PERGAMON

European Journal of Cancer 39 (2003) 78–85

European Journal of Cancer

www.ejconline.com

Phase II study of carboplatin in patients with advanced or recurrent endometrial carcinoma. A trial of the EORTC Gynaecological Cancer Group

F.H. van Wijk[a], C. Lhommé[b,*], G. Bolis[c], V. Scotto di Palumbo[d], S. Tumolo[e], M. Nooij[f], C.F. de Oliveira[g], J.B. Vermorken[h]

[a]*Medical Research Fellow, EORTC Data Center, Brussels, Belgium*
[b]*Department of Gynaecology, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif Cedex, France*
[c]*Department of Obstetrics and Gynaecology, Istituto L. Mangiagalli, Milan, Italy*
[d]*Department of Obstetrics and Gynaecology, Ospedale Generale Provinciale San Camillo de Lellis, Riete, Italy (formerly Ospedale Generale di Zona San Carlo di Nancy, Rome, Italy*
[e]*Department of Medical Oncology, Azienda Ospedaliera 'San Maria Degli Angeli', Pordenone, Italy (formerly: Centro di Riferimento Oncologico, Aviano, Italy*
[f]*Department of Medical Oncology, Leiden University Medical Centre, Leiden, The Netherlands*
[g]*Department of Gynaecology, Hospitais da Universidade de Coimbra, Coimbra, Portugal (formerly: Insituto Portugues de Oncologia Coimbra, Coimbra, Portugal*
[h]*Department of Oncology, University Hospital Antwerp, Edegem, Belgium (formerly: Free University, Amsterdam, The Netherlands)*

Received 11 July 2002; received in revised form 8 August 2002; accepted 12 September 2002

Abstract

The aim of this study was to investigate the efficacy and toxicity of carboplatin given as monotherapy in endometrial adenocarcinoma. Cisplatin is one of the most active drugs in gynaecological cancer types, but at the cost of an associated high toxicity. In this high-risk population of endometrial cancer patients, it is necessary to have chemotherapy regimens with a low toxicity. Patients eligible for this study were those with histologically-confirmed endometrial adenocarcinoma with evidence of recurrent and/or metastatic disease. Carboplatin was administered every 4 weeks as a first- (dose: 400 mg/m^2) or second- (dose: 300 mg/m^2) line chemotherapy. Of the 64 patients who entered the trial, 60 were eligible, 53 patients were evaluable for toxicity and 47 for efficacy. A total of 169 cycles of carboplatin was given with a median of 2 cycles per patient (range 1–11 cycles) to a median cumulative dose of 798 mg/m^2 (range 290–3879 mg/m^2). No grade 4 toxicity or toxic deaths occurred. White Blood Cell (WBC) toxicity grade 3 was noted five times, mainly in the radiotherapy pre-treated patients. Grade 3 non-haematological toxicity consisted mainly of nausea and vomiting (21%). There was a total of eight responses (3 Complete Responses (CR) and 5 Partial Responses (PR) with an overall response rate (ORR) of 13% (95% Confidence Interval (CI) 6–25). No responses occurred in patients treated with prior chemotherapy. In evaluable patients, the ORR in all patients ($n=47$) and in those receiving first-line chemotherapy ($n=33$) were, 17% (95% CI 8–31) and 24% (95% CI 11–42), respectively. After a median follow-up of 379 days, the median duration of response was 488 days (range 141–5303 days) with two very long responses in patients with a CR. Carboplatin has a low toxicity and is active in chemotherapy-naive advanced endometrial carcinoma patients. These results lead us to propose its use in association in first-line chemotherapy in recurrent or advanced endometrial carcinoma patients. The choice of the initial dose can be determined according to whether the patients have received prior radiotherapy treatment.

Keywords: Adenocarcinoma; Carboplatin; Chemotherapy; Clinical trial phase II; Endometrial carcinoma

* Corresponding author. Tel.: +33-142-114-377; fax: +33-142-115-214.
E-mail address: lhomme@igr.fr (C. Lhommé).

0959-8049/03/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0959-8049(02)00504-X

1. Introduction

Endometrial cancer is the most common genital tract malignancy in women. While most patients are cured with surgery and/or radiotherapy alone [1], systemic therapy (hormonal therapy or chemotherapy) is required in cases of initial advanced disease and at the time of relapse. At the time of this trial, prior phase II trials have identified in endometrial adenocarcinoma several chemotherapeutic single agents associated with demonstrable objective responses in at least 20% of patients, including cyclophosphamide, anthracyclines, 5-fluorouracil [2] and hexamethylmelamine [3].

Cisplatin is one of the most active drugs in other gynaecological cancer types [4,5] and so platinum-containing regimens have also been studied in endometrial cancer. With single agent cisplatin given as first-line chemotherapy, Tropé [6] and Deppe [7] both reported in 1980, and Seski [8] observed in 1982, 36, 31 and 42% response rates, respectively. Turbow [9] reported a 47% overall response rate to cisplatin, doxorubicin and cyclophosphamide (PAC) in 19 patients at the cost of moderate to severe toxicity. Tropé [10] observed a 60% response rate to cisplatin and doxorubicin in 19 patients and Bayer [11] achieved a 27% CR rate in 11 patients with the combination of cisplatin, cyclophosphamide and 5-fluorouracil.

In these studies, the median duration of response was short and most patients experienced moderate to severe toxicity. In this high risk population of patients, who are often old and in poor general condition, it is necessary to use chemotherapy regimens that have a low toxicity. Cisplatin and carboplatin have the same activity in ovarian carcinoma. Carboplatin is less nephrotoxic, less neurotoxic and induces less gastrointestinal toxicity allowing a better quality of life. Therefore, it was decided in 1985 to test the efficacy and toxicity of carboplatin in endometrial adenocarcinoma as first- or second-line chemotherapy treatment.

2. Patients and methods

2.1. Trial design

This protocol was designed to determine the objective response rate (ORR), time to response, duration of response and tolerance of carboplatin as monotherapy for endometrial cancer.

2.2. Eligibility

Patients eligible for this study were those with histologically-confirmed endometrial adenocarcinoma with evidence of recurrent and/or metastatic disease. Carboplatin was administered as a first- or second-line treatment after anthracycline-based chemotherapy. Patients had to have measurable lesions outside previously irradiated areas, age <75 years, life expectancy $>$ 2 months, World Health Organization (WHO) performance $\leqslant 2$, white blood cell count (WBC) $\geqslant 4.0\times10^9$/l, platelet count $\geqslant 120\times10^9$/l, blood urea $\leqslant 8.0$ mmol/l and/or serum creatinine $\leqslant 120$ μmol/l and/or creatinine clearance $\geqslant 60$ ml/min/1.73 m^2 and bilirubin $\leqslant 50$ μmol/l. All patients entering the study had to give their oral informed consent.

Excluded were those who had received prior radiotherapy, hormonal therapy or chemotherapy within 4 weeks, had a concomitant or prior second cancer (except basal cell carcinoma of the skin), brain involvement or leptomeningeal disease, poor medical risk due to non-malignant disease or uncontrolled infection, bone lesions or serous effusions as single tumour response parameters and expected difficulty with follow-up.

Investigations at baseline included a medical history and physical gynaecological examination, assessment of performance status, laboratory profile, urinalysis, electrocardiograph, measurement of indicator lesion(s), whether clinically or by X-ray, computed tomography (CT) scan, ultrasound, endoscopy or bone scan (if indicated).

2.3. Treatment and dose adjustments

Treatment consisted of a 30-min intravenous (i.v.) administration of carboplatin (Paraplatin®) every 4 weeks, 400 mg/m^2 for patients who had not received prior chemotherapy and 300 mg/m^2 for patients who had received prior chemotherapy. Ancillary treatment was given as medically indicated. Radiotherapy was allowed concomitantly for control of bone pain, provided that all evaluable lesions were not included in the irradiated field.

The dose schedule was modified as follows: drug administration was delayed, up to two weeks, if the WBC $<3.0\times10^9$/l or the platelet count $<120\times10^9$/l. If 6 weeks after the last dose of carboplatin, recovery had not occurred to this extent, dose adjustments were made. The dose was reduced to 75% if WBC was 2.0–3.0×10^9/l or platelet count was 100–120×10^9/l and to 50% if WBC was 1.5–1.9×10^9/l or platelet count was 75–99×10^9/l. Patients went off study if WBC was $<1.5\times10^9$/l or the platelet count was $<75\times10^9$/l. Dose adjustments were also made according to nadir values in the previous course as measured by weekly blood counts. Adjustments to 75% if WBC was $<1.5\times10^9$/l or platelet count was $<75\times10^9$/l and to 50% if WBC was $\leqslant 1.0\times10^9$/l or platelet count was $\leqslant 50\times10^9$/l. No dose-modifications were required for renal or gastrointestinal dysfunction. Treatment had to be continued in case of objective response or stable disease. Treatment had to be stopped on evidence of disease progression, unacceptable toxicity or patient refusal.

2.4. Response evaluation

The state of measurable disease was assessed before treatment and every two cycles. To be evaluable for response, patients should have had at least two cycles of chemotherapy and the second and following treatment cycles should not have been postponed for more than two weeks. Objective evidence of response was documented on the basis of measurement of clinical palpable lesions (to be confirmed by CT scan or ultrasound) or measurements of lesions detectable by X-rays, CT scan or ultrasound. Changes in liver function and carcinoembryonic antigen levels had to be confirmed by other examinations. A complete response (CR) was defined as a complete disappearance of all clinically detectable tumours together with a return of the relevant blood chemistries to normal values for at least 4 weeks. A partial response (PR) consisted of a 50% or more decrease in total tumour size of the measured lesions, being confirmed by a further observation no less than four weeks later, without any new lesions. Bone lesions should partially decrease in size or recalcification of lytic lesions should occur for at least 4 weeks. No change (NC) was defined as a change of less than 50% reduction or less than 25% increase in the size of one or more measurable lesions after at least eight weeks from start of therapy. Progression of disease (PD) represented an increase greater than 25% in the size of one or more measurable lesions or the appearance of new lesions. Early progressive disease was defined as progression that occurred after one cycle of carboplatin. Early tumour death was defined as death occurring during the first 8 weeks due to tumour progression and early toxic death was defined as death occurring in the first 8 weeks due to toxicity. The duration of response and stable disease dated from commencement of treatment until documentation of progression. The duration of CR dated from the moment complete remission was first recorded until documentation of progression. Survival and time to progression will be dated from the commencement of treatment.

2.5. Toxicity evaluation

Haematological and non-haematological toxicity due to the carboplatin regimen were evaluated and documented using WHO criteria. Patients were evaluable for toxicity if they had received at least one cycle of carboplatin.

2.6. Statistical consideration

Gehan's sequential two step statistical test was used to define the number of patients required to detect activity of the treatment. The lowest limit of therapeutic activity considered to be of interest is a response rate of 20%. Patients who had received previous chemotherapy or radiotherapy and those who had not were registered and evaluated in two separate groups. The Kaplan-Meier method was used to analyse the median follow-up time, time to progression (TTP) and the overall survival (OS).

3. Results

3.1. Patient characteristics

Between October 1985 and August 1988, 64 patients with histologically-confirmed endometrial adenocarcinoma and evidence of advanced or recurrent disease were entered into this trial. Four patients were found to be ineligible, two patients because of the presence of all of their lesions a previously irradiated area, one because they had received cancer treatment within four weeks prior to registration and one because of an absence of measurable lesions. In the 60 eligible patients, seven patients were not evaluable for all of the analyses, two because of inadequate dosage and five for inadequate follow-up. Seven additional patients were not evaluable for efficacy, due to protocol violations (6 patients), incomplete data (2 patients) and/or intercurrent disease (1 patient). One of these patients was evaluable for response, but not for the duration of response. Therefore, 53 patients in total were evaluable for toxicity and 47 for efficacy.

Characteristics of all eligible patients are shown in Table 1. Mean age of the eligible patients was 70 years (range 52–84 years). Treatment received prior to carboplatin administration included surgery for 53 patients, radiotherapy for 38 patients, hormonal therapy for 15 patients, of which two patients had a response, and anthracycline-based chemotherapy for 17 patients, of which one was in adjuvant setting. Of the other 16 patients, 4 patients received monotherapy (mitoxantrone) and 12 polychemotherapy (mainly cyclophosphamide, doxorubicin, cisplatin (CAP) protocol, 9 patients), 7 patients experienced a response, of which 5 were treated with the CAP protocol.

3.2. Extent of exposure

A total of 169 cycles of carboplatin was given to the 53 evaluable patients, with a median of 2 cycles per patient (range 1–11 cycles) to a median cumulative dose of 798 mg/m^2 (range 290–3879 mg/m^2). The median number of cycles was also 2 in both groups, with a maximum of 11 cycles for the non-chemotherapy pre-treated patients ($n=38$) and 6 for patients pre-treated with chemotherapy ($n=15$). The median total dose administered was 789 mg/m^2 in the non-chemotherapy pre-treated and 588 mg/m^2 in the chemotherapy pre-treated patients. The treatment was delayed in 16

Table 1
Pre-treatment characteristics of the eligible patients

	N
Number	60
Median age in years (range)	70 (52–84)
Performance status	
WHO 0	23
WHO 1	18
WHO 2	17
Unknown	2
FIGO classification	
I	29
II	7
III	11
IV	11
Unknown	2
Extent of disease at registration	
Primary tumour	4
Loco-regional recurrent	9
Metastatic disease	26
Primary not excised and metastatic	3
Loco-regional recurrent and metastatic	16
Unknown	2
Prior treatment	
Surgery	53
Radiotherapy	38
Chemotherapy	17
Hormonal therapy	15

WHO, World Health Organization; FIGO, International Federation of Gynecology and Obstetrics.

patients (30%), mainly in the non-chemotherapy pre-treated patients (88%). Twelve patients (23%) required at least one dose reduction. The median relative dose intensity was 90% (range 43–104%) in the non-chemotherapy pre-treated patients and 100% (range 73–102%) in the chemotherapy pre-treated group.

3.3. Toxicity

The haematological toxicity was acceptable, as presented in Table 2. The median WBC count nadir for all cycles was 3.4×10^9/l (range 1.2–12.1×10^9/l), and the median platelet count nadir was 120×10^9/l (range 26–413×10^9/l). WBC toxicity grade 3 was noted only five times during the first two courses and mainly in the radiotherapy pre-treated patients (80%). Antibiotics were administered once during the last cycle to 3 radiotherapy pre-treated patients (5%).

Table 2
Haematological toxicity grades 3 and 4

Number of patients[a]		WBC[b]		PLT[c]	
		Grade 3	Grade 4	Grade 3	Grade 4
Total		5	0	6	0
Prior treatment					
Prior radiotherapy	No	1		3	
	Yes	4		3	
Prior chemotherapy	No	4		3	
	Yes	1		3	

[a] 53 Patients evaluable for toxicity.
[b] White blood cells.
[c] Platelets.

Grade 3 thrombocytopenia was observed 11 times in 6 patients, often in the radiotherapy pre-treated or chemotherapy pre-treated patients, but more frequent in the first group. A blood transfusion was required for 9 patients, during more than one cycle for 3 patients. 5 out of the 9 patients (56%) were pre-treated with radiotherapy, and 2 (22%) were pre-treated with chemotherapy. For most of the patients, the first transfusion was administered during the first cycle (67%).

Non-haematological toxicity among all of the patients evaluable is presented in Table 3. In 1 patient (2%), aged 74 years, a grade 3 consciousness toxicity was reported during the treatment and neuroleptics were used. The only other grade 3 non-haematological toxicity consisted of nausea and vomiting (21%), mainly in the non-chemotherapy pre-treated patients (24 vs. 13%). Anti-emetic therapy was used in 34 patients (64%). Diarrhoea grades 1 and 2 occurred in 11 patients (seven with prior radiotherapy), 1 patient with diarrhoea before carboplatin. Two grade 1 or one grade 2 peripheral neuropathies were reported (all in patients without prior cisplatin chemotherapy). No renal, grade 4 haematological or non-haematological toxicities or toxic deaths occurred.

3.4. Response

All 60 eligible patients were analysed for response (Table 4). Eight patients achieved an objective response to therapy, with three of these achieving a CR. Thus,

Table 3
Non-haematological toxicity during treatment[a]

Toxic effect	WHO grading		
	1	2	3
Nausea/vomiting			
Consciousness	1	0	1
Diarrhoea	10	1	0
Alopecia[b]	3	1	0
Peripheral neuropathy	2	1	0
Drug fever	2	0	0
Pulmonary	1	0	0
Drug fever	2	0	0
Cutaneous	1	0	0
Local	1	0	0
Oral	1	0	0
Allergy	1	0	0
Other	3	2	0

[a] 53 Evaluable patients.
[b] 3 Patients suffered from alopecia due to prior chemotherapy.

Table 4
Response rate (intent-to-treat basis) (60 eligible patients)

WHO[a] response	Total ($N=60$)[b]		Chemotherapy pre-treated ($N=17$)		Radiotherapy pre-treated ($N=38$)		Hormonotherapy pre-treated ($N=15$)	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)
CR[c]	3	(5)	0	(0)	0	(0)	0	(0)
PR[d]	5	(8)	0	(0)	1	(3)	1	(7)
SD[e]	7	(12)	3	(18)	7	(18)	4	(27)
PD[f] and early PD	28	(47)	10	(59)	20	(53)	5	(33)
Early death (malignant disease)	2	(3)	1	(6)	1	(3)	1	(7)
Early death (other causes)	1	(2)	0	(0)	1	(3)	0	(0)
Not assessable	14	(23)	3	(18)	8	(21)	4	(27)
Overall response rate (%)								
Eligible patients ($n=60$)						13 (95% CI[g] 6–25)		
Patients assessable for response ($n=47$)						17 (95% CI 8–31)		
Non chemotherapy pre-treated patients assessable for response ($n=33$)						24 (95% CI 11–42)		

[a] World Health Organization.
[b] Pre-treatment unknown in two patients and hormonal therapy unknown in three patients.
[c] Complete response.
[d] Partial response.
[e] Stable disease.
[f] Progressive disease.
[g] 95% Confidence interval.

there was a 13% ORR (95% Confidence Interval (CI) 6–25). Among the 17 patients pre-treated with chemotherapy, there were no objective responses. One PR was observed in the radiotherapy pre-treated (no prior hormonal therapy) patients and one PR in the hormonaltherapy pre-treated patients (no prior radiotherapy). Thus, patients in the no prior chemotherapy group ($n=41$) responded significantly better than those with prior chemotherapy ($P=0.05$), like those with no prior radiotherapy ($P=0.002$). Response analysis showed an ORR of 17% (95% CI 8–31) in the evaluable patients ($n=47$) and of 24% (95% CI 11–42) in the evaluable chemotherapy-naive patients ($n=33$). The maximum time to response was 296 days, with a median of 66 days. The median duration of follow-up was 379 days. Median TTP was 84 days (95% CI 58–171) and median duration of responses 488 days (range 141–5303 days). Duration of the three complete responses was 77, 4347, and 5007 days. Median OS of all patients was 261 days (95% CI 151–440) and 1013 days for responders. Two patients with CR were still alive without evidence of disease 11+ and 14+ years, respectively, after the start of carboplatin treatment. Both patients did not receive prior radiotherapy, chemotherapy or hormonal therapy and the tumour sites were the regional and metastatic nodes for the first patient and the primary tumour for the second.

Table 5
Single agent carboplatin in endometrial carcinoma

Reference	*N*[a]	Prior treatment (%)[b]			Starting dose in mg/m^2 (if RT pre-treated)	CR (*n*)	PR (*n*)	ORR[g] (%)
		RT[c]	CT[d]	HT[e]				
Burke	33 (27)	67	0	21	360 (270)	3	6	33
Long	26 (25)	80	0	76	400 (300)	0	7	28
Green	32 (23)	78	0	43	400 (400)	2	5	30
Present study	64 (47)	66	30	23	400 (400)[f]	3	5	17[h]

[a] Number of patients entered (number of evaluable patients).
[b] % of evaluable patients (for Burke % of entered patients).
[c] Radiotherapy.
[d] Chemotherapy.
[e] Hormonal therapy.
[f] 300 if pre-treated with chemotherapy.
[g] Overall response rate of the evaluable patients.
[h] 24% In the 33 evaluable chemotherapy-naive patients.

Table 6
Platinum and paclitaxel in endometrial carcinoma

Reference	Drug combination (dose in mg/m^2)	N[a]	Toxicity	Grading[b] (% patients[c])			CR (n)	PR (n)	RR[c] (%)
				2	3	4			
Dimopoulos	Cisplatin (75)[d] Paclitaxel (175/3h)	24					7	9	67
			Granulocytopenia	13	13	9			
			Alopecia	9	91	0			
			Nausea/emesis	48	9	0			
			Neurotoxicity	13	9	0			
Price	Carboplatin (AUC 5) Paclitaxel (135–175/3h)	20					0	5	63
			Leukcopenia	11	32	47			
			Thrombocytopenia	0	0	5			
			Alopecia	100	0	0			
			Nausea	0	0	0			
			Numbness/tingling	5	5	0			
Hoskins[e]	Carboplatin (AUC 5–7) Paclitaxel (175/3h)	22							55
			Neutrophil nadir	0.9×10^9/l					
			Platelet nadir	143×10^9/l					
			Febrile neutropenia	3%					
Scudder	Carboplatin (AUC 5) Paclitaxel (175/3h) Amifostine (740)	57					6 months PFS 78% 6 months OS 86% (estimated)		
			Neutropenia, Lymphopenia, Pain, Anaemia		41	33			

OS, overall survival; NCI, National Cancer Institute; PFS, progression-free survival; G-CSF, granulocyte-colony stimulating factor; AUC, Area Under the Curve.

[a] Number of patients entered.

[b] WHO criteria used by Dimopoulos, and NCI criteria used by Price.

[c] % of the evaluable patients.

[d] Together with G-CSF support.

4. Discussion

Our study indicates that carboplatin is safe and active in advanced endometrial cancer. Nevertheless, as shown in Table 5, our ORR of 17% in evaluable patients is lower compared with ORRs reported by Long [12], Green [13] and Burke [14] (28, 30 and 33%, respectively). The main difference in the patient populations is the difference in prior treatments. No patients received prior chemotherapy in the other studies. In this study, 41 patients received carboplatin as first-line chemotherapy and four patients had received mitoxantrone only, which is now known to be inefficient in endometrial cancer (one PR in 51 evaluable patients included in three studies [15–17]). So, 12 patients (20%) had received carboplatin in second-line after anthracycline and mainly cisplatin-based polychemotherapy (9 patients), including four patients after failure on cisplatin. As none of our chemotherapy pre-treated patients showed any response, the administration of carboplatin in second-line treatment, even after failure on cisplatin, might be a reliable explanation for the difference in the ORRs. Prior radiotherapy in our evaluable population (66%) is comparable to the three published studies (Table 5). Prior hormonal therapy percentages are comparable, except for a higher percentage treated in the Long study. Thus, in our study 21 patients (35%) were treated after first-line chemotherapy and/or hormonal therapy. Horton [18,19] demonstrated that responding or failing to prior progestagen therapy had a significant influence on the outcome of subsequent chemotherapy trials, the results being worse in patients who failed to respond to progestagen. He showed that this proved to be true for both trials with single agent chemotherapy and combination chemotherapy. This appeared to be true in our population also, where no response to carboplatin was observed among the 11 patients who did not respond to prior hormonal therapy. The second main difference with the other studies is the adjustment of the initial dosage of carboplatin according to prior treatment, none in one study [13] or a decrease of 25% in case of prior radiotherapy in the two others

[12,14]. In our study, we chose to decrease the initial dose only in cases of prior chemotherapy. It is not possible to assess the impact on the efficacy of taking the initial dose into account: in the three prior studies (similar percentages of patients with prior radiotherapy), ORRs are similar with or without dose adjustments and dose effect relationships for platinum have never been demonstrated in endometrial cancer. Only Long reported ORRs according to prior radiotherapy. The ORR is lower in patients pre-treated with radiotherapy (20 vs. 60%), but this lower response rate is possibly due to tumoral biological resistance in the irradiated area.

As expected, toxicity was acceptable for patients treated with carboplatin. It consisted mainly of grade 3 haematological toxicity among the radiotherapy pre-treated patients. In this group of patients, more blood transfusions were required. The toxicity level was not higher among the chemotherapy pre-treated patients. It is not possible to assess whether this was due to an absence of impact of the dose or due to the initial dose reduction. In recent studies, doses of carboplatin were determined according to Area Under the Curve (AUC). This seems a better mehtod of dose determination than according to Body Surface Area, as was used in older studies, because this older population of patients often have renal insufficiency and increased haematological toxicity.

In endometrial cancer, the response rate seems to be increased with the use of cisplatin [6–8] compared with carboplatin, but at the cost of considerable toxicity resulting in a poorer quality of life. Green [13] showed a long duration of response to carboplatin up to 814+ days, we also observed this, a maximum duration of 5303 days was obtained in our trial. Pending the demonstration of agents capable of inducing more prolonged responses, the simplicity of outpatient treatment and limited toxicity make carboplatin a good current choice for frontline therapy [14].

Paclitaxel seems to be a good candidate for endometrial cancer treatment (ORRs of 36 and 37% have been reported) [20,21]. Data concerning its association with cisplatin and carboplatin are shown in Table 6. Combination with cisplatin appears active, but caused an unacceptable incidence of neurotoxicity [22]. Main toxicity observed with the combination of carboplatin and paclitaxel was grade 3 or 4 haematological toxicity, which did not require hospitalisation [23,24]. In combination with carboplatin and amifostine, six-month PFS and OS compared very favourably with the historical benchmark of cisplatin and doxorubicin chemotherapy, with favourable toxicity profile [25]. According to all of these data, it now needs to be demonstrated that this combination has an advantage for the patient, concerning not only the response rate, but also an improvement of survival and quality of life. One ongoing French randomised phase II study is comparing carboplatin plus paclitaxel with cisplatin plus doxorubicin.

Our publication shows the results of an old phase II trial with carboplatin in endometrial cancer. The number of included and evaluable patients is higher than any of the previously published studies. Moreover, its importance is still high because only a few phase II trials with a low number of patients in each have been carried out. This is the only study including patients receiving carboplatin in the second-line. Responses were observed in chemotherapy-naive patients and this leads us to propose it as a first-line treatment. Toxicity was mild, but more transfusions were required after radiotherapy. The choice of the initial dose can be determined according to whether the patient has received prior radiotherapy treatment.

So, carboplatin is a good candidate in polychemotherapy in first-line and/or in front-line therapy for endometrial cancer.

Acknowledgements

This study was supported by the Pharmaceutical Research and Development Division of the Bristol Myers Company, Brussels, Belgium. We thank the following physicians from the following Institutes who treated the patients in the present cohort: M.S. Aapro, Hopital Cantonal Universitaire de Geneve, Geneve, Switzerland (current hospital: Clinique de Genolier, Centre Anticancéreux, Genolier, Switzerland); L.V.A. Beex, St Radboud University Hospital, Nijmegen, The Netherlands; J.P. Guastalla, Centre Leon Berard, Lyon, France; A. Herruzo, Hospital Virgen de las Nievas Granada, Spain; P. Kerbrat, Centre Eugene Marquis, Rennes, France; A.J. Lacave, Hospital General de Asturias, Oviedo, Spain; C. Mangioni, Ospedale San Gerardo, Monza, Italy; J.P. Neijt, University Medical Centre Utrecht, The Netherlands; T. Osario, Insituto Portugues de Oncologia do Porto, Portugal; S. Pecorelli, Universita di Brescia, Italy; M. Piccart, Institut Jules Bordet, Brussels, Belgium; W. ten Bokkel Huinink, Antoni van Leeuwenhoekhuis, Amsterdam, The Netherlands; M.E.L. van der Burg, Dijkzigt Hospital, Rotterdam, The Netherlands; P.H.B. Willemse, Academic Hospital Groningen, The Netherlands; J. Wils, St. Laurentius Hospital, Roermond, The Netherlands; P. Zola, Clinica Universita Torino, Italy (current hospital: Ospedale Mauriziano Umberto I, Torino, Italy).

References

1. Glassburn JR. Carcinoma of the endometrium. *Cancer* 1981, **48**(Suppl. 2), 575–581.
2. Deppe G. Chemotherapeutic treatment of endometrial carcinoma. *Clin Obstet Gynecol* 1982, **25**, 93–99.
3. Seski JC, Edwards CL, Copeland LJ, Gershenson DM. Hexam-

ethylmelamine chemotherapy for disseminated endometrial cancer. *Obstet Gynecol* 1981, **58**, 361–363.
4. Thigpen T, Shingleton H, Homesley H, *et al*. Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. *Cancer* 1981, **48**, 899–903.
5. Thigpen T, Blessing JA. Current therapy of ovarian carcinoma: an overview. *Semin Oncol* 1985, **12**(3 Suppl 4), 47–52.
6. Tropé C, Grundsell H, Johnson JE, Cavallin-Stähl E. A phase II study of cisplatin for recurrent corpus cancer. *Eur J Cancer* 1980, **16**, 1025–1026.
7. Deppe G, Cohen CJ, Bruckner HW. Treatment of advanced endometrial adenocarcinoma with *cis*-dichlorodiammine platinum (II) after intensive prior therapy. *Gynecol Oncol* 1980, **10**, 51–54.
8. Seski JC, Edwards CL, Herson J, Rutledge FN. Cisplatin chemotherapy for disseminated endometrial cancer. *Obstet Gynecol* 1982, **59**, 225–228.
9. Turbow MM, Ballon SC, Sikic BI, Koretz MM. Cisplatin, doxorubicin and cyclophosphamide chemotherapy for advanced endometrial carcinoma. *Cancer Treat Rep* 1985, **69**, 465–467.
10. Tropé C, Johnsson JE, Simonsen E, *et al*. Treatment of recurrent endometrial adenocarcinoma with a combination of doxorubicin and cisplatin. *Am J Obstet Gynecol* 1984, **149**, 379–381.
11. Bayer GK, Koch PD. High response rate with combination chemotherapy for advanced endometrial cancer. *Proc Am Ass Cancer Research* 1982, **1**, 121.
12. Long HJ, Pfeifle DM, Wieand HS, *et al*. Phase II evaluation of carboplatin in advanced endometrial carcinoma. *J Natl Cancer Inst* 1988, **80**, 276–278.
13. Green JB, Green S, Alberts DS, *et al*. Carboplatin therapy in advanced endometrial cancer. *Obstet Gynecol* 1990, **75**, 696–700.
14. Burke TW, Munkarah A, Kavanagh JJ, *et al*. Treatment of advanced or recurrent endometrial carcinoma with single-agent carboplatin. *Gynecol Oncol* 1993, **51**, 397–400.
15. Hilgers RD, Von Hoff DD, Stephens RL, *et al*. Mitoxantrone in adenocarcinoma of the endometrium: a Southwest Oncology Group study. *Cancer Treat Rep* 1985, **69**, 1329–1330.
16. Muss HB, Bundy BN, DiSaia PJ, Ehrlich CE. Mitoxantrone for carcinoma of the endometrium: a phase II trial of the Gynecologic Oncology Group. *Cancer Treat Rep* 1987, **71**, 217–218.
17. Veenhof KHN, George M, Forni M, *et al*. Mitoxantrone in advanced and/or recurrent endometrial carcinoma. *Eur J Cancer* 1990, **26**, 650.
18. Horton J, Begg CB, Arsenault X, *et al*. Comparison of adriamycin with cyclophosphamide in patients with advanced endometrial cancer. *Cancer Treat Rep* 1978, **62**, 159–161.
19. Horton J, Elson P, Gordon P, *et al*. Combination chemotherapy for advanced endometrial cancer. An evaluation of three regimens. *Cancer* 1982, **49**, 2441–2445.
20. Ball HG, Blessing J, Lentz S, Mutsch DC. A phase II trial of paclitaxel in advanced and recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol* 1996, **62**, 278–281.
21. Lissoni A, Zanetta G, Losa G, *et al*. Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. *Ann Oncol* 1996, **7**, 861–863.
22. Dimopoulos MA, Papadimitriou CA, Georgoulias V, *et al*. Paclitaxel and cisplatin in advanced or recurrent carcinoma of the endometrium: long-term results of a phase II multicenter study. *Gynecol Oncol* 2000, **78**, 52–57.
23. Price FV, Edwards RP, Kelley JL, *et al*. A trial of outpatient paclitaxel and carboplatin for advanced, recurrent, and histologic high-risk endometrial carcinoma: preliminary report. *Semin Oncol* 1997, **24**(Suppl. 15), 78–82.
24. Hoskins P, Swenerton K, Pike J, *et al*. Carboplatin/paclitaxel ±irradiation for advanced or recurrent endometrial cancer. *Proc Am Soc Clin Oncol* 2001, **20**, 206a.
25. Scudder SA, Liu PY, Smith HO, *et al*. Paclitaxel (PCT) and carboplatin (C) with amifostine (A) in advanced or recurrent endometrial cancer: a Southwest Oncology Group Trial (9720). *Proc Am Soc Clin Oncol* 2001, **20**, 205a.