Phase II study of a combination of cyclophosphamide, adriamycin and cisplatin in advanced Fallopian tube carcinoma

An EORTC Gynecological Cancer Group Study

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Summary

Objective: To investigate the clinical activity and toxicity of a combination chemotherapy consisting of cyclophosphamide (C), adriamycin (A) and cisplatin (P) for patients with primary adenocarcinoma of the Fallopian tube having FIGO stage III-IV disease.

Methods: The CAP-regimen consisted of cyclophosphamide 600 mg/m^2, adriamycin 45 mg/m^2, and cisplatin 50 mg/m^2 administered intravenously on day one every 28 days.

Results: Twenty-four eligible patients with histologically-confirmed Fallopian tube adenocarcinoma were entered in the trial. Fourteen patients had FIGO stage III, and ten had stage IV disease. The median number of CAP cycles was six. Ten patients had a complete and six had a partial response (response rate: 67%, 95% confidence limits: 45-84%). WHO grade III-IV side-effects included haematological toxicity, nausea/vomiting and alopecia. Furthermore, mild signs of cisplatin-related peripheral neurotoxicity were observed. At a median follow-up of 40 months, nine patients were alive and 15 had died due to malignant disease. The median time to progression was 13 months for all patients. The median overall survival was 24 months and the 1-, 3- and 5-year survival and their 95% confidence limits were 73% (54-92%), 25% (4-46%) and 19% (0-38%), respectively.

Conclusion: The present data confirm the therapeutic activity of the CAP-regimen in primary Fallopian tube adenocarcinoma. The response rate is moderate and the toxicity profile is acceptable.

Key words: Fallopian tube carcinoma; Phase II trial; Chemotherapy; Cyclophosphamide; Adriamycin; Cisplatin.

Introduction

Carcinoma of the Fallopian tube is the least common site of origin for a malignant neoplasm of the female genital tract. Primary Fallopian tube adenocarcinoma comprises less than 1% of gynecological malignancies [1, 2]. Histological similarity to epithelial ovarian carcinoma reflects the adaptation of the same classification system and therapy modalities. In contrast with patients with ovarian cancer, approximately 2/3 of tubal carcinomas are diagnosed with disease confined to the tubes and pelvic structures [1, 3, 4]. The prognosis of Fallopian tube carcinoma has generally been regarded as poor, with an overall survival that parallels that of epithelial ovarian cancer [2, 5-8]. Cytoreductive surgery and first-line platinum-based combination chemotherapy were considered as optimal therapy [1, 9-16].

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The Gynecological Cancer Group of the European Organization for Research and Treatment of Cancer (EORTC/GCG) initiated a prospective clinical trial to investigate the anti-tumour activity and toxicity of CAP in treating women with primary adenocarcinoma of the Fallopian tube.

The CAP-regimen as used in our study was based on the results of a randomised trial in ovarian cancer conducted by the Gynecologic Oncology Group. Omura and colleagues randomised 440 evaluable women with advanced ovarian carcinoma to chemotherapy consisting of doxorubicin/cyclophosphamide (AC) versus cyclophosphamide/doxorubicin/cisplatin (CAP). The clinical complete response rate, duration of response, and survival in measurable cases showed a statistically-significant advantage for CAP [17]. Later studies and meta-analysis suggested that the addition of doxorubicin to cyclophosphamide and cisplatin might increase long-term survival in advanced ovarian cancer [18].

In the present study, a variation on the CAP regimen was used in patients with primary advanced Fallopian tube carcinoma. A 28-day regimen given over a minimum of six cycles was chosen based on our previous experience in ovarian cancer [19].

Patients and Methods

From September 1985 to November 1993, patients with advanced Fallopian tube cancer were entered into a prospective clinical trial conducted by the EORTC/GCG. Included were patients with histologically-confirmed primary Fallopian tube adenocarcinoma, presenting with measurable and/or evaluable residual disease after initial cytoreductive surgery [20]. Previous radiation or chemotherapy was not allowed. Patients had normal bone marrow-, kidney-, and liver-functions and a negative history for cardiac abnormalities and previous or concurrent cancer. All patients were informed of the treatment and the involved risks, and gave their informed consent.

Operative management consisted of total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, and cytoreduction in an attempt to maximally debulk any metastatic lesions. All tumours were staged on the basis of operative and histopathological findings according to the International Federation of Gynecology and Obstetrics (FIGO) Ovarian Cancer system as proposed by Dodson and colleagues [21].

Patients were treated with CAP chemotherapy following surgery. The dosage and schedule of administration of chemotherapy consisted of: cyclophosphamide 600 mg/m^2 by i.v. push, adriamycin 45 mg/m^2 by i.v. push, and cisplatin 50 mg/m^2 by intravenous (i.v.) infusion over a 4-hour period with (pre)hydration of one litre of normal saline. This triple therapy was administered on day one and the regimen was repeated at 28-day intervals. Adriamycin was excluded from the regimen when the maximum cumulative dose of 500 mg/m^2 was reached.

Before each course of chemotherapy, physical and gynecological examinations were performed, WHO performance status and toxicity grading were assessed, renal function was monitored closely and patients underwent a complete blood count and appropriate chemical survey. Nadir counts were performed during and between the administration of successive chemotherapy cycles. In the event of grade II-IV myelosuppression (white blood cell count (WBC) $< 3.0 \times 10^9$/l or platelet count (PLA) $< 75 \times 10^9$/l), chemotherapy was postponed until recovery up to normal blood counts. If only some improvement of the blood counts was seen (WBC: 3.0-3.9 x 10^9/l and PLT: 75-99 x 10^9/l), the doses of cyclophosphamide and adriamycin were reduced by 50% of the initial dose during further treatment, and cisplatin was restarted at the full dose. In the event of renal impairment (creatinine clearance $\leq$ 40 ml/min), cisplatin was excluded from the regimen. In the event of hepatic toxicity based on elevated bilirubin levels (25-50 µmol/l or > 50 µmol/l), the dose of adriamycin was reduced by 50% or 75% of the initial dose, respectively. Before CAP administration and following every third cycle a chest X-ray and ECG were carried out, and indicator lesions were measured bidimensionally using the same instrumental test as previously used.

Patients were considered clinically assessable for response if residual disease was detectable by either CT-scanning or ultrasound before the CAP chemotherapy started. Treatment response was assessed according to WHO criteria [20]. If gross residual disease (> 2 cm) remained after primary cytoreductive surgery and tumour shrinkage was observed on CAP, interval debulking was performed after the third cycle. In the absence of disease progression, the desired minimum of six cycles following adequate tumour debulking was administered for response evaluation. Second-look laparotomy was performed in selected patients having a clinical complete remission or resectable tumour mass after the sixth or ninth cycle. All complete responders received up to nine CAP cycles and patients with a partial response or stable disease continued protocol treatment until residual tumour became resectable, disease progressed, or unacceptable toxic side-effects were observed.

Statistical considerations

The main endpoint was response to treatment. Survival and side-effects were also reported.

The sample size calculation was based on the 2-stage Gehan design [22] aiming to include 14 patients and then including additional patients according to the number of responses observed in the first stage. This guarantees that the probability of an active treatment (real response rate ≥ 20%) exhibiting no responses in the first 14 patients (that is, false negative result) is 0.05 and allows the effectiveness of the treatment regimen to be estimated with a standard error of 10%.

The survival curve was estimated using the Kaplan-Meier technique [23].

Results

Out of 36 patients registered in this trial, 12 were considered ineligible: nine had recurrent disease, one had no measurable lesions and two had incorrect histology (tubal carcinosarcoma (1) and epithelial ovarian carcinoma (1)).

The present analysis is based on 24 eligible patients (Table 1). The WHO performance status was 0 for ten, I for 11 and II for three women. Age varied between 46 and 74 years with a median of 64 years. At registration 14 patients had FIGO stage III and ten had FIGO stage IV disease. Since primary tumour debulking was not adequate in three patients, these women underwent interval debulking after the third CAP course. The median number of CAP cycles was six, and all but four patients received the required minimum of six courses.

Pre-and post-treatment evaluations were assessed clinically in 14 patients and surgically in ten women. Based on all eligible patients, the response rate was 16/24 (67%, 95% confidence limits: 45-84%) with ten and six patients having complete and partial responses, respectively. Furthermore four patients had stable disease, three developed progressive disease during CAP and one was not evaluable for response. In two patients (no. 4 and 7) residual tumour mass became resectable after the third course of CAP and patient 16 underwent secondary cytoreductive surgery after the sixth course.

Table 1. — *Clinical data and outcome of 24 patients with advanced Fallopian tube adenocarcinoma treated with CAP.*

Patient number	Age (years)	FIGO stage	Number of cycles	Response	Time to progression (months)	Status + survival from the start of CAP (months)
1.	56	IIIa	3	PD	3	DOD 5
2.	55	IV	11	CR*	26	DOD 29
3.	63	IV	6	PR*	20	DOD 24
4.	73	III	6	PR	15	DOD 20
5.	64	IV	6	CR*	30	DOD 44
6.	57	III	6	CR*	—	AWNED 84
7.	59	IV	9	CR*	24	DOD 26
8.	67	IV	5	PR	5	DOD 6
9.	58	IV	6	PR	5	DOD 9
10.	68	III	6	CR*	—	Alive 74
11.	66	IV	9	CR	24	DOD 34
12.	67	III	6	SD	5	DOD 9
13.	67	III	6	CR*	—	Alive 45
14.	63	III	6	CR*	14	DOD 31
15.	59	III	6	SD	7	DOD 7
16.	55	IV	18	SD	19	DOD 20
17.	63	IV	6	SD	—	AWED 6
18.	68	III	3	PD	8	DOD 8
19.	64	IIIa	6	PD	6	AWED 8
20.	61	IV	6	CR*	13	AWED 13
21.	72	III	3	ID	—	Alive 7
22.	74	III	7	PR	20	AWED 23
23.	67	III	6	CR	11	DOD 20
24.	46	III	6	PR*	—	AWED 12

Note: Abbreviations: AWED: alive with evidence of disease; AWNED: alive with no evidence of disease; CR: complete response; DOD: died of disease; ID: insufficient data; PD: progressive disease; PR: partial response; SD: stable disease.
* Surgical response.

Table 2. — *Toxicity and side-effects during treatment (worst value of WHO grading).*

Side-effects N=24	0	1	2	3	4	Grade 3/4
Haemoglobin	2	12	5	4	1	21%
Leucocytes	4	2	6	9	3	50%
Platelets	17	1	4	2	0	8%
Haemorrhage	23	1	0	0	0	0
Mucositis	20	3	1	0	0	0
Nausea/Vomiting	0	4	8	12	0	50%
Diarrhoea	20	4	0	0	0	0
Pulmonary toxicity	21	2	1	0	0	0
Neutropenic fever	23	1	0	0	0	0
Allergic reaction	23	1	0	0	0	0
Cutaneous reaction	21	3	0	0	0	0
Local reaction	22	2	0	0	0	0
Alopecia	0	1	7	15	1	67%
Infection	21	2	1	0	0	0
Cardotoxicity	21	3	0	0	0	0
Neurotoxicity, state of consciousness	22	1	1	0	0	0
Neurotoxicity, peripheral	19	5	0	0	0	0

Side-effects due to the CAP-regimen are documented using WHO toxicity criteria (Table 2). A total of 19 patients had at least one type of grade III or IV toxicity. During CAP treatment myelosuppression was reported in 22 patients and 15 of them had grade III or IV haematological toxicity. According to the protocol, treatment was delayed in five patients and the doses of cyclophosphamide and adriamycin were reduced to 50% of the initial dose in nine patients. The median leucocyte count nadir was 1.9 x 10^9/l (range: 0.6-6.7), the median platelet count nadir was 142 x 10^9/l (range: 36-357) and the median haemoglobin nadir was 5.7 mmol/l (range: 3.5-7.2). Mild/moderate signs of haemorrhage and infection with different grades of bone marrow suppression were documented. One woman (pt. 23) experienced epistaxis having a normal platelet count and blood pressure.

Cisplatin-related peripheral neurotoxicity was mild in five patients and no cisplatin-related nephrotoxicity was reported. Three patients experienced mild symptoms of transient adriamycin-related cardial disturbances halfway through the CAP treatment. One of them (pt. 22) experienced temporary asymptomatic dysrhytmia, and none of them had recurrent cardiac problems during CAP treatment and follow-up.

One patient (no. 16) received 18 cycles of CAP chemotherapy and she experienced only grade III nausea/vomiting and hair loss. This woman underwent debulking surgery after the sixth cycle and showed the same toxicity-profile before and after cycle six. Adriamycin was excluded from the regimen after the eleventh cycle according to the protocol.

Five patients received further radio-or chemotherapy 1-14 months following CAP treatment: one patient (no. 11) underwent abdominal and pelvic radiotherapy, and four patients received second-line chemotherapy consisting of ifosfamide/adriamycin (pt. 15), single carboplatin (pt. 22), carboplatin/endoxan (pt. 23) or intra-peritoneal cisplatin (pt. 24).

At a median follow-up of 40 months, nine patients were alive with or without evidence of disease and 15 patients had died due to malignant disease. Details on time to progression are given in Table 1. The median overall survival was 24 months (Figure 1) and the 1-, 3- and 5-year survival and their 95% confidence limits were 73% (54-92%), 25% (4-46%) and 19% (0-38%).

Discussion

The literature concerning the use of first-line chemotherapy in primary Fallopian tube carcinoma is scarce. Initially single alkylating agents were used either in the presence or absence of progestational agents. Combination chemotherapy subsequently replaced single agent therapy, and survival was marginally improved [13].

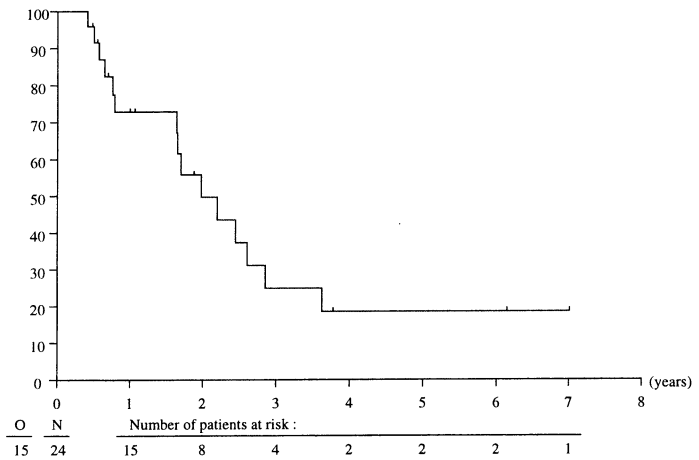

Figure 1. — Overall survival. O = Number of observed events. N = Number of patients at risk.

Table 3. — *First-line cisplatin-based chemotherapy for patients with (advanced) Fallopian tube adenocarcinoma, and measurable residual lesions (> 2 cm) prior to administration of chemotherapy..*

Author	Chemotherapy regimen	Number of patients	Complete Response Surgical	Complete Response Clinical	Partial Response	Response rate
Raju 1981 [2]	PCh	2	–	–	–	
Denham 1984 [8]	PCh	1	–	–	1	
Deppe 1980 [26]	CAP / PA + progestins	2	2	–	–	
Jacobs 1986 [16]	CAP	2	1	–	1	
Maxson 1987 [14]	CAP (N=7) / CP (N=1)	8	–	4	2	75%
Peters 1989 [13]	CAP (N=13) / CP (N=3)	16	6	6	1	81%
Morris 1990 [12]	CAP	7	–	–	3	43%
Barakat 1991 [15]	CAP / CP	33	15	NA	NA	NA
Muntz 1991 [11]	CAP (N=5) / CP (N=2)	7	2	1	2	71%
Pectasides 1994 [10]	CAP	9	4	2	2	89%
Cormio 1997 [9]	CAP	24	10	5	4	79%
Present series	CAP	24	–	10	6	67%
Rose 1990 [24]	P-based	4	1	–	2	
Nappi 1996 [25]	PEC	2	1	–	–	
Friedrich 1997 [3]	PT	2	–	1	1	

Note. Abbreviations: A: doxorubicin (adriamycin); C: cyclophosphamide; Ch: chlorambucil; E: epirubicin; P: cisplatin; T: treosulfan.

Since 1980, combination chemotherapy including cisplatin has proven to be effective and seems superior to previous regimens [13, 15]. In a PubMed search of published trials between 1966 and 1999, seven phase II trials [9-15] and seven case reports [2, 3, 8, 16, 24-26] testing the activity of various cisplatin-based chemotherapeutic regimens for patients with advanced Fallopian tube adenocarcinoma were identified (Table 3). Most experience has been gained with schedules containing cyclophosphamide and cisplatin with or without adriamycin (C(A)P).

In the subsequent review of the literature, only patients having measurable disease (> 2 cm) prior to the administration of chemotherapy were selected. In nine published articles [9-16, 26] first-line chemotherapy with CAP/CP was reported. Deletion of adriamycin from the regimen was the most frequently-occurring treatment modification. In these studies the majority of patients had newly-diagnosed cancer, but six women had recurrent disease without prior chemotherapy or irradiation. Seventy-one out of 107 women with measurable residual disease at the initiation of cytotoxic chemotherapy, showed an overall response rate of approximately 66%. Furthermore 39 of 57 complete responses were pathologically confirmed.

The highest response rate was observed by Pectasides [10]. Four of six complete responses were pathologically confirmed, and three of these women remained free of disease for more than four years. However,

it should be noted that all complete responses except one were obtained for patients with small residual disease (2-5 cm). The Piraeus group also treated two patients having clinically-measurable disease with carboplatin/cyclophosphamide and they observed clinical complete responses in both.

Barakat and colleagues also studied patients with FIGO stage II-IV tubal cancer [15]. Even though the investigated group was small, they showed a significant difference in 5-year survival for patients having no residual disease compared with women having any residual disease following primary cytoreductive surgery. Unfortunately their report lacks separate information concerning response to C(A)P for these subgroups.

The present study of 24 women with advanced Fallopian tube carcinoma treated with CAP subsequent to cytoreductive surgery showed a response rate of 67% (95% confidence limits: 45-84%). Though the population size was too small to define response rates precisely, this finding corroborates the overall response rate of the previous nine articles. Our CAP schedule was associated with severe haematological and gastrointestinal toxicity that could be controlled by treatment delay, dose reductions and concomitant treatment.

Because of the rarity of Fallopian tube carcinoma, large studies have spanned long time periods during which various treatment modalities were employed [4-7, 16, 27-29]. In these publications the medical reports of women with primary adenocarcinoma of the Fallopian tube were retrospectively studied and the general characteristics and the results of various methods of treatment were described. Despite the limitations of a (multicenter) retrospective analysis, these studies showed unanimously that surgical stage of disease at diagnosis and the amount of residual disease after initial surgery are significant prognostic factors. A randomised clinical trial is required to compare the different postoperative therapy modalities, but the scarcity of this tumour renders prospective trials almost impossibile.

In an early evaluation of 73 patients having FIGO stage I-IV primary Fallopian tube carcinoma, Klein and colleagues found an improvement in survival for postoperative radiation compared to chemotherapy in a non-randomised trial. However, almost all patients with advanced disease received chemotherapy [27, 30].

In conclusion, therapy usually follows the guidelines for epithelial ovarian cancer. Therefore radical tumour debulking with subsequent platinum-based chemotherapy remains the current therapy of choice for advanced Fallopian tube carcinoma [1].

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