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# Original article

## Second-line carboplatin and gemcitabine in platinum sensitive ovarian cancer – a dose-finding study by the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Ovarian Cancer Study Group

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**Summary**

*Background:* Despite the progress that has been achieved in the last years, recurrence rates in ovarian cancer patients are still considerably high and the majority of patients ultimately become candidates for second-line treatment. Carboplatin re-induction is a broadly adopted regimen in patients with recurrences occurring six months or later after first-line treatment. Gemcitabine is among the candidates as combination partner in second-line regimens.

*Patients and methods:* We performed a study with escalating doses of gemcitabine combined with carboplatin in 26 platinum-pretreated patients with recurrent ovarian cancer and a treatment-free interval of 6+ months. Dose-limiting toxicity (DLT) and a maximum tolerable dose (MTD) recommendable for further trials was evaluated.

*Results:* The DLT was myelosuppression, mainly thrombocytopenia. No dose limiting non-hematological toxicities were observed. The MTD of gemcitabine was 1,000 mg/m$^2$ given on days 1 + 8 of a three-week schedule combined with carboplatin AUC 4 given on day 1. The majority of evaluable patients showed an objective response (62.5%), and median progression-free and overall survival were 10 and 18+ months, respectively.

*Conclusion:* Gemcitabine–carboplatin given according to the MTD is well tolerated and active against recurrent platinum-sensitive disease. A randomized trial comparing carboplatin with or without gemcitabine in platinum-sensitive ovarian cancer has already been initiated.

**Key words**: carboplatin, gemcitabine, ovarian cancer, second-line treatment

### Introduction

Despite the progress which has been achieved by introducing platinum–paclitaxel combination chemotherapy into first-line treatment of advanced ovarian cancer, the majority of patients still develop recurrent disease [1–4]. Nevertheless, recurrence does not inevitably mean immediate fatal outcome. Some patients with recurrent disease can survive for several months and even years after responding to second-line chemotherapy. Thus, there is a need for the evaluation and development of effective second-line chemotherapy regimens.

Retrospective evaluation of several series with platinum-based second-line chemotherapy has led to an empirical definition of at least two subgroups of patients with recurrent ovarian cancer: those with platinum refractory and those with platinum sensitive ovarian cancer. Platinum sensitivity is generally defined according to a progression-free interval of more or less than 6–12 months after platinum containing first-line chemotherapy [5]. Patients with refractory disease usually have a poor prognosis and even the most active drugs achieve only short lasting responses in about 15%–20% of patients [6]. Results in patients with platinum sensitive tumors are superior, second-line single agent platinum chemotherapy being among the most active regimens in patients with platinum-sensitive disease [7–12]. Several phase II studies have reported promising results with platinum-based combination therapy, including response rates of about 50%–60% gained by combining platinum with etoposid [13, 14], paclitaxel [15-17], or alkylating agents [18–22]. Retrospective analysis of the data gained by platinum-based combination regimens suggest an improved efficacy [6], but this has not been confirmed by randomized trials. A randomized comparison between carboplatin single agent and a carboplatin–anthracyline combination revealed a higher response rate and more toxicity in the combination arm [23]. However, this did not translate in statistically significant superior overall or progression-free survival. Unfortunately, the statistical power of this trial was not sufficiently large enough to draw definitive conclusions. Another randomized trial run by our group (AGO Study Group Ovarian Cancer) to answer this question compared carboplatin

single agent vs. a carboplatin–paclitaxel combination. The trial had to be terminated early, due to an unexpected high level of neurotoxicity seen with the combination regimen. This applied especially to patients who suffered from persistent neurotoxicity induced by first-line cisplatin–paclitaxel. Therefore, the question of whether platinum combination is more effective than single agent platinum as a second-line treatment for patients with recurrent ovarian cancer remains to be answered.

The unexpected neurotoxicity with the re-induction carboplatin–paclitaxel regimen showed the need to choose a platinum combination more carefully before testing in a randomized study. Screening published results of phase II studies suggested that gemcitabine with carboplatin might be a potentially useful combination. Phase II studies with gemcitabine have shown activity in ovarian cancer, including patients with prior platinum or paclitaxel exposure [24–27]. Furthermore, the non-hematologic toxicity profiles of both agents, including neurotoxicity, do not overlap. Therefore, our group decided to further evaluate a carboplatin–gemcitabine combination. The primary aim of this study was the development of a feasible regimen of this combination which could be recommended for future phase III testing. The evaluation of the activity of this combination in a cohort similar to those for whom a phase III study was planned (i.e., patients with platinum sensitive relapsed ovarian cancer) was the secondary aim.

## Patients and methods

This dose-finding study was conducted according to GCP guidelines. Approval from ethics committees was obtained and each patient gave written informed consent. A stepwise recruitment of patient in cohorts of six patients per dose level with escalating gemcitabine doses was planned, thus defining the maximum tolerated dose (MTD). Inclusion criteria included histologically confirmed epithelial ovarian cancer or primary peritoneal adenocarcinoma recurring after a minimum of a six-month treatment free interval following one prior platinum-containing chemotherapy. Other inclusion criteria were standard for phase I–II studies and included Eastern Cooperative Oncology Group performance status of 0–2, an adequate bone-marrow function (absolute neutrophil count $> 1.49 \times 10^9$/l and platelet count $> 99 \times 10^9$/l), and an adequate renal and hepatic function (creatinine and bilirubin $< 1.51 \times$ upper limit of normal). Patients were ineligible if they had prior malignancies (excluding non-melanomatous skin cancer), more than one prior chemotherapy, prior gemcitabine exposure, active infection, bowel obstruction, or mental disorder.

Gemcitabine dose was started at 800 mg/m$^2$ in dose level I, with planned escalation of 200 mg/m$^2$ in each dose level. Gemcitabine was infused over 30' on days 1 and 8 of a 21 day cycle. Carboplatin was given as a one hour infusion following gemcitabine on day 1 only. Carboplatin doses were calculated according to the Calvert formula [28] with a target area under the concentration curve (AUC) of 5. The glomerular filtration rate was estimated according to the Jeliffe formula [29]. This protocol was amended to reduce the carboplatin dose to an AUC of 4 after observation of considerable myelosuppression at dose levels I and II, respectively. The recommended premedication regimen consisted of single-dose 20 mg dexamethasone and single-dose 5-HT$_3$ antagonist given before chemotherapy on day 1. No premedication was recommended before gemcitabine on day 8. Primary prophylaxis with granulocyte colony stimulating factors (G-CSF) was not allowed.

Blood counts were monitored weekly, or twice a week if patients had an ANC $< 0.5 \times 10^9$/l. Non-hematological toxicities were monitored before each course and for three weeks following the last course. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria [30].

Dose-limiting toxicity (DLT) was defined as (1) ANC $< 0.5 \times 10^9$/l lasting for more than 7 days, (2) febrile neutropenia, (3) grade 4 thrombocytopenia, (4) clinically relevant non hematological toxicity grade 3 or higher, (5) treatment delays of more than 14 days due to myelosuppression. Re-treatment was delayed until platelet counts had reached $100 \times 10^9$/l and ANC was $> 1.49 \times 10^9$/l. Patients were evaluated for DLT in all of the first three courses. The next higher dose level was opened for enrollment if no DLT occurred in the first course in at least five of six patients at a dose level. Depending on the observed toxicity an additional cohort of six patients could be enrolled into each dose level. Maximum tolerated dose (MTD) was only defined after analysis of the first three consecutive courses in each patient at a dose level. MTD, as recommendation for further trials, was defined as the dose level with less than three of six patients having had a toxicity defined as DLT within the first three consecutive courses.

Bidimensionally measurable tumors were not strictly mandatory for inclusion, but patients who presented with measurable tumors were evaluated for response. Pelvic examinations were performed by an experienced gynecologist before each course. Imaging techniques appropriate for tumor measurement were performed every other course. Transvaginal and transcutaneous ultrasound as well as conventional radiologic techniques and computer tomography were accepted. The same diagnostic tool which was used primarily for tumor measurement before study entry was used to evaluate response during the course of therapy and after completion of treatment. Response was defined according to the UICC criteria [31]. Disease-free and overall survival was calculated from the date of study entry and analysed according to the Kaplan–Meier method. Follow-up visits were performed every three months. Disease-free survival, overall survival, and objective responses were descriptively analysed to give an impression of the activity of this regimen.

## Results

From July 1997 to June 1998, twenty-six patients were enrolled. One patient was found ineligible because she had received more than one prior chemotherapy regimen. The remaining 25 patients received 123 chemotherapy courses. Patient characteristics were well balanced in all dose levels and are described in Table 1. All but one patient had ovarian cancer, one patient had primary peritoneal cancer. The mean age was 59.8 years, and 13 patients had an Eastern Collaborative Oncology Group (ECOG) performance status of 0. Performance status 1 and 2 were reported for 10 and 2 patients, respectively. Seventeen tumors were of serous histology, six were undifferentiated epithelial tumors, and mucinous and endometroid histology occurred one each. All of the patients had received one prior platinum containing regimen. Platinum was combined with a taxan in 21 patients (paclitaxel 20; docetaxel 1) and with an alkylating agent in four patients. Sixteen of the twenty-four patients with ovarian cancer had measurable disease and were evaluable for response; all courses were evaluable for toxicity, and all patients could be included in progression-free and overall survival analysis.

*Table 1* Patient characterics

| | Level 1 (800 mg/m$^2$, AUC 5) | Level 2 (1,000 mg/m$^2$, AUC 5) | Level 2A (1,000 mg/m$^2$, AUC 4) |
|---|---|---|---|
| Patients | 12 | 6 | 7 |
| Courses | 58 | 32 | 33 |
| Median age (years) | 62 (44–76) | 54 (47–66) | 59 (46–78) |
| Median GFR (ml/min) | 76 (45–109) | 73 (60–85) | 65 (51–167) |
| Diagnosis | | | |
| Ovarian cancer | 11 | 6 | 7 |
| Peritoneal cancer | 1 | – | – |
| Measurable disease | 9 | 5 | 2 |
| First-line treatment | | | |
| Carboplatin – Taxol | 5 | 1 | 4 |
| Cisplatin – Taxol | 3 | 2 | 1 |
| Carboplatin – Taxol – epirubicin | 2 | – | 2 |
| Carboplatin – Taxotere – doxil | – | 1 | – |
| Carboplatin – cyclophosphamide | 2 | 1 | – |
| Cisplatin – treosulfan | – | 1 | – |
| Interval since last course | | | |
| 6–12 months | 2 | 3 | 5 |
| > 12 months | 10 | 3 | 2 |

*Table 2* Hematological toxicity

| % of: | Level 1 58 courses | | Level 2 32 courses | | Level 2A 33 courses | |
|---|---|---|---|---|---|---|
| NCI CTC grade | 3 | 4 | 3 | 4 | 3 | 4 |
| Anemia | 7 | – | 3 | – | 3 | – |
| Thrombocytopenia | 16 | 10 | 13 | 16 | 15 | 6 |
| Neutropenia | 16 | 11 | 26 | 7 | 34 | 6 |
| Secondary G-CSF | 10 | | 3 | | 9 | |
| Platelet transfusion | 2 | | 2 | | – | |

*Dose escalation – dose limiting toxicity (DLT)*

The first six patients were entered into dose level 1 (gemcitabine 800 mg/m$^2$, carboplatin AUC 5). One patient developed DLT during the first course with thrombocytopenia grade 4. One further patient had a pulmonary embolism which was not considered a treatment related toxicity, but attributed to her underlying disease. However, it led to enrollment of six more patients at dose level 1. No further DLT in the first course of level 1 was observed, thus allowing further dose escalation. A third cohort of six patients were entered at dose level 2 (gemcitabine 1,000 mg/m$^2$, carboplatin AUC 5). No DLT was observed during course 1 of dose level 2.

However, at this time DLT was observed in courses 2 and 3 of dose level 1 and thus further dose escalation was held until completion of at least three courses in all patients in dose levels 1 and 2. Four out of the twelve patients in dose level 1 developed grade 4 thrombocytopenia during courses 2 and 3. In addition three of six patients in dose level 2 had developed thrombocytopenia grade 4 within the first three courses.

This resulted in an amendment and dose level 2A was added, carboplatin AUC 4 with gemcitabine 1,000 mg/m$^2$. Seven patients were enrolled in this dose level. None developed DLT in course 1. Only two patients had thrombocytopenia grade 4 in subsequent courses. According to our definition, dose level 2A was regarded as MTD, consisting of gemcitabine 1,000 mg/m$^2$ days 1 + 8, followed by carboplatin AUC 4 on day 1.

*Toxicity*

Hematological toxicity consisted mainly of grade 3–4 thrombocytopenia which occurred in 26%, 39% and 21% of courses at dose level 1, level 2 and level 2A, respectively (Table 2). The maximum grade 4 thrombocytopenia seen in any course at levels 1, 2, and 2A were 25%, 67%, and 14% respectively. Platelet transfusion were given to one patient each at dose level 1 and 2. Grade 4 neutropenia was quite common and was observed in 42%, 33%, and 29% of patients at the three dose levels, respectively. However, only one patient developed neutropenic fever. This was probably due to the short lasting neutropenia which rarely exceeded five days. G-CSF was used in some patients, although not prophylactically. Anemia was not of major clinical relevance.

Dose-limiting treatment related non-hematological toxicities were not observed at any dose level. Non-hematological toxicity was rarely observed higher than grade 2 and occured equally in each level. Therefore, non-hematological toxicity are reported for all dose levels, patients and courses (Table 3). No treatment related death occurred. Three patients each reported constipation and abdominal pain/cramps which the investigator classified as probably disease related. Only one patient reported edema which resolved spontaneously. One patient experienced transient grade 3 hypersensitivity with

*Table 3* Non-hematological toxicity of carboplatin–gemcitabine 25 patients with 123 courses.

| NCI CTC grade | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Emesis | 20 | 16 | – | – |
| Nausea | 60 | 16 | – | n.a |
| Diarrhea | 12 | 8 | | |
| Constipation | 36 | 16 | 12 | – |
| Mucositis | 48 | – | – | – |
| Infection | 32 | 20 | – | 1 |
| Myalgia | 24 | 4 | – | – |
| Pain | 52 | 4 | 12 | – |
| Neurotoxicity (PNS) | 44 | 8 | – | – |
| Ototoxicity | 4 | 4 | – | – |
| Alopecia | 64 | 16 | n a | n.a |
| Edema | 32 | 8 | 4 | – |
| Hypersensitivity | 24 | – | 4 | – |
| Arrhytmia | 8 | – | – | – |

Abbreviation n a. – not applicable.
Numbers are % of 25 patients, the worst course per patient is counted

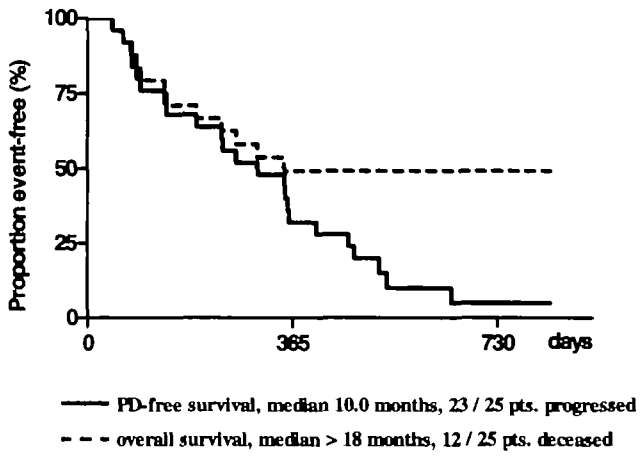


*Figure 1* Survival and progression-free survival after a median follow-up of 23 months (range 19–30 months; Kaplan–Meier curves).

bronchial obstruction, which resolved on discontinuation of carboplatin infusion and administration of anti-allergic medication. This patient continued treatment with single-agent gemcitabine without any further hypersensitivity reaction.

*Actual dose*

At dose level 1, nine out of twelve patients completed five or more courses; two patients received four courses and treatment was discontinued due to progressive disease; one patient refused treatment after two courses. Treatment delay of more than one week was observed in 15.4% (9 of 58) of the courses at dose level 1. At dose level 2, four out of six patients received five or more treatment courses. The remaining two patients discontinued treatment after course 2 and 3 due to progressive disease. Treatment delay of more than one week was observed in 13% (4 of 32) of the courses at dose level 2. At dose level 2A, five out of seven patients received 5 or more treatment courses, and two patients stopped treatment after course 3 because of disease progression. Treatment delays beyond seven days were reported in 2 of 33 courses at dose level 2A.

*Efficacy*

Sixteen patients with epithelial ovarian cancer had bidimensionally measurable disease and were evaluable for objective response. Four patients achieved a complete response and six patients showed partial responses resulting in an overall reponse rate of 62.5 % (10 of 16 patients). Two patients each had stable disease or tumor progression. The remaining nine patients were not included into response analysis because they did not show measurable disease at study entry. Four of these nine patients experienced progression during the treatment period. All patients could be included in the analysis of progression-free and overall survival. Survival and progression-free survival data after a median observation period of 23 months (range 19–30 months) are presented in Figure 1. The median progression-free and overall survival for all patients were 10 and 18+ months, respectively.

## Discussion

Despite the progress that had been achieved by the incorporation of paclitaxel into first-line platinum-based treatment of advanced ovarian cancer, survival rates are still disappointing and eventually the majority of patients will develop recurrences. Patients with treatment-free intervals exceeding 6–12 months may respond to second-line treatment. No standard treatment has been established, but re-challenge with platinum is a reasonable option in these patients [32]. Several phase II studies have reported promising results with platinum-based combination therapy with response rates of about 50%–60%. However, no combination has proven superior to single agent platinum. Furthermore, an ideal combination partner for platinum has not been defined. A combination partner for platinum should have both proven activity after platinum and paclitaxel and a toxicity profile that should allow re-treatment in patients with at least subclinical neurotoxicity following platinum–paclitaxel.

Gemcitabine is one of the new drugs with promising activity and a toxicity profile not containing neurotoxicity, thus being a candidate for further development. Gemcitabine single agent has been evaluated within four phase II studies in platinum-pretreated [24–26] and in one study even platinum- and paclitaxel-pretreated patients [27] with relapsed ovarian cancer. These studies have utilized a 28 days schedule with gemcitabine given at doses of 800–1,250 mg/m$^2$ on days 1, 8, and 15. No relevant neurotoxicity attributable to gemcitabine was observed and responses occurred in each trial. The first clinical developement of a carboplatin–gemcitabine

combination was done in lung cancer patients. Again, these studies used a 28-day schedule with gemcitabine 1,000 mg/m$^2$ administered on days 1, 8, and 15. Carboplatin was given at doses of AUC 4–5.2. The major toxicity in these trials was thrombocytopenia grade 4 occurring in 20%–80% of patients [33, 34]. As in our trial, no dose-limiting non-hematologic toxicites were reported. Concerning myelosuppression, we made similar observations when we combined carboplatin AUC 5 with gemcitabine 800–1,000 mg/m$^2$ in levels 1 and 2. At these levels, severe thrombocytopenia occurred in more than 25% of patients. However, the carboplatin dose-intensity used in our trial was 20%–25% higher than in the above mentioned lung cancer trials. Therefore, we decided to reduce the carboplatin dose to AUC 4 resulting in a dose-intensity of AUC 1.33 per week. We felt this was a safe approach, because a carboplatin dose of AUC 4 had previously been evaluated in a randomized trial proving equivalence for carboplatin AUC 4 and AUC 8 when combined with cyclophosphamide 600 mg/m$^2$ in the treatment of advanced ovarian cancer [35]. After carboplatin dose reduction, the gemcitabine dose could be maintained at 1,000 mg/m$^2$. At this dose, myelosuppression rates were less excessive. Even more, no relevant drug-related non-hematologic toxicity was observed (esp. no neurotoxicity). Overall, toxicity at the MTD was generally mild and did not cause dose reduction in subsequent courses.

We observed objective responses in the majority of patients with measurable disease, including some clinical complete responses. The median progression-free survival of 10 months compared well with other published trials evaluating carboplatinum-based combinations in similar patient cohorts with relapsed platinum sensitive ovarian cancer. Furthermore, median survival was not reached yet after a median observation period of almost two years when only 12 of 25 patients have deceased. Again, results from published trials in similar cohorts did not report superior results. Two studies evaluating carboplatin–paclitaxel in 39 and 104 platinum-sensitive patients reported median progression-free survival of 9–11 months, and median survival of 10–20.5 months, respectively [36, 37]. Another trial evaluating carboplatin-cyclophosphamide in 28 platinum-sensitive patients reported 8 and 12 months, median progression-free and overall survival, respectively [19].

The promising results of our study led to the initiation of a randomized phase III AGO – NCIC (National Cancer Institute of Canada) – EORTC (European Organisation for the Research and Treatment of Cancer) Intergroup trial comparing carboplatin AUC 5 single agent with gemcitabine 1,000 mg/m$^2$ administered on days 1 and 8 plus carboplatin AUC 4 given on day 1, both treatment arms repeated every three weeks. Since December 1999, patients with recurrent ovarian cancer and a treatment interval of at least six months following one platinum-based first-line therapy are enrolled into this currently open trial (AGO protocol # 2.5).

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