFSR) after 12 months. Secondary end points were the comparisons of PFS, OS, response, toxicity, quality of life and treatment preference regarding standard treatment. Based on the results of the phase I/II study, it was designed as superiority trial. Response was defined according to the RECIST criteria as well as on the CA125 response criteria of the GCIG, modified according to Levy et al. [17–19]. Quality of life was assessed by the 30-item Quality-of-Life questionnaire (QLQ C 30) and Ovar 28 (1.0) of the European Organization for Research and Treatment of Cancer (EORTC). Toxicity was classified according to the NCI-CTC criteria version 3.0.

**statistical analysis**

Based on data of the ICON study, the 1-year PFSR for the standard arm was assumed to be 50% [4]. A sample size of 275 patients in each arm was target to detect an absolute difference of 12.5% PFSR at 12 months with a power of 80% and a significance level of 5%. This calculation was based on the assumption of an equal number of patients in both arms and a dropout rate of 5%.

Comparison of the experimental and standard arm for the primary end point was analyzed for the intention to treat (ITT) cohort using Fisher’s exact test. Additionally, subgroup analyses were carried out for comparison of the experimental arm and the different chemotherapy schedules of the standard arm. Differences between groups were evaluated by Fisher’s exact test, \( \chi^2 \) test or Mann–Whitney U-test where appropriate. Survival curves and median survival for OS and PFS were estimated according to the Kaplan–Meier method and log-rank tests were used for univariate statistical comparisons. Differences for indicators of quality of life were analyzed by Student’s \( t \)-test for cross-sectional data and by general linear models for longitudinal data. All analyses were carried out with PASW 19.0 (SPSS Inc., Chicago, IL).

**results**

Between March 2007 and December 2009, 591 patients were screened and 550 patients were eligible. Patients were randomized to the experimental arm and the standard arms with 275 patients each. Figure 1 depicts the trial profile.

**Abbreviations:**
- TC = Topotecan and Carboplatin
- GC = Gemcitabine and Carboplatin
- PC = Paclitaxel and Carboplatin
- PLDC = Pegylated Liposomal Doxorubicin and Carboplatin
For descriptive analysis, patients in the standard arm were further divided into 3 groups: 191 patients receiving carboplatin in combination with gemcitabine, 79 patients receiving carboplatin in combination with paclitaxel and 5 patients receiving carboplatin in combination with PLDC. Patients’ characteristics were well balanced (Table 1, supplementary Table S4, available at Annals of Oncology online). All patients experienced first (80.5%) or second relapse (19.5%) without distribution difference between both arms (\(P = 0.830\)).

A total of 393 patients (71.5%) completed at least 6 cycles of chemotherapy. Patients in the standard arm received significantly less delayed all planned chemotherapy cycles than those in the experimental arm [209 patients (76.0%) in the standard arm versus 184 patients (66.9%) in the experimental arm, \(P = 0.023\)]. Main reasons for early cessation of chemotherapy in the experimental arm compared with the standard treatment arm were hematologic toxicity (16.3% versus 17.2%), non-hematologic toxicity (19.8% versus 23.4%), progressive disease (25.6% versus 28.1%), patient’s wish (12.8% versus 9.4%). Statistically no differences concerning the various reasons for therapy cessation could be pointed out (\(P = 0.580\)). Therapy alterations (dose reductions) were more frequently necessary in the standard treatment arm (in 35.9%) than in the experimental arm (in 23.0%), \(P = 0.001\). This was due to hematologic toxicity in 53.1% of the patients in the standard treatment arm and in 22.6% in the experimental arm.

### primary end point

The median follow-up was 20 months (range: 0–52 months). One year after randomization, 37.0% of patients in the experimental and 40.2% of patients in the standard treatment arm did not progress (Figure 2). No difference in PFS 12 months after therapy could be noted between both arms (\(P = 0.470\)). In the standard arm, 49.3% of patients treated with paclitaxel, 36.8% of patients treated with gemcitabine and 25.0% of patients treated with pegylated doxorubicin remained progression-free within 1 year after completion of chemotherapy (\(P = 0.215\)). There was no significant difference in PFS after 12 months between the experimental arm and the standard arm when both cohorts were stratified for age (<60 years; \(P = 0.704\) and >60 years; \(P = 0.155\)), number of chemotherapy line (second line, \(P = 0.367\) and third line; \(P = 0.835\)) and histology (serous; \(P = 0.609\) and non-serous; \(P = 0.568\)).

### secondary end points

Overall, 262 patients (47.6%) died; disease progressed in 426 patients (77.5%). The median PFS in the experimental arm was

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| Table 1. Baseline characteristics of study participants |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristic                  | Experimental arm | Standard arm | \(P\) value |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age (median years)              | 61              | 61              | 0.44            |                 |                 |                 |                 |                 |
| Range (years)                   | 29–84           | 24–80           |                 |                 |                 |                 |                 |                 |
| ECOG performance status         |                 |                 |                 |                 |                 |                 |                 |                 |
| 0                               | 127 (46.2%)     | 154 (56.0%)    | 0.07            |                 |                 |                 |                 |                 |
| 1                               | 131 (47.6%)     | 109 (39.6%)    |                 |                 |                 |                 |                 |                 |
| 2                               | 15 (5.5%)       | 12 (4.4%)      |                 |                 |                 |                 |                 |                 |
| n.k.                            | 2 (0.7%)        | 0              |                 |                 |                 |                 |                 |                 |
| FIGO stage at initial diagnosis |                 |                 |                 |                 |                 |                 |                 |                 |
| I                               | 21 (7.6%)       | 16 (5.8%)      | 0.48            |                 |                 |                 |                 |                 |
| II                              | 22 (8.0%)       | 17 (6.2%)      |                 |                 |                 |                 |                 |                 |
| III                             | 204 (74.2%)     | 202 (73.5%)    |                 |                 |                 |                 |                 |                 |
| IV                              | 25 (9.1%)       | 39 (14.2%)     |                 |                 |                 |                 |                 |                 |
| n.k.                            | 3 (1.1%)        | 1 (0.4%)       |                 |                 |                 |                 |                 |                 |
| Histology                       |                 |                 |                 |                 |                 |                 |                 |                 |
| Serous-papillary                | 210 (76.3%)     | 210 (76.4%)    | 0.69            |                 |                 |                 |                 |                 |
| Endometrioid                    | 22 (8.0%)       | 18 (6.5%)      |                 |                 |                 |                 |                 |                 |
| Mucinous                        | 4 (1.5%)        | 5 (1.8%)       |                 |                 |                 |                 |                 |                 |
| Undifferentiated                | 7 (2.5%)        | 13 (4.8%)      |                 |                 |                 |                 |                 |                 |
| Other (i.e. clear cell,         | 32 (11.6%)      | 29 (10.6%)     |                 |                 |                 |                 |                 |                 |
| transitional)                   |                 |                 |                 |                 |                 |                 |                 |                 |
| Grade                           |                 |                 |                 |                 |                 |                 |                 |                 |
| 1                               | 13 (4.7%)       | 9 (3.3%)       | 0.48            |                 |                 |                 |                 |                 |
| 2                               | 88 (32.0%)      | 85 (30.9%)     |                 |                 |                 |                 |                 |                 |
| 3                               | 162 (58.9%)     | 160 (58.2%)    |                 |                 |                 |                 |                 |                 |
| n.k.                            | 12 (4.4%)       | 21 (7.6%)      |                 |                 |                 |                 |                 |                 |
| Recurrence free interval (months)|                 |                 |                 |                 |                 |                 |                 |                 |
| None                            | 0               | 2 (0.7%)       | 0.35            |                 |                 |                 |                 |                 |
| <6 months                       | 0               | 1 (0.4%)       |                 |                 |                 |                 |                 |                 |
| 6–12 months                     | 176 (64.0%)     | 180 (65.5%)    |                 |                 |                 |                 |                 |                 |
| >12 months                      | 99 (36.0%)      | 92 (33.5%)     |                 |                 |                 |                 |                 |                 |
| Prior chemotherapy              |                 |                 |                 |                 |                 |                 |                 |                 |
| None                            | 0               | 2 (0.7%)       | 0.11            |                 |                 |                 |                 |                 |
| Platinum                        | 10 (3.6%)       | 3 (1.1%)       |                 |                 |                 |                 |                 |                 |
| Platinum plus taxane            | 263 (95.6%)     | 267 (97.1%)    |                 |                 |                 |                 |                 |                 |
| Platinum/taxane/topotecan       | 2 (0.7%)        | 3 (1.1%)       |                 |                 |                 |                 |                 |                 |
| Second recurrence               | 55 (20.0%)      | 52 (18.9%)     | 0.83            |                 |                 |                 |                 |                 |

n.k., not known; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

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Figure 2. Progression-free survival.
10 months [95% confidence interval (CI) 9.2–10.8] compared with 11 months in the standard treatment group (95% CI 10.1–11.9), P = 0.414 (Figure 2). Stratified for groups with disease-free survival of 6–12 months and more than 12 months after first-line platinum-based chemotherapy, the median PFS did not differ between the experimental and standard arm (P = 0.937 and 0.351, respectively).

The median OS was 27 months (95% CI 24.0–30.0), 25 months in the experimental arm (95% CI 22.4–27.6) and 31 months with standard treatment (95% CI 26.0–36.0), P = 0.163, supplementary Figure S1, available at Annals of Oncology online. The median OS was also not different between the experimental and standard arm (P = 0.062 and 0.846, respectively) when cohorts were stratified for disease-free interval of 6–12 months and more than 12 months after first-line platinum-based therapy.

Overall response [complete response (CR) plus partial response (PR)], according either to CA125 levels or RECIST criteria, was observed in 304 patients (74.1%) out of 410 cases available for response evaluation. Overall response was achieved in 73.1% of patients in the experimental arm compared with 75.1% in the standard arm (P = 0.149). Responses are summarized in Table 2, supplementary Tables S5 and S6, available at Annals of Oncology online.

Grade 3 and 4 toxicities were seen in all treatment groups and are shown in Table 3 (see also supplementary Tables S2 and S3, available at Annals of Oncology online). Hematologic toxicities grade 3 and 4 were significantly more frequent in the standard treatment arm compared with the experimental arm, P < 0.001.

At baseline, overall quality of life was significantly worse in the experimental arm (P = 0.039) and patients suffered significantly more frequently from loss of appetite than in the standard arm (P = 0.025). This difference was not persistent during and after chemotherapy. Most quality-of-life parameters worsened during chemotherapy for all treatment groups in a similar pattern. But, during chemotherapy, patients receiving the topotecan combination were more heavily affected by diarrhea (P = 0.035); however, symptoms were not severe on average, see also supplementary Table S7, available at Annals of Oncology online. When comparing the different combined platinum-based therapies, patients treated with paclitaxel were significantly more severely affected in their quality of life by peripheral neuropathy and other side-effects (P = 0.012).

Regarding preferences for the three different regimens of the standard treatment arm (see supplementary Table S1, available at Annals of Oncology online), the choice for one specific regimen was made by patient and treating physician together in 58.5%. Reasons for choosing the combination carboplatin and paclitaxel were a better rhythm of therapy in 36.1%, less hematologic toxicity in 14.5% and good previous tolerance in 12.7%. The combination carboplatin and gemcitabine was mainly chosen because of a lower rate of neuropathy in 52.0% and a lower rate of alopecia in 31.0%. The decision for the combination of carboplatin and pegylated doxorubicin was made due to a lower rate of neurophathy in 46.2% and a better rhythm of therapy in 23.1%. For patients, a lower rate of alopecia (in 42.7%), less neuropathy (23.6%) and a better rhythm of therapy were the most important decision criteria. The treating physician also focused on these points in 10.2%, 27.1% and 19.5%, respectively.

discussion

The clinical management of ROC remains a great challenge. Thus, implementation of less toxic and at best superior therapies remains focus of the main research. Previous studies suggested a potential activity of the combination of TC for patients with platinum-sensitive ovarian cancer [15].

However, this phase III trial failed to show superiority of topotecan plus carboplatin (TC) compared with standard platinum combinations in platinum-sensitive ROC. Neither response rates nor progression-free or OS and quality of life differed significantly between both randomized arms, but severe hematologic toxicity (leucopenia, neutropenia and thrombopenia) was lower for the TC group.

Nevertheless, this large study provides important information for our daily clinical routine as different established chemotherapy combinations were analyzed in this study. Up to this point, there has been no randomized trial that had compared the combination of gemcitabine plus carboplatin with other platinum-based combinations. Although the treatment choice was at the
physician’s discretion and thus not on a random basis, this is the first trial to do so. Furthermore, this is a study with previous taxane therapy as inclusion criteria in contrast to other studies that are combining carboplatin with other chemotherapy agents such as in the study by Pfisterer et al. [6] where only 10 patients (out of 252 with a previous platinum-based combination) had received prior docetaxel combination therapy.

As expected, hematological events were the most frequent toxicities in the treatment with TC but in most cases without relevant clinical consequences. However, adverse events occurred less frequently in the experimental arm compared with standard platinum combinations in our study. Patients treated with the combination of GC exhibited significantly more grade 3 and 4 hematologic toxicities.

Regarding preference for one platinum-based standard regimen, patients and physicians preferred most commonly carboplatin plus gemcitabine. This is the first prospective study that analyzed a patient’s preference in a setting of platinum-sensitive ROC patients and the first study that compared standard treatments in platinum-sensitive ROC. Alopecia was the side-effect that mattered most to PC. Therefore, patients’ expectations and preferences should be further investigated and implemented regularly into the treatment decision-making process.

To conclude, our findings demonstrated feasibility and activity of the TC regimen in patients with platinum-sensitive ROC. Carboplatin plus topotecan was well tolerated with moderate rates of severe and long-lasting toxicity compared with PC or GC platinum-based regimen, but PFS and OS could not be significantly improved. Furthermore, the 3-day schedule may be inconvenient for the patients.

Carboplatin plus gemcitabine was chosen by the majority of patients and physicians as preferred standard platinum combination due to the lower rate of alopecia. However, we should discuss that there are no reliable randomized efficacy studies comparing GC with the other regimens as PC and in the post CALYPSO-study area with CPLD. Further trials including patient preference are warranted.

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