Original article

Annals of Oncology 14: 441–448, 2003
DOI: 10.1093/annonc/mdg112

Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group

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Received 5 August 2002; accepted 11 October 2002

Background: Combination chemotherapy yields better response rates which do not always lead to a survival advantage. The aim of this study was to investigate whether the reported differences in the efficacy and toxicity of monotherapy with doxorubicin (DOX) versus combination therapy with cisplatin (CDDP) in endometrial adenocarcinoma lead to significant advantage in favour of the combination.

Patients and methods: Eligible patients had histologically-proven advanced and/or recurrent endometrial adenocarcinoma and were chemo-naïve. Treatment consisted of either DOX 60 mg/m^2 alone or CDDP 50 mg/m^2 added to DOX 60 mg/m^2, every 4 weeks.

Results: A total of 177 patients were entered and median follow-up is 7.1 years. The combination DOX–CDDP was more toxic than DOX alone. Haematological toxicity consisted mainly of white blood cell toxicity grade 3 and 4 (55% versus 30%). Non-haematological toxicity consisted mainly of grade 3 and 4 alopecia (72% versus 65%) and nausea/vomiting (36 % versus 12%). The combination DOX–CDDP provided a significantly higher response rate than single agent DOX (P <0.001). Thirty-nine patients (43%) responded on DOX–CDDP [13 complete responses (CRs) and 26 partial responses (PRs)], versus 15 patients (17%) on DOX alone (8 CR and 7 PR). The median overall survival (OS) was 9 months in the DOX–CDDP arm versus 7 months in the DOX alone arm (Wilcoxon P = 0.0654). Regression analysis showed that WHO performance status was statistically significant as a prognostic factor for survival, and stratifying for this factor, treatment effect reaches significance (hazard ratio = 1.46, 95% confidence interval 1.05–2.03, P = 0.024).

Conclusions: In comparison to single agent DOX, the combination of DOX–CDDP results in higher but acceptable toxicity. The response rate produced is significantly higher, and a modest survival benefit is achieved with this combination regimen, especially in patients with a good performance status.

Key words: chemotherapy, cisplatin, doxorubicin, endometrial carcinoma, randomised clinical trial, phase III

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Introduction

Endometrial cancer remains one of the commonest gynaecological malignancies. Whilst many patients with early stage disease are cured by either surgery or radiotherapy, or a combination of the two [1], 40% of patients are either not amenable to such treatment due to metastatic disease, or subsequently relapse following primary treatment. Such patients require systemic therapy in the form of either hormonal or cytotoxic therapy [2–6]. Although the latter has been less extensively studied in endometrial cancer, it is has been shown that response rates with single-agent chemotherapy are comparable with those observed following hormonal treatment, and response duration is generally longer. Thus there is a need to define the optimal chemotherapy regime. Whilst several phase II trials have identified chemotherapeutic single agents with demonstrable objective response in endometrial adenocarcinoma, of which doxorubicin (DOX) and cisplatin (CDDP) seem to be the most active single agents [2–6], the reported series are small and include patients with widely-varying pre-treatment conditions, together with variable response criteria.

As the combination of doxorubicin and cisplatin (DOX–CDDP) has been shown to be of benefit in treating other gynaecological malignancies [7], the current study, a multi-centre prospective randomised trial, was designed to compare combination therapy with DOX–CDDP versus DOX alone in endometrial carcinoma.

Patients and methods

Trial design

This protocol was designed as a randomised phase II/III study to determine the antitumour activity of combination DOX–CDDP, versus single-agent DOX, in patients with advanced primary endometrial cancer (i.e. beyond the stage of local treatment), and in those with recurrent disease. The second objective was to determine the toxicity of both treatment arms in comparable patients.

Eligibility

Patients eligible for this study were those with histologically-proven advanced and/or recurrent adenocarcinoma of the corpus uteri, all of whom were first considered for radiotherapy and all of those with well differentiated tumours for hormone therapy. Eligibility criteria were as follows: measurable or evaluable lesions outside previously irradiated areas, with documented progression; age ≤75 years; life expectancy ≥3 months; World Health Organization (WHO) performance status ≤2; and adequate bone marrow, renal and liver function. All patients gave informed consent.

Excluded patients were those with the following: prior chemotherapy, radiotherapy or hormone therapy within 4 weeks of trial entry; unresolved toxic manifestations of their prior treatment; a concomitant or prior second cancer, other than adequately-treated basal or squamous cell carcinoma of the skin; brain or leptomeningeal involvement; pleural effusion, ascites, bone lesions detectable only by bone scan or sclerotic bone metastases as the single tumour response parameter; poor medical risk due to non-malignant disease, such as active bacterial or other infection, heart failure or uncontrolled hypertension; and expected difficulty with follow-up.

Baseline investigations included a medical history and physical gynaecological examination, assessment of performance status, laboratory profile, urinalysis, electrocardiogram, clinical and/or radiological measurement of indicator lesion(s), computed tomography (CT) scan or ultrasound.

Treatment and dose adjustments

Treatment consisted of DOX 60 mg/m^2 and CDDP 50 mg/m^2 or DOX 60 mg/m^2 every 4 weeks. Cisplatin was only given after adequate diuresis had been obtained with prehydration. Ancillary treatment was given as medically indicated. Radiotherapy was allowed concomitantly for control of bone pain or other reasons, provided that all evaluable lesions were not included in the irradiated field.

The drug cycle was delayed by 1 week if toxicity persisted at the day of the next cycle. If the treatment had to be delayed for two consecutive weeks, the following dose adjustments were made: if the white blood cell (WBC) count was 2.0–2.9 $\times$ 10^9/l or the platelet count 50–99 $\times$ 10^9/l, the DOX dose was reduced to 50% and the CDDP dose remained at 100%; patients went off study if the WBC was <2.0 $\times$ 10^9/l and/or the platelet count was <50 $\times$ 10^9/l after 2 weeks delay. Doxorubicin dose adjustments according to haematological and hepatic toxicity were made as follows: according to nadir values on day 15, adjustment to 50% was made if WBC was 1.0–1.9 $\times$ 10^9/l and/or the platelet count was 50–74 $\times$ 10^9/l; to 25% if WBC was <1.0 $\times$ 10^9/l and/or the platelet count was <50 $\times$ 10^9/l; to 50% if bilirubin was >25 µmol/l; and to 25% if bilirubin was >50 µmol/l. In cases of mucositis, the DOX dosage was reduced to 50%. Dose adjustments of CDDP were made according to renal and neurological toxicity: if the creatinine value rose above 125% of baseline values, or the creatinine clearance decreased similarly, half the dose was administered. Cisplatin was discontinued completely in patients developing WHO grade II paresthesia and/or muscle weakness. Clinical evidence of hearing loss was also a reason to discard CDDP. Antiemetics were used according to local treatment protocol if gastrointestinal toxicity developed.

A total of at least two courses were given, unless this was not in the best interest of the patient. The combination treatment was stopped on evidence of disease progression after two courses, or of rapid progression (>50% increase in volume or new lesions). If remission of the disease was achieved, treatment was continued until either severe disease progression or severe toxicity developed. DOX was discontinued after seven courses (cumulative dose of 420 mg/m^2) regardless of the response. Complete responders in the combination arm then continued the treatment with CDDP alone for up to 4 months from the moment of complete response. Treatment at disease progression was not defined per protocol.

Toxicity and response evaluation

The overall assessment of response involved all parameters including unidimensional (evaluable) and bidimensional measurable lesions, and non-measurable manifestations. Lesions that could be measured by CT scan or ultrasound were considered suitable for assessment of response provided that they were measurable with one or two diameters, had a minimal diameter of 5 cm and were proven to be malignant disease. Evaluation was performed after 8 weeks of treatment, or after at least two courses of treatment. Toxicity was assessed according to WHO criteria. Patients were evaluable for toxicity if they had received at least one cycle of treatment, and evaluable for overall response after they had received at least two cycles of chemotherapy, with the second and following treatment cycles not having been postponed for more than 2 weeks. The duration of overall response was dated from commencement of treatment until documentation of progression, and the duration of complete response (CR) from the moment complete remission was first recorded until documentation of progression. Survival will be dated from commencement of treatment.

A CR was defined as disappearance of all known disease, determined by two observations not less than 4 weeks apart. A partial response (PR) was defined as a decrease of at least 50% in the sum of the product of the largest perpendicular diameters of all measurable lesions, plus the sum of the

diameter of all evaluable lesions, as determined by two observations not less than 4 weeks apart, without progression or new lesions. There also had to be an objective improvement in non-evaluable but clinically evident malignant disease, and no increase of any manifestations of malignant disease. No change was defined as a reduction of less than 50%, or an increase of less than 25%, in the size of one or more measurable lesions, without evidence of either new lesions or an increase in any manifestation of malignant disease, until the first evaluation date. Progression of disease was defined as an increase of greater than 25% in the size of one or more measurable lesions, or the appearance of a new lesion, and also by the occurrence of positive cytology of pleural effusion or ascitic fluid. Early progressive disease was defined as progression that occurred after one cycle. Early tumour death was defined as death occurring during the first 8 weeks due to tumour progression, whilst toxic death was defined as death to which drug toxicity was thought to have made a major contribution.

Statistical considerations

The trial was designed as a randomised phase II trial to be extended into a comparative phase III trial in the case of sufficient responses. The phase II part of the trial required a minimum of 20 patients in each arm, with five patients to be added per each response observed during the first step. With respect to the comparative phase III part of the trial, it was assumed that the median duration of survival in the control (DOX) arm would be 8 months, and the addition of CDDP would be justified if it could increase the median duration of survival to 1 year. A total of 192 deaths were required to detect such a difference, with a two-sided type I error of 0.05 and a power of 80% [8]. During randomisation, patients were stratified according to institution, degree of differentiation (well versus moderate/poor), type of disease (locally advanced versus recurrent) and performance status, using the minimisation technique [9]. Survival curves were estimated using the Kaplan–Meier technique [10]. Duration of survival, time to progression (TTP) and progression-free survival (PFS) were compared between both treatment arms using a two-sided log-rank test [11]. Cox's proportional hazards model was used, retrospectively stratified for differentiation, type of disease and performance status [12]. Response rates were compared using chi-square tests; the percentages in the tables are exact, whilst those in the text are rounded for clarity.

Results

Patient characteristics

From September 1988 to June 1994, 177 patients with advanced inoperable or recurrent endometrial cancer were randomised by 35 institutions, with 90 patients in the DOX–CDDP combination arm and 87 in the single-agent DOX arm. The study was stopped early as recruitment decreased dramatically after the publication of the Gynecologic Oncology Group results in 1993. Five patients had no follow-up data (three, DOX–CDDP; two, DOX). Twelve patients were found to be ineligible either due to inadequate disease stage (two, DOX–CDDP; two, DOX), absence of measurable lesions (one, DOX–CDDP; three, DOX), the lesions all being in a prior irradiated area (one, DOX–CDDP; one, DOX), bad physical condition (one, DOX–CDDP) or prior treatment (one, DOX).

Baseline characteristics of all patients are shown in Table 1; these were similar in both treatment arms. Median age was 63 years (range 40–76) and 79% of all patients had a WHO performance status of 0 or 1. International Federation of Gynecology and Obstetrics (FIGO) stage at initial diagnosis was stage IV in 25% of patients. The tumour was well differentiated in 19% of patients, and 59% had recurrent disease. Treatment received prior to this protocol included surgery in 85% of patients, radiotherapy in 50% (23% of patients had had a response), hormone therapy in 23% and chemotherapy in 1%.

Extent of exposure

A total of 790 cycles were given to all patients, with 480 to patients in the DOX–CDDP arm, with a median of six cycles (range 0–15), and 310 to patients in the DOX arm, with a median of three cycles (range 0–7). DOX was given in 740 cycles: 430 in the combination arm and 310 in the single-agent arm. DOX was delayed in 25 cycles (6%) in the combination arm, and in 13 cycles (4%) in the single-agent arm. DOX reductions were mainly made in the combination arm (13% versus 5%). CDDP was given in 480 cycles, with a delay reported in 33 cycles (7%) and a dose reduction in 12 cycles (3%). In a single instance, the DOX and CDDP doses were both escalated in the combination arm, with no escalation reported in the single-agent DOX arm.

Toxicity

Toxicity evaluation was based on the 165 patients (83 DOX–CDDP and 82 DOX) who received at least one cycle. The combination DOX–CDDP was more toxic than DOX alone. Haematological toxicities are presented in Table 2. The median WBC nadir was $1.9 \times 10^3/mm^3$ (range 0.2–17.7) in the DOX–CDDP arm, and $2.6 \times 10^3/mm^3$ (range 0.1–10.2) in the DOX arm. The median platelet count nadir was $147 \times 10^3/mm^3$ (range 11–720) in the DOX–CDDP arm, and $232 \times 10^3/mm^3$ (range 26–538) in the DOX arm. WBC toxicity grade 3 and 4 was noted in 55% of DOX–CDDP patients and in 30% of DOX patients. Antibiotics were administered to nine patients: five in the combination arm and four in the single-agent DOX arm. In 13% of DOX–CDDP patients, thrombocytopenia grade 3 and 4 was reported. Grade 3 thrombocytopenia was reported in 5% of DOX patients; no grade 4 thrombocytopenia occurred in this arm. Six patients required a blood transfusion, five of whom had received the combination treatment. Haematological toxicity occurred mainly among the radiotherapy pre-treated patients, being WBC grade 3 and 4 in 50%, versus 32%, and thrombocytopenia grade 3 and 4 in 11%, versus 6%. This toxicity was not found to be cumulative by increasing the number of cycles.

Analysis of the non-haematological toxicity is presented in Table 3. The frequency of grade 3 or 4 non-haematological toxicity in the combination arm compared with the single-agent arm was alopecia (72% versus 65%), nausea/vomiting (36% versus 12%), oral (6% versus 0%), infection (2% versus 1%), cardiac (1% versus 1%) and level of consciousness (0% versus 1%). Antiemetic therapy was used in 431 cycles (90%) of combination treatment and in 226 (73%) of DOX alone. No diarrhoea of grade 3 or 4 was noted. Almost all grade 1 and 2 diarrhoea occurred in the radiotherapy pre-treated patients, except for two patients in the DOX arm. Only grade 1 and 2 neuropathies were reported, mainly in the combination arm (25% versus 4%). Non-haematological toxicities were also found not to be cumulative.

Table 1. Baseline characteristics

	Treatment		
	DOX–CDDP	DOX	Total
No. of patients	90	87	177
Median age, years (range)	63 (40–76)	63 (41–76)	63 (40–76)
WHO performance status			
0	29	39	68
1	42	29	71
2	15	17	32
Unknown	4	2	6
FIGO classification			
I	37	24	61
II	15	17	32
III	13	17	30
IV	19	25	44
Unknown	6	4	10
Type of disease			
Advanced primary	36	36	72
Recurrent	54	51	105
Tumour differentiation			
Well	18	16	34
Moderately/poorly	72	71	143
Extent of disease at registration			
Primary tumour	1	3	4
Locoregional recurrent	9	10	19
Metastatic disease	46	31	77
Primary not excised and metastatic	9	15	24
Locoregional recurrent and metastatic	21	25	46
Unknown	4	3	7
Prior treatment			
Surgery	79	73	151
Radiotherapy	40	48	88
Chemotherapy	0	1	1
Hormonotherapy	25	15	40

CDDP, cisplatin; DOX, doxorubicin; FIGO, International Federation of Gynecology and Obstetrics; WHO, World Health Organization.

Extensive toxicity was more often the reason for stopping treatment in the DOX–CDDP arm than in the single-agent DOX arm (10% versus 2%). One patient in the DOX–CDDP arm died of toxicity 2 weeks after the start of the first cycle; the cause of death being pneumonia, despite treatment with antibiotics. Myelosuppression due to toxicity could not be excluded as cause of death, despite the WBC count not being excessively low ($0.8 \times 10^3/mm^3$). No fatal toxicities were reported in the DOX arm.

Efficacy evaluation

Efficacy analysis was performed on all randomised patients (n = 177). Eight patients had no response assessed due to early death (four, DOX–CDDP arm; four, DOX arm). Response to treatment is summarised in Table 4. The combination of DOX–CDDP provided a significantly higher response rate than the single-agent DOX arm (P <0.001). Thirty-nine patients (43%) responded to DOX–CDDP [95% confidence interval (CI) 33–54], 13 CRs and 26 PRs, versus 15 patients (17%) on DOX (95% CI 3–15), 8 CRs and 7 PRs (Table 4). With respect to the type of disease, 29% had advanced and 31% recurrent disease. As the distribution of the type of disease among the responders was also broadly equal in both arms, no correlation was seen between the type of disease and the response rate. Prior radiotherapy and hormonotherapy did not seem to influence the response rate in

Table 2. Haematological toxicity grade 3 and 4[a]

Toxicity	Treatment	
	DOX–CDDP, *n* (%)	DOX, *n* (%)
WBC		
Grade 3	37 (44.6)	14 (17.1)
Grade 4	9 (10.8)	11 (13.4)
Platelets		
Grade 3	9 (10.8)	4 (4.9)
Grade 4	2 (2.4)	0 (0.0)

[a]165 evaluable patients.
DOX–CDDP, doxorubicin and cisplatin; DOX, doxorubicin; WBC, white blood cells.

either arm, and there were no major differences in the response rate of the various tumour sites between the treatment arms.

After a median follow-up of 86 months, 82 patients (91%) treated with DOX–CDDP had died compared with 78 patients (90%) treated with DOX. Of the patients in the combination arm, 73 had died because of malignant disease, one of toxicity, four of cardiovascular disease, one of another chronic disease and three for unknown reasons. In the single-agent treatment arm, 73 had died because of malignant disease, three of cardiovascular disease and two for other reasons.

The Kaplan–Meier curves, that illustrate overall survival (OS), TTP and duration of response, are shown in Figures 1, 2 and 3. Median OS was 9 months (95% CI 7–14) in the DOX–CDDP arm versus 7 months (95% CI 4–9) in the DOX arm. The Kaplan–Maier curve reveals no significant difference in survival between the two treatment arms (log-rank, $P = 0.107$; Wilcoxon, $P = 0.064$). Overall median TTP for all treated patients was 8 months (95% CI 7–11) in the DOX–CDDP arm and 7 months (95% CI 6–10) in the DOX arm. The estimated median PFS was 8 months (95% CI 7–11) in the DOX–CDDP arm and 7 months (95% CI 6–10) in the DOX arm. Median duration of response was 9 months in the DOX–CDDP arm versus 24 months in the DOX arm ($P = 0.008$). Forty-three of 54 responders (34 of 39 in the DOX–CDDP arm and 9 of 15 in the DOX arm) had progressed at the cut-off date.

A Cox regression analysis was performed to identify prognostic factors for survival. After taking account of age, WHO performance status, FIGO stage, extent of disease and degree of differentiation, only WHO performance status appeared to be statistically significant. Stratifying only for this variable, the treatment effect increased, reaching a significant difference in favour of the combination arm ($P = 0.024$, hazard ratio = 1.46, 95% CI 1.05–2.03).

Discussion

Treatment of advanced or recurrent endometrial cancer with prostagens yields an overall response rate of 30%, with a higher response in patients with well differentiated tumours and in those with long time intervals before relapse [3]. However, as hormone receptors predict well for response to hormonal treatment, it is imperative to find effective cytotoxic agents for the initial management of those patients who are receptor negative.

Table 3. Non-haematological toxicity during treatment[a]

Toxic effect	WHO grading							
	1		2		3		4	
	DOX–CDDP	DOX	DOX–CDDP	DOX	DOX–CDDP	DOX	DOX–CDDP	DOX
Alopecia	1	5	14	15	59	50	1	3
Nausea/vomiting	9	28	34	29	29	10	1	0
Infection	7	4	6	1	0	1	2	0
Oral	18	16	7	7	5	0	0	0
Cardiac	5	1	1	0	1	1	0	0
Consciousness	4	0	0	1	0	1	0	0
Diarrhoea	15	3	7	4	0	0	0	0
Peripheral neuropathy	18	2	3	1	0	0	0	0
Drug fever	3	3	4	0	0	0	0	0
Pulmonary	4	0	0	1	0	0	0	0
Cutaneous	2	2	1	0	0	0	0	0
Local	6	1	0	0	0	0	0	0
Allergy	1	2	0	0	0	0	0	0
Other	14	7	6	3	1	1	0	0

[a]165 evaluable patients.
DOX–CDDP, doxorubicin and cisplatin; DOX, doxorubicin; WHO, World Health Organization.

Table 4. Response rate (intention-to-treat basis)

WHO response	Total[a], *n* (%)	DOX–CDDP, *n* (%)	DOX, *n* (%)
CR	21 (11.9)	13 (14.4)	8 (9.2)
PR	33 (18.6)	26 (28.9)	7 (8.0)
SD	41 (23.2)	21 (23.3)	20 (23.0)
PD and early PD	45 (25.4)	13 (14.4)	32 (36.8)
Early death (malignant disease)	5 (2.8)	2 (2.2)	3 (3.4)
Early death (toxicity)	1 (0.6)	1 (1.1)	0 (0.0)
Early death (other cause)	2 (1.1)	1 (1.1)	1 (1.1)
Insufficient data	27 (15.3)	12 (13.3)	15 (17.2)
Unknown	2 (1.1)	1 (1.1)	1 (1.1)

[a]177 evaluable patients.
CR, complete response; DOX, doxorubicin; DOX–CDDP, doxorubicin and cisplatin; PD, progressive disease; PR, partial response; SD, stable disease; WHO, World Health Organization.

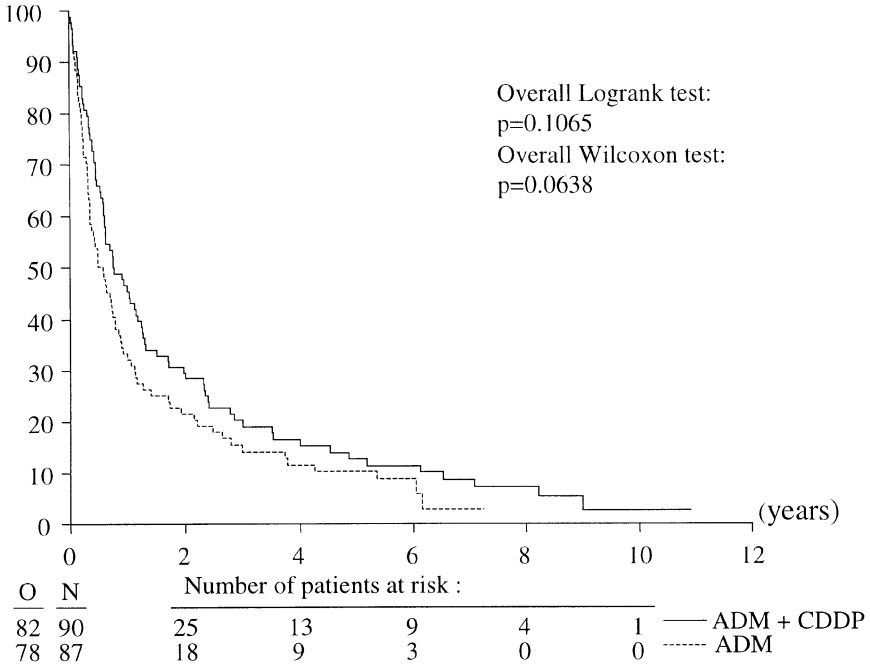

Figure 1. Kaplan–Maier plot of overall survival according to treatment arm.

Since 1950, phase II trials have identified several chemotherapeutic agents with a demonstrable objective response in endometrial adenocarcinoma, including anthracycline, carboplatin, CDDP, cyclophosphamide, 5-fluorouracil and hexamethylmelamine [5, 6, 13–15]. Experience with single-agent chemotherapy has identified DOX and CDDP to be the most consistently active agents investigated. Single-agent DOX was utilised in four trials with overall response rates of 19–37%, as summarised in two articles [5, 6]. Since 1975, single-agent CDDP has been used in endometrial cancer, with reported response rates between 4% and 100% [5, 6, 14]. The large range in response rate of the different trials can be explained by the difference in patient population. Most trials including chemotherapy pre-treated and chemotherapy-naïve patients showed a significant difference in response rate, being worse in patients who received prior cytotoxic therapy. Therefore, these results of previous studies suggest that CDDP is only of use as a first-line agent in endometrial carcinoma, as in breast cancer [16].

The combination of DOX–CDDP in endometrial cancer has been evaluated in seven trials since 1984 [17–23]. Most of these reports describe small trials without a control arm. In these trials, response rates from 33% to 82% were reported in the 93 evaluated patients. Seltzer et al. [18] showed in their trial that this drug combination did not appear to be effective in the treatment of recurrent endometrial cancer, although in contrast, our trial has not shown any difference in response rate among primary advanced

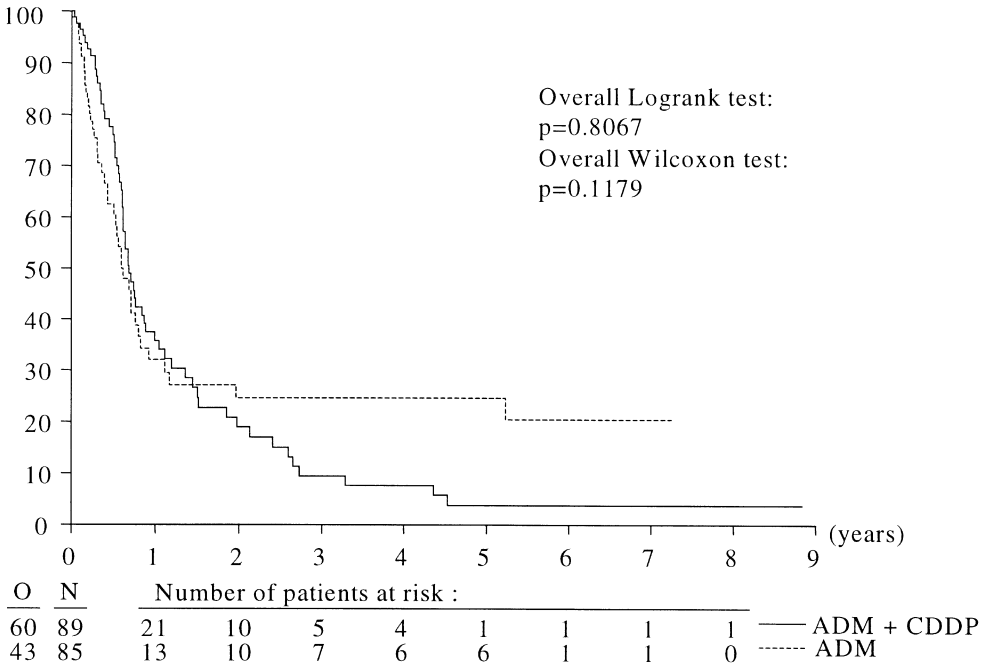

Figure 2. Kaplan–Maier plot of time to progression according to treatment arm.

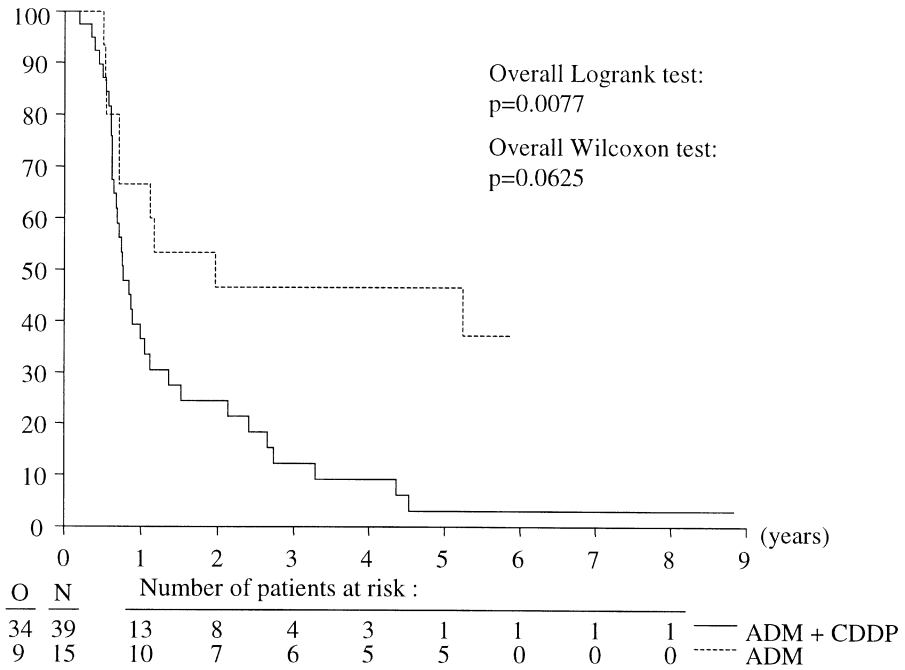

Figure 3. Kaplan–Maier plot of duration of response according to treatment arm.

and recurrent disease. In a trial of the Gynecologic Oncology Group, Thigpen et al. [22] used single-agent DOX as a control arm, whilst Long et al. [23] compared the use of methotrexate, vinblastine, DOX and CDDP to DOX–CDDP, the latter showing a response rate of 26% with the combination of DOX–CDDP in only 15 patients. Thigpen et al. [22] showed a response rate of 45% with combination treatment and a 27% response rate in the single-agent arm among 223 evaluable patients, although there was no overall survival benefit of the combination treatment in his cohort.

An initial analysis performed on 113 evaluable patients from our trial showed a difference in the duration of survival between both treatment arms in favour of the combination arm (12.4 versus 7.6 months) [24]. However, the final analysis has shown a

smaller difference, with some evidence of an early separation followed by a convergence in the survival curve. There is also evidence that the duration of response may be longer on the DOX arm for the few responding patients, as shown in Figure 3. This long duration of remission may be due to chance alone, or to the possible influence of prior hormonal therapy (some patients could have had a non-documented oestrogen withdrawal) or demonstrate a subgroup of patients with highly DOX-sensitive tumours. Although the median number of cycles in the DOX–CDDP arm was higher than in the DOX arm, explained by the fact that CDDP alone was continued in responding patients in the combination arm, no major differences were noted between the treatment arms in the response of the various tumour sites, and therefore the addition of CDDP does not seem to influence the response of specific sites.

Combination treatment was more toxic than DOX alone, with observed toxicity being mainly primarily haematological and gastrointestinal. However, in general, this was acceptable, and similar to that observed in earlier trials.

Thus, overall, our randomised controlled trial shows that in comparison to single-agent DOX, the combination of DOX–CDDP results in higher toxicity, but also a significantly higher response rate, and overall provides a moderate benefit in survival in patients with a good performance status.

Acknowledgements

We thank Dr Anne Appleton of the Institut Multi-disciplinaire d'Oncologie (IMO), Clinique de Genolier, Switzerland, for assistance with editing of the manuscript.

References

1. Glassburn JR. Carcinoma of the endometrium. Cancer 1981; 48 (Suppl 2): 575–581.
2. Kelly RM, Baker WH. Progestational agents in the treatment of carcinoma of the endometrium. N Engl J Med 1961; 264: 216.
3. Donovan JF. Nonhormonal chemotherapy of endometrial adenocarcinoma: a review. Cancer 1974; 34: 1587–1592.
4. Carbone PP, Carter SK. Endometrial cancer: approach to development of effective chemotherapy. Gynecol Oncol 1974; 2: 348–353.
5. Deppe G. Chemotherapeutic treatment of endometrial carcinoma. Clin Obstet Gynecol 1982; 25: 93–99.
6. Cohen CJ. Cytotoxic chemotherapy for patients with endometrial carcinoma. Clin Obstet Gynaecol 1986; 13: 811–824.
7. Bruckner HW, Cohen CJ, Goldberg JD et al. Improved chemotherapy for ovarian cancer with *cis*-diamminedichloroplatinum and adriamycin. Cancer 1981; 49: 2441–2445.
8. George SL, Desu MM. Planning the size and duration of a clinical trial studying the time to some critical event. J Chron Dis 1974; 27: 15–24.
9. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31: 103–115.
10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457–481.
11. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966; 50: 163–170.
12. Cox DR. Regression models and life-tables. J R Stat Soc B 1972; 34: 187–202.
13. Thigpen JT, Blessing JA, Ball H et al. Hexamethylmelamine as first-line chemotherapy in the treatment of advanced or recurrent carcinoma of the endometrium: a phase II trial of the Gynecologic Oncology Group. Gynecol Oncol 1988; 31: 435–438.
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. Thigpen JT, Blessing JA, Homesley H et al. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 1989; 33: 68–70.
16. Martin M. Platinum compounds in the treatment of advanced breast cancer. Clin Breast Cancer 2001; 3: 190–208.
17. Deppe G, Malviya VK, Malone JM et al. Treatment of recurrent and metastatic endometrial carcinoma with cisplatin and doxorubicin. Eur J Gynaecol Oncol 1984; 15: 263–266.
18. Seltzer V, Vogl SE, Kaplan BH. Adriamycin and *cis*-diamminedichloroplatinum in the treatment of metastatic endometrial adenocarcinoma. Gynecol Oncol 1984; 19: 308–313.
19. Tropé C, Johnson JE, Simonsen E et al. Treatment of recurrent endometrial carcinoma with a combination of doxorubicin and cisplatin. Am J Obstet Gynecol 1984; 149: 379–381.
20. Pasmantier MW, Coleman M, Silver RT et al. Treatment of advanced endometrial carcinoma with doxorubicin and cisplatin: effect on both untreated and previously treated patients. Cancer Treat Rep 1985; 69: 539–542.
21. Barrett RJ, Blessing JA, Homesley H et al. Circadian-timed combination doxorubicin–cisplatin chemotherapy for advanced endometrial carcinoma: a phase II study of the Gynecologic Oncology Group. Am J Clin Oncol 1993; 16: 494–496.
22. Thigpen TJ, Blessing JA, Homesley H et al. Phase III trial of doxorubicin ± cisplatin in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group (GOG) study. Proc Am Soc Clin Oncol 1993; 12: 261 (Abstr).
23. Long HJ, Nelimark RA, Cha SS. Comparison of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) versus doxorubicin and cisplatin (AC) in advanced endometrial carcinoma. Proc Am Soc Clin Oncol 1995: 14: 282 (Abstr).
24. Aapro M, Bolis G, Chevallier B et al. Doxorubicin versus doxorubicin plus cisplatin in endometrial carcinoma: a randomized study of the EORTC Gynecological Cancer Cooperative Group (GCCG) (Meeting abstract). Ann Oncol 1994; 5 (Suppl 8): 98.