Carboplatin and Nonpegylated Liposomal Doxorubicin in Primary Advanced or Recurrent Endometrial Cancer

A Phase 2 Trial Conducted by AGO Austria

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Objective: Recurrent/advanced endometrial carcinoma carries a poor prognosis. Chemotherapy usually consists of cisplatin/doxorubicin and paclitaxel or the doublet of carboplatin and paclitaxel. We report on final results of the Austrian phase 2 AGO trial of nonpegylated doxorubicin citrate and carboplatin in 39 patients with primary advanced or relapsed endometrial cancer. The main primary end point is response rate, and the main secondary end point is feasibility.

Methods: Thirty-nine patients received 60 mg/m^2 nonpegylated doxorubicin citrate and carboplatin (area under the curve, 5) every 3 weeks for 6 to 9 cycles or until progression. Best response during therapy, progression-free survival, and the toxicity profile were recorded.

Results: Thirteen patients (33%) had primary advanced disease, and 26 patients (67%) had recurrent disease. Seventy-five percent of the tumors were adenocarcinomas, 15% were serous carcinomas, and 5% were clear cell and mixed müllerian carcinomas. We observed 1 complete response (3%) and 16 partial responses (41%) in the intention-to-treat population. The median progression-free survival was 7.2 months, and the median overall survival was 14.7 months. Overall, 177 cycles were administered; the mean number of cycles per patient was 4.5. Ten percent of patients received 9 cycles of chemotherapy, and 44% of patients received 6 cycles of chemotherapy. Grade 3/4 neutropenia occurred in 17%, grade 3/4 anemia in 5%, and grade 3/4 thrombopenia in 12% of the cycles. In 6% of the cycles, febrile neutropenia was noticed. Grade 3/4 nausea was seen in 5% of cycles. One patient (3%) experienced cardiac toxicity and had a reduction in the left ventricular ejection fraction to below 50%.

Conclusions: The reported combination demonstrates considerable activity and should be evaluated further.

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All patients gave written informed consent according to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice rules before study entry. The protocol was approved by the ethics committee of the Innsbruck Medical University, Austria, and registered at the European Trial Database (EudraCT number 2007-004060-40). The study was conducted and sponsored by the AGO (Arbeitsgemeinschaft für Gynäkologisch Onkologie) Austria. The study center is located at the Innsbruck Medical University.

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The protocol was developed at the ninth joint Federation of European Cancer Societies /American Association for Cancer Research / American Society Clinical Oncology Workshop on Methods in Clinical Cancer Research, Flims, Switzerland, 2007.

Key Words: Advanced endometrial cancer, Chemotherapy, Carboplatin, Nonpegylated liposomal doxorubicin

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Patients with early endometrial cancer can expect good prognosis, but once endometrial cancer has spread beyond the uterus and the regional lymph nodes, prognosis declines rapidly. Intra-abdominal carcinomatosis as well as hepatic, pulmonary, bone, and central nervous system metastases are common. Therefore, treatment strategies for primary advanced or recurrent disease (beside surgery) have focused on hormonal therapy, cytotoxic chemotherapy, and radiotherapy with or without chemotherapy.[1–5] Because many patients with advanced or recurrent endometrial carcinoma present with advanced age and significant comorbidities, research in this field should focus on feasible systemic therapy regimens with acceptable toxicity and better efficacy.

Several randomized studies have addressed the issue of optimal systemic therapy for this group of patients. The combination of doxorubicin and cisplatin is widely used in advanced endometrial cancer after publication of the GOG 107,[3] GOG 163,[4] and GOG 122[5] studies. The response rate (RR) and progression-free survival (PFS) of the combination are superior to doxorubicin alone without disadvantageous difference in overall survival (OS). However, although the combination of doxorubicin and cisplatin is efficient, it is a toxic scheme. This applies mainly to patients in a palliative setting. Less toxic combinations are desirable in terms of improving quality of life.

The main objective of this study was to assess whether the combination of liposomal-encapsulated nonpegylated doxorubicin citrate (NPLD, Myocet; Cephalon Pharma GmbH, Martinsried, Germany) and carboplatin for primary advanced or recurrent/metastatic endometrial cancer is feasible and active. When this trial started, the combination of cisplatin and doxorubicin was regarded as standard of care. The combination of carboplatin and NPLD was considered to exert a comparable activity.

MATERIALS AND METHODS

Eligibility Criteria and Baseline Assessment

Patients with histologically confirmed advanced or recurrent endometrial cancer, older than 18 years, Eastern Cooperative Oncology Group performance status of 0 to 2, and estimated life expectancy of at least 12 weeks were eligible. Previous adjuvant chemotherapy was allowed, as long as anthracycline-containing regimens had been terminated 12 months, those containing platinum at least 6 months before study participation. Previous radiotherapy was allowed but had to be completed at least 4 weeks before the study was commenced. Measurable lesion for efficacy evaluation with RECIST (Response Evaluation Criteria in Solid Tumors, 2000)[6] was essential. Patients with cerebral metastases were not eligible. Concurrent nonstudy systemic treatment or radiotherapy was not allowed. Sufficient bone marrow function (platelet count, $\geq 100 \times 10^9$/L; absolute neutrophil count, $\geq 1.5 \times 10^9$/L; hemoglobin level, ≥10.0 g/dL) and adequate liver and kidney function (bilirubin level, ≤1.25 upper limit of normal; aspartate transaminase/alanine transaminase level, <3 upper limit of normal; creatinine level, ≤1.25 upper limit of normal; glomerular filtration rate, ≥50 mL/min) were necessary for inclusion. Left ventricular ejection fraction had to be greater than 50% within 4 weeks before inclusion; history of myocardial infarction within 6 months preceding enrollment was not allowed. Patients with heart failure less than New York Heart Association class II or symptoms of congestive heart failure showing left ventricular ejection fraction (LVEF) 50% or greater were allowed. For patients with third degree or complete heart block, a pacemaker had to be in place. Patients with a second malignancy diagnosed within the last 5 years or concomitant medical illness including uncontrolled infection, uncontrolled angina, or any other relevant illness that potentially interfered with study procedures were not eligible. All patients gave written informed consent according to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice rules before study entry. The protocol was approved by the ethics committee of the Innsbruck Medical University, Austria, and registered at the European Trial Database (EudraCT number 2007-004060-40).

Baseline evaluation included a complete physical examination and history, record of signs and symptoms, complete blood count and biochemistry with CA-125 determination, estimation of glomerular filtration rate, electrocardiogram, echocardiogram or multigated angiography scan, abdominopelvic computed tomography (CT) scan or nuclear magnetic resonance imaging, and chest CT, magnetic resonance imaging, or x-ray within 28 days. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire QLQ-C30 was used.

Treatment

Nonpegylated doxorubicin citrate was administered intravenously over 60 minutes at 60 mg/m^2 followed by carboplatin (area under the curve [AUC], 5) over 30 minutes on day 1 of a 21-day cycle. Premedication was administered according to the hospital standard. For subsequent cycles, the absolute neutrophil count had to be greater than or equal to 1.5×10^9/L, platelet count greater than or equal to 100×10^9/L, and hemoglobin level greater than or equal to 10.0 g/dL. Therapy could be delayed for up to maximum of 14 days. Dose adjustments were performed for hematological and other adverse events. First dose reduction to carboplatin (AUC, 4), second to NPLD 45 mg/m^2, was done for hematologic toxicity grade 3 or 4 in the previous cycle or for grade 2 mucositis/cutaneous toxicity if it did not recover to grade 1 by

14 days. If any other major organ toxicity grade 3 or 4 occurred, the patient had to go off protocol. Any additional dose reduction was possible outside the protocol at the discretion of the investigator. If patients showed LVEF 50% or more or a 20% decrease in LVEF as compared with baseline or signs of cardiac toxicity, the patient was excluded.

Therapy was performed until progressive disease (PD), unacceptable toxicity, or patient's withdrawal.

Assessment of Response

The primary aim of the study was to evaluate the objective RR to experimental treatment. Best response throughout the trial was used for assessment. If complete response (CR) or partial response (PR) was observed, the regimen was designated active. Secondary end points were duration of PFS, OS, and the safety and feasibility of therapy. Clinical evaluation of response, including serum CA-125, was done on day 1 of each cycle; radiologic evaluation was done after every 3 cycles or at the investigator's discretion. Response evaluation was performed according to the RECIST (2000).[6] In the case of disappearance of all clinical and radiological evidence of tumor, CR was diagnosed, whereas PR was defined as a decrease of at least 30% in the sum of lesion diameter (LD) of target lesions in comparison to baseline LD. An increase of at least 20% in the total LD of measured lesions since the treatment started was designated PD. Steady state of disease without sufficient shrinkage to qualify as PR or sufficient increase to qualify as PD was defined as stable disease.

Progression-free survival was calculated from the date of enrollment until the end of the follow-up period, the date of progression, or death. Progression was defined as any new tumor lesion, growth of any known tumor lesion, or death from any cause. Overall survival was calculated from the date of enrollment until the end of follow-up or until death from any cause.

Assessment of Toxicity

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3. Toxicity was analyzed for patients having received at least 1 dose of chemotherapy. Physical examination and vital signs were recorded before each cycle of chemotherapy. Complete blood counts were performed at baseline and weekly. Laboratory examinations were planned at baseline and before each cycle. Electrocardiographic monitoring was performed at each cycle; echocardiography with LVEF assessment was planned after every 3 cycles. The study was deemed feasible if more than 50% (n = 20) of all eligible patients underwent all 6 cycles of therapy.

Statistical Analysis

The study used Simon 2-stage design with an early stopping rule in the event of insufficient therapy activity. The hypothesis was that the regimen would obtain an RR of at least 35% ($\alpha = 0.05$, $\beta = 0.10$). In the first accrual stage, a response in at least 7 of the first 23 patients was postulated to continue the trial. In the second phase of the study, additional 16 patients were enrolled to complete the accrual rate of 39 patients. The regimen was considered to be active if 14 or more responses were observed.

RESULTS

From December 2007 to September 2011, 39 patients were enrolled. Baseline characteristics of the patients are shown in Table 1. Four patients (10%) were not evaluable for response evaluation, 2 because of hypersensitivity at the beginning of the first NPLD administration after which chemotherapy was immediately discontinued, 1 patient refused therapy after the first cycle due to toxicity (febrile neutropenia), and 1 patient was lost to follow-up after the second cycle. In the whole collective response, evaluation was possible in 35 patients. After evaluation of all patients, we found response to the regimen in 17 patients (43% of intention-to-treat cohort, Table 2). In the group of patients in whom analysis per protocol was possible, response was seen in 49% (n = 17; CR in 1, PR in 16). Two patients died during therapy because of progression, namely, one each after the second and the third cycle.

TABLE 1. Baseline characteristics

Characteristics	Values
Age, median (range), y	66.7 (48–78)
ECOG performance status, n (%)	
0	16 (41)
1	19 (48)
2	4 (10)
Parity, median (range)	2 (0–6)
Body surface area AUC, median (range), m^2	1.79 (1.45–2.22)
Primary advanced disease, n (%)	12 (31)
Recurrent disease (first recurrence after primary therapy), n (%)	27 (69)
FIGO stage, n (%)	
I	18 (46)
II	1 (3)
III	9 (23)
IV	11 (28)
Grading, n (%)	
G1	8 (21)
G2	13 (33)
G3	18 (46)
Histology, n (%)	
Endometrioid adenocarcinoma	29 (75)
Serous carcinoma	6 (15)
Clear cell carcinoma	2 (5)
Mixed müllerian carcinoma	2 (5)
Previous adjuvant chemotherapy (6 cycles each)	6 (15)
All radiotherapy, n (%)	22 (56)
Brachytherapy/teletherapy, n (%)	20 (51)/7 (18)

ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

TABLE 2. Response rates

	No. Patients Intended to Treat	Treatment per Protocol
CR	1 (3%)	3%
PR	16 (41%)	46%
Stable disease	8 (21%)	23%
PD	10 (25%)	29%

Four patients (10%) were not evaluable for response evaluation.
CR, complete response; PR, partial response; PD, progressive disease.

The median duration of PFS was 7.2 months, and the median OS was 14.7 months.

Overall, 177 cycles of chemotherapy were administered with a median of 4.5 cycles/patient (Table 3). Seventeen of all accrued patients (44%) received 6 cycles of chemotherapy, and 4 (10%) received 9 cycles.

The number of toxicities—with the exception of alopecia—is given as a proportion of all administered cycles. We observed grade 3/4 anemia, leukopenia, and thrombopenia in 5%, 17%, and 12% of cycles, respectively. Febrile neutropenia was seen in 6% of cycles. Granulocyte-colony stimulating factor (GCSF) support was given in 124 cycles (71%) and 28 patients (72%), respectively. Grade 3/4 nausea/vomiting and diarrhea were observed in 5% and 2% of administered cycles, respectively. Grade 1 alopecia occurred in 10 patients (26%), whereas 18 patients (46%) experienced alopecia grade 2. We did not see grade 3/4 mucositis/stomatitis, palmoplantar erythrodysesthesia, myalgia/arthralgia, or peripheral neuropathy. One patient showed a reduction in LVEF from 60% to 48% after 6 cycles of therapy. The LVEF reduction was designated grade 2 toxicity according to NCI-CTC, version 3, because the reduction was asymptomatic, but below 50%, and no intervention was necessary.

In 15 cycles (8%), a hypersensitivity reaction was observed during therapy, CTC grade 1 in 11 cycles (6%) and grade 2 in 1 cycle (1%). In 3 cases, grade 3 hypersensitivity was observed, namely, in 2 patients after commencement of therapy, after which the patients went off study, and in 1 case, a hypersensitivity reaction occurred during the third cycle (Table 4).

DISCUSSION

In the European Union, endometrial cancer is the most common malignancy of the female genital tract, with an estimated incidence of 16 in 100,000 women per year and a mortality rate of 4 to 5 cases in 100,000 women per year.[7] About 75% of women with endometrial carcinoma are diagnosed in stage I with tumor confined to the uterus at the time of diagnosis. Therefore, 5-year survival rates in countries with the highest incidence are high, namely, between 72% in Europe and 84% in the United States.[8,9] However, unexpectedly, a number of patients recur despite International Federation of Gynecology and Obstetrics stage 1 disease. Recently, L1CAM expression in endometrioid cancers has been shown to be associated with highly aggressive tumors leading to significantly higher recurrence and death rates.[10] When the disease recurs or is diagnosed at more advanced stages, prognosis is poor. In our cohort, 18 patients (46%) experienced recurrence after baseline stage I tumor.

It was shown that in primary advanced or recurrent endometrial cancer, RRs for single-agent chemotherapy are comparable with those observed after hormonal treatment, but response duration in patients receiving chemotherapy is generally longer.[1–3] A European Organisation for Research and Treatment of Cancer trial in 2003 observed significantly better RRs with a combination of doxorubicin and cisplatin than with cisplatin alone (RR, 43% vs 17%).[2] The combination of doxorubicin and cisplatin became even more widely used for chemotherapy of advanced endometrial cancer after publication of the GOG 107[3] and GOG 163[4] studies. In the GOG 107 study, overall RR for cisplatin/doxorubicin was 42% with a complete RR of 19%. The median PFS was 5.7, and the median OS was 9 months. The doublet combination of cisplatin and doxorubicin in the GOG 163 trial showed an RR of 40%, PFS of 7.2, and OS of 12.3 months. In the GOG 177 trial, CR to cisplatin/doxorubicin (AP) was 7% with an overall RR of 34% in comparison to a triplet combination with additional paclitaxel (TAP), showing an RR of 57% (CR, 22%).[11] The triplet combination was superior to standard treatment in terms of overall RR, median PFS, and OS, but it demonstrated increased toxicity and especially significantly more peripheral neuropathy. As a result of that trial, TAP remains the most active regimen studied in randomized trials, but its toxicity profile is a major barrier to clinical use.

A GOG trial by Randall et al[5] showed that combination chemotherapy with doxorubicin and cisplatin improved PFS and OS as compared with whole abdominal radiation in patients with advanced endometrial carcinoma (PFS after 60 months 50% vs 38%, OS 55% vs 42%, $P < 0.01$), whereas higher acute toxicity (especially high-grade hematologic and gastrointestinal toxicity) was observed in the chemotherapy group.

When our protocol was started in 2007, the combination of anthracyclines and cisplatin was still most commonly used for chemotherapy of endometrial carcinoma. However, due to the still high toxicity of the doublet combination in a group of patients with often poor outcome and comorbidities such as age, obesity, hypertension, and diabetes, it seemed to be necessary to use less toxic combinations of the same

TABLE 3. Number of cycles administered

No. Cycles	n (%)	Cumulative, n (%)
0	2 (5)	2 (5)
1	4 (10)	6 (15)
2	4 (10)	10 (25)
3	6 (15)	16 (40)
4	1 (3)	17 (43)
5	1 (3)	18 (46)
6	17 (44)	35 (90)
9	4 (10)	39 (100)

Overall, 177 cycles were administered; median, 4.5 cycles/patient.

TABLE 4. Number of toxicities of all cycles (NCI-CTC, version 3)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	64 (36%)	59 (33%)	9 (5%)	0
Neutropenia	27 (15%)	32 (18%)	17 (10%)	10 (7%)
Febrile neutropenia			5 (3%)	5 (3%)
Thrombocytopenia	47 (27%)	12 (7%)	11 (6%)	10 (6%)
Stomatitis/mucositis	49 (28%)	3 (2%)	0	0
Palmoplantar erythrodysesthesia	3 (2%)	0	0	0
Myalgia, arthralgia	35 (20%)	2 (1%)	0	0
Nausea/vomiting	56 (32%)	35 (20%)	8 (5%)	0
Diarrhea	23 (13%)	6 (3%)	2 (1%)	1 (1%)
Peripheral neuropathy	37 (21%)	3 (2%)	0	0
Hypersensitivity reactions	11 (6%)	1 (1%)	3 (2%)	0
Cardiac toxicity	0	1 (1%)	0	0
Alopecia (given in a proportion of patients)*	10 (26%)	18 (46%)	NA	NA

*Given in proportion of intention-to-treat population (n = 39).
NA, not applicable.

groups of substances. The NPLD dose was set equal to the dose of doxorubicin.[11,12] In all 39 patients, the combination of NPLD and carboplatin showed an RR of 41%, which is comparable to previous data. However, if one takes into account that in 4 patients no response evaluation was possible, we observed response to therapy in nearly half of all evaluable patients (n = 17 of 35, 49%). In addition, the median PFS and OS of 7.2 and 14.7 months, respectively, achieved with the combination of NPLD, and carboplatin are comparable to previous data.

As a consequence of GOG 177 with superior data for the triplet combination and emerging carboplatin and paclitaxel as an alternative regimen in the treatment of endometrial cancer, the GOG 209 trial was designed to compare TAP with a combination of carboplatin and paclitaxel (TC). Preliminary results were presented at the 2012 Annual Meeting on Women's Cancer by Miller et al,[13] who reported an RR of 51.3% for TAP, which is comparable with data from the GOG 177, and an RR of 51.2% for TC. Rates for PFS and OS were much higher than previously described, namely, PFS 13.3 and 13.5 months for TC versus TAP, and OS 36.5 and 40.3 months, respectively. In both arms, about two thirds of patients received 6 or more cycles of chemotherapy (72.9% for TAP, 79.2% for TC). This number is higher than the number of completed cycles in our trial, where 54% of patients received 6 or more cycles of chemotherapy. The GOG 209 trial did not allow prior chemotherapy, as compared with our study in which 6 patients (15%) had received previous chemotherapy. A retrospective trial by Sovak et al[14] published in 2007 reported 43% objective RR for a combination of paclitaxel and carboplatin and a PFS of 5.3 and OS of 13.2 months in 63 eligible patients. Even retrospectively, that trial shows slightly lower RRs than that of ours and the published data described previously.

A detailed overview of toxicities observed in our study is shown in Table 4. Our data showed lower toxicity rates except for thrombopenia, which was observed in 36% of patients (grade 3 in 6 patients, grade 4 in 8 patients). High-grade neutropenia was less frequent in our study (grade 3 in 10 patients [26%], grade 4 in 7 patients [18%]) than described before, but we observed febrile neutropenia in 5 patients (13%) (grade 3 in 3 patients [8%], grade 4 in 2 patients [5%]). In 124 (71%) among 177 cycles of chemotherapy, GCSF support was given. However, nearly one third of patients (11 [28%]) did not need GCSF. Dose reduction, mainly due to myelotoxicity, was performed in 9 patients (23%) according to the protocol. In contrast to drug regimens comprising doxorubicin or paclitaxel, we observed low rates of neuropathy, grade 1/2 in 21% and 2% of patients, and alopecia in less than half of the patients (Table 4); this fact, especially in a palliative setting, might be an advantage of the drug combination used here.

Currently, mainly 2 chemotherapy regimens—doxorubicin/cisplatin (AP) and doxorubicin/cisplatin/paclitaxel (TAP)—are established for the treatment of primary advanced or recurrent endometrial carcinoma. The triplet combination shows higher response, PFS and OS rates, but it is accompanied by the disadvantage of higher toxicity. Preliminary data for the GOG 209 trial show comparable RRs for TAP and carboplatin/paclitaxel (TC), which is known to be well-tolerated in terms of feasibility but leads to high-grade neuropathy and alopecia in a significant proportion of patients. Our data show comparable RRs with a toxicity profile—mainly thrombopenia—that seems to be manageable and does not lead to prolonged disorders. However, dose reduction has to be given consideration. A trial by Pujade-Lauraine et al[15] in 2010 showed efficacy in ovarian cancer with a combination of carboplatin (AUC, 5) and pegylated doxorubicin 30 mg/m^2 administered every 4 weeks with good tolerability; even if the used anthracycline is different to the one used in this trial, a reduced dose of NPLD as well as upfront GCSF support might be discussed for further evaluation.

Our study data show comparable response, good feasibility, and tolerable toxicity for the combination of NPLD and carboplatin in patients with advanced or recurrent endometrial carcinoma. Nevertheless, further evaluation of the combination

will be necessary to allow more individualized treatment with the option of an additional regimen of chemotherapy in patients with high morbidity.

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