PERGAMON

European Journal of Cancer 39 (2003) 1129–1140

European Journal of Cancer

www.ejconline.com

Lack of impact of platinum dose intensity on the outcome of ovarian cancer patients: 10-year results of a prospective randomised phase III study comparing carboplatin–cisplatin with cyclophosphamide–cisplatin

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Received 19 August 2002; accepted 13 January 2003

Abstract

This prospective multicentre phase III trial was conducted to assess whether increased platinum dose intensity (DI) by combining carboplatin with cisplatin has an impact on overall survival (OS) and progression-free interval (PFI) compared with the standard combination of cyclophosphamide and cisplatin in patients with epithelial ovarian cancer. A total of 253 patients with epithelial ovarian cancer of stages International Federation of Gynecology and Obstetrics (FIGO) IC–IV were randomised to receive either cyclophosphamide (600 mg/m^2, intravenously (i.v.), day 1) and cisplatin (100 mg/m^2, i.v., day 2) ($n=125$) as the standard regimen or carboplatin (300 mg/m^2, i.v., day 1) and cisplatin (100 mg/m^2, i.v., day 2) ($n=128$), every 28 days for six courses. The median follow-up was 6.0 years. 124 patients randomised to the platinum dose-intensified arm and 123 patients randomised to the standard arm met all of the eligibility criteria. Patient characteristics were well balanced between the two treatment groups. All eligible patients randomised were included in the analysis of OS and PFI. The median OS of the standard and platinum dose-intensified arms were 41.2 (95% Confidence Interval (CI): 29.2–50.7) and 43.0 months (95% CI: 34.3–63.2), respectively ($P=$Non-significant (N.S.). The median PFI in the standard arm was 29.7 (95% CI: 17.4–41.7) versus 23.1 months (95% CI: 17.8–35.4) in the platinum dose-intensified arm, respectively ($P=$N.S.). Toxicity, comprising leucopenia, granulocytopenia, thrombocytopenia, anaemia, emesis and nausea, was statistically significantly higher in the platinum dose-intensified arm than in the standard arm. Unexpectedly, no statistically significant differences were found between the 2 arms' overall neuro- and ototoxicity. When converting carboplatin-platinum into cisplatin-platinum on the basis of an equivalence ratio of 4:1, patients in the platinum dose-intensified arm received a total platinum dose 1.58 times the platinum dose of the standard arm. With 35.0 mg/m^2/week being administered, the total platinum DI of the dose-intensified arm was statistically significantly ($P<0.0001$) higher than that of the standard regimen (with 22.0 mg/m^2 being administered). Calculating the average administered relative dose intensities of the regimens yielded almost identical results with 0.56 and 0.58 for the standard and experimental arms, respectively. Thus, by conventional means, a 1.6-fold increase in the platinum DI could be reached by combining carboplatin and cisplatin without unacceptable morbidity. Nevertheless, this did not translate into any therapeutic benefit for the patient, even in the optimally debulked group of patients for whom dose-intensification would have been expected to be of benefit.

Keywords: Platinum dose-intensity; Cisplatin/carboplatin combination therapy; Ovarian cancer; Randomised trial; Phase III study

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0959-8049/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0959-8049(03)00152-7

1. Introduction

At the start of this trial in 1990, the combination of cyclophosphamide and cisplatin had become standard therapy for epithelial ovarian cancer [1–3]. An Italian gynaecological oncology group conducted a study to assess the impact of cisplatin in the standard regimen by comparing single agent cisplatin with three- and two-agent chemotherapy [4]. This trial failed to demonstrate that either of the combination regimens were superior to single-agent cisplatin with regard to the rate of pathological complete remissions (pCR) that was measured as a likely predictor of long-term overall survival.

Intensive chemotherapy resulted in a rate of approximately 65% of pCR in optimally debulked patients [5], but more than half of these patients with pCR eventually relapsed. Even at 7 years, the survival curves in the Dutch study comparing cisplatin-containing therapy with cisplatin-free therapy, yielded incomparably excellent results, and the curves did not reach a plateau [6]. This study prompted a search for altered strategies of primary therapy in ovarian cancer in order to obtain higher percentages of pCR and to maintain them once reached. Patients who might benefit most from these new therapies were also to be tested. Therefore, high-risk patients, and those with lower stages, e.g. FIGO IC, were to be treated similarly to patients with advanced stage disease.

Data on cisplatin, the most effective drug available, were analysed providing evidence of a dose-dependent effect both *in-vitro* using a clonogenic assay [7] and in clinical trials using different dosages of cisplatin [8,9]. Regarding the new strategies, the concept of dose intensity (DI), which advocates for an efficacy that does not simply depend on the absolute drug concentration reached, but merely on the dose per time unit, was examined in ovarian cancer patients [10]. In retrospective analyses, significant correlations between the amount of cisplatin per time unit given and the response rate or the overall survival were documented. One way to transform this concept into clinical practice is by using an increased dose. Due to an unacceptable increase in toxicity that followed an increase in the dose [11], cisplatin was substituted with the analogue carboplatin which had been proven to be of equivalent efficacy, but, in general, to be significantly less toxic, although the pattern dose-limiting toxicities are different with cisplatin treatment resulting in neuro-, oto-, nephro-, and gastrointestinal toxicity and carboplatin in haematotoxicity as its dose-limiting toxicity [12].

Data from three non-randomised studies—one phase I/II and two phase II studies testing the combination of cisplatin and carboplatin—did show the feasibility of this regimen with regard to toxicity and efficacy [13–15]. The Belgian study aimed to maximise the platinum doses without excessive toxicities being experienced by 25 ovarian cancer patients who had been previously untreated with cytotoxic drugs [13]. Carboplatin was given on day 1 followed by cisplatin 24 h later. The dose levels of 300/100 mg/m^2 carboplatin/cisplatin were recommended for further phase II/III studies. The Danish trial reported on 42 previously untreated ovarian cancer patients with residual disease who were treated with carboplatin (300 mg/m^2, day 1) and cisplatin (50 mg/m^2, days 2 and 3) [14].

These data and our own *in-vitro* investigations, revealing less than synergistic effects in the ovarian cancer cell line, OVCAR-3, led us to perform a pilot study combining carboplatin (300 mg/m^2, day 1) with cisplatin (100 mg/m^2, day 2) in 20 previously untreated ovarian cancer patients [15]. We concluded, like others, that this combination did increase the platinum DI and was effective and feasible. This result led us to initiate a multicentre prospective randomised phase III study to test the concept of platinum DI by combining cisplatin with carboplatin and the putative impact on the outcome of ovarian cancer patients.

2. Patients and methods

2.1. Patient selection

Eligible patients were required to have a histologically-confirmed diagnosis of epithelial ovarian cancer including central reference pathology review; stages IC–IV according to the International Federation of Gynecology and Obstetrics (FIGO) [16] excluding borderline tumours, with or without residual disease, with measurable or non-measurable disease; performance status according to the World Health Organization (WHO) of 3 or less; be aged 75 years or younger; have a life expectancy of at least 2 months; normal renal function (i.e. creatinine clearance of $\geqslant$1 ml/s/1.73 m^2) and adequate bone marrow function (i.e. leucocytes $\geqslant 3.5\times10^9$/l, granulocytes $\geqslant 1.5\times10^9$/l, platelets $\geqslant 100\times10^9$/l). Patients with previous chemo- and/or radiotherapy, with an expected inadequacy of follow-up, and with a second malignancy with the exception of *in-situ* cervical cancer or adequately treated basal cell or squamous cell carcinoma of the skin were excluded from the randomisation.

In addition, only patients with an adequate surgical tumour staging and therapy were eligible. This was a total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), omentectomy, and pelvic/para-aortic lymphadenectomy for early ovarian cancer patients (FIGO stages IC and II) and for the advanced ovarian cancer patients (FIGO stages III and IV), this included a maximal tumour reduction ('debulking') comprising of TAH, BSO, omentectomy and optional lymphadenectomy. Peritoneal lavage before removal of

any organ or tumour, registration of locialisation in the detail and the extent of tumour spread before and after surgery, biopsy of all suspicious areas as well as random-blind biopsies and the assessment of the presence and volume of ascites were the defined staging procedures that were required within six weeks prior to study entry.

The study was performed after approval by the local ethical committees of each participating centre. Written informed consent was obtained from each patient before registration.

2.2. Treatment plan

Patients assigned to the standard therapy arm received cyclophosphamide (Cyclo; Endoxan®, ASTA Medica) at a dosage of 600 mg/m^2 intravenously (i.v.) over 1 h on day 1. Mesna (Uromitexan®, ASTA Medica) was applied i.v. immediately before the application as well as 4 and 8 h after the termination of the Cyclo infusion. On day 2, 100 mg/m^2 of cisplatin (Cis; Platinol®, Bristol-Myers Squibb), dissolved in 2000 ml saline, was administered i.v. Vigorous prehydration with 500 ml mannitol 10% and 1000 ml ionic-equilibrated saline given over 2 h was done before the application of Cis followed by a 2-h posthydration phase with 2000 ml ionic-equilibrated saline. Patients assigned to the experimental therapy arm received carboplatin (Carbo; Paraplatin®, Bristol-Myers Squibb) at a dosage of 300 mg/m^2 i.v. on day 1, after the application of 1000 ml saline in order to equilibrate putative inadequate fluid intake, followed by 100 mg/m^2 of Cis i.v. on day 2. Pre- and posthydration were identical to the standard arm. Both regimens were applied every 4 weeks for a total of six courses.

2.3. Dose modification

When adverse effects occurred, strict criteria were adopted to prevent or at least standardise a reduction in DI. The dose modifications were determined by the most severe toxicity and foreseen by the protocol:

a. in cases of myelosuppression at the start of the next course: treatment was delayed for 1–3 weeks and restarted at the same dosage as soon as leucocytes reached $\geqslant 3.5\times10^9$/l, granulocytes $\geqslant 1.5\times10^9$/l and platelets $\geqslant 100\times10^9$/l, respectively. Patients who could not restart therapy after a 3-week delay were taken off study;
b. according to the nadir counts: if the counts of leucocytes dropped $<0.8\times10^9$/l and/or granulocytes $<0.3\times10^9$/l and/or platelets $<50\times10^9$/l, respectively, during therapy, the Carbo dose had to be reduced to 200 mg/m^2; if the counts of leucocytes dropped $<0.5\times10^9$/l and/or granulocytes $<0.2\times10^9$/l and/or platelets $<25\times10^9$/l, respectively, the Carbo dose had to be reduced to 150 mg/m^2 and, in the case of platelet nadirs at $<20\times10^9$/l, to 100 mg/m^2. The dose modification was continued until normalisation of the nadirs. The subsequent drug doses could be escalated by 25% increments for each subsequent course until the planned dose was reached and if no further severe myelosuppression was noted. No dose modification for Cis were foreseen;
c. in cases of renal dysfunction, i.e. creatinine clearance <1 ml/s, before the application of either Cis or the combined platinum regimen: therapy was delayed and creatinine clearance was determined after intensive i.v. hydration by ionic-equilibrated saline. Therapy was only applied if the creatinine clearance normalised;
d. in cases of disabling (WHO grade 3 or 4) neurotoxicity or ototoxicity, respectively: both drugs, Cis and Carbo, were reduced by 50%.

2.4. Pretreatment and follow-up evaluation

Complete blood cell counts including differential blood counts were repeated weekly. Blood chemistry including creatinine, creatinine clearance and CA-125 serum levels, assessment of WHO performance status and physical/gynaecological examination were undertaken monthly before each retreatment. Neurological examinations and audiograms were performed at study entry, as well as after four and six courses of therapy and when clinically indicated. The assessment of the disease status by means of ultrasonography and/or computed tomography as well as chest X-ray was performed before the start, as well as after four and six courses of therapy. After the termination of treatment, physical/gynaecological examination were performed every 3 months for the first 3 years, every 6 months between 3 and 5 years and at yearly intervals thereafter.

2.5. Response and toxicity evaluation

Clinical response and toxicity were assessed in accordance with the WHO criteria [17]. Patients had to receive a minimum of two courses to be evaluable for response and a minimum of one drug application to be evaluable for toxicity.

Response evaluation was foreseen after four and six courses of therapy. Patients with no evidence of disease (NED), clinical complete remission (cCR) and clinical partial remission (cPR) after four courses continued the same therapy for two more courses, whereas patients with progressive disease (PD) and no change (NC) were taken off the first-line therapy. Second-look-laparotomy with peritoneal washings and multiple biopsies both in

random-blind and suspicious areas was intended to be performed in patients with NED following six courses of chemotherapy, in those persisting to have cCR since course 4 and in those reaching cCR since then. A negative second-look laparotomy denoted a pathological CR (pCR). In cases of microscopic disease with a greater than 50% decrease in the size of peritoneal nodules, patients were considered to be in pathological PR (pPR). Patients with objective remissions (p/c CR and p/c PR) together with those presenting with NC and NED were summarised as the freedom from progression (FFP) subgroup. Toxicity was checked at monthly intervals.

2.6. DI evaluation

The calculation of DI, planned and received, was performed as described by Levin and Hryniuk in Ref. [10]. For this analysis, the time period to administer the six courses of therapy plus the duration of one complete course (4 weeks) was considered as DI planned and the time period to administer the number of courses of therapy given plus the duration of one course thereafter as DI received.

2.7. Statistical methods

2.7.1. Outcome variables

The major efficacy criteria were progression-free interval (PFI) and overall survival (OS); in addition, the response rate, specifically the rate of pCR, as well as toxicity were evaluated and compared. PFI was the time interval between the start of chemotherapy and the first evidence of progression at any time; OS was measured from the same time point until death. Only eligible patients were included in the analysis for PFI and OS. Patients who died for reasons other than toxicity before the first re-evaluation were included in the subgroup of patients with PD.

2.7.2. Sample size

The estimation of the sample size by using the program STPLAN [18] was done based on the following assumptions: alternative hypothesis: 35% versus 50% probability of survival at 3 years in the two respective therapy groups; at all time points constant hazard ratios. By using the test of Mantel [19] at a one-sided level of significance of 0.05 based on a yearly recruitment of 70 patients, a duration of recruitment of 3.5 years (i.e. $n=244$) and a follow-up period of 4 years, a power of 0.88 was obtained. Power means the probability of a significant result ($P<0.05$) if the true and unknown treatment effect is at least as strong as specified by the alternative hypothesis.

2.7.3. Randomisation

Patients were centrally registered at the documentation unit of the Vienna University and then allocated to the treatment arms using a computer program for the adaptive randomisation scheme according to Pocock and Simon [20]. This scheme guarantees established prognostic factors (residual tumour volume, stage, histological differentiation, grade, preoperative performance status, histological typing, age, ascites and institution) to be balanced in both treatment groups.

2.7.4. Analyses

Comparisons of treatment groups with respect to binary and categorical outcome variables were performed using the Chi-square test. With respect to ordered categorical outcome variables, the groups were compared by the Wilcoxon Rank Sum test, and the *t*-test was used to test for differences in continuous outcome variables. Survival probabilities were estimated by the Kaplan–Meier method [21]. Univariate and multivariate Cox regression analyses [22] were performed to evaluate the influence of therapy and other prognostic factors on the survival probability. Relative risks (with 95% Confidence Intervals (CIs)) were given to describe the strength of the prognostic factors. The median follow-up time was estimated using the reverse Kaplan–Meier method [23]. All *P*-values are the results of two-sided tests. *P* values smaller than 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

253 patients with epithelial ovarian cancer from 27 different institutions entered into the trial between June 1990 and December 1993 were randomised (Fig. 1). 6 patients were considered ineligible due to creatinine clearance <1 ml/s ($n=3$), postoperative mortality ($n=1$), endometrial cancer ($n=1$) and pretherapeutic deafness ($n=1$). The characteristics of all 247 eligible randomised patients are detailed in Table 1, reflecting that the prognostic factors were well balanced between both groups.

10 patients of the Carbo–Cis arm ($n=124$) and 8 patients of the Cyclo–Cis arm ($n=123$) received less than two courses of therapy. The reasons for this were refusal of therapy in 7 patients (in 6 before and in 1 after the first course) and 5 patients (in 3 before and in 2 after the first course), in the Carbo–Cis arm and Cyclo–Cis arm, respectively, as well as the stopping of therapy due to toxicity in 6 patients, 3 patients in each arm (in the Carbo–Cis group: creatinine clearance <1 ml/s ($n=2$), persistant leucopenia ($n=1$); in the Cyclo–Cis group: creatinine clearance <1 ml/s ($n=1$), ototoxicity ($n=1$), persistant intractable vomiting ($n=1$)). No treatment-related deaths occurred. Overall, 6 patients died due to tumour progression before completion of

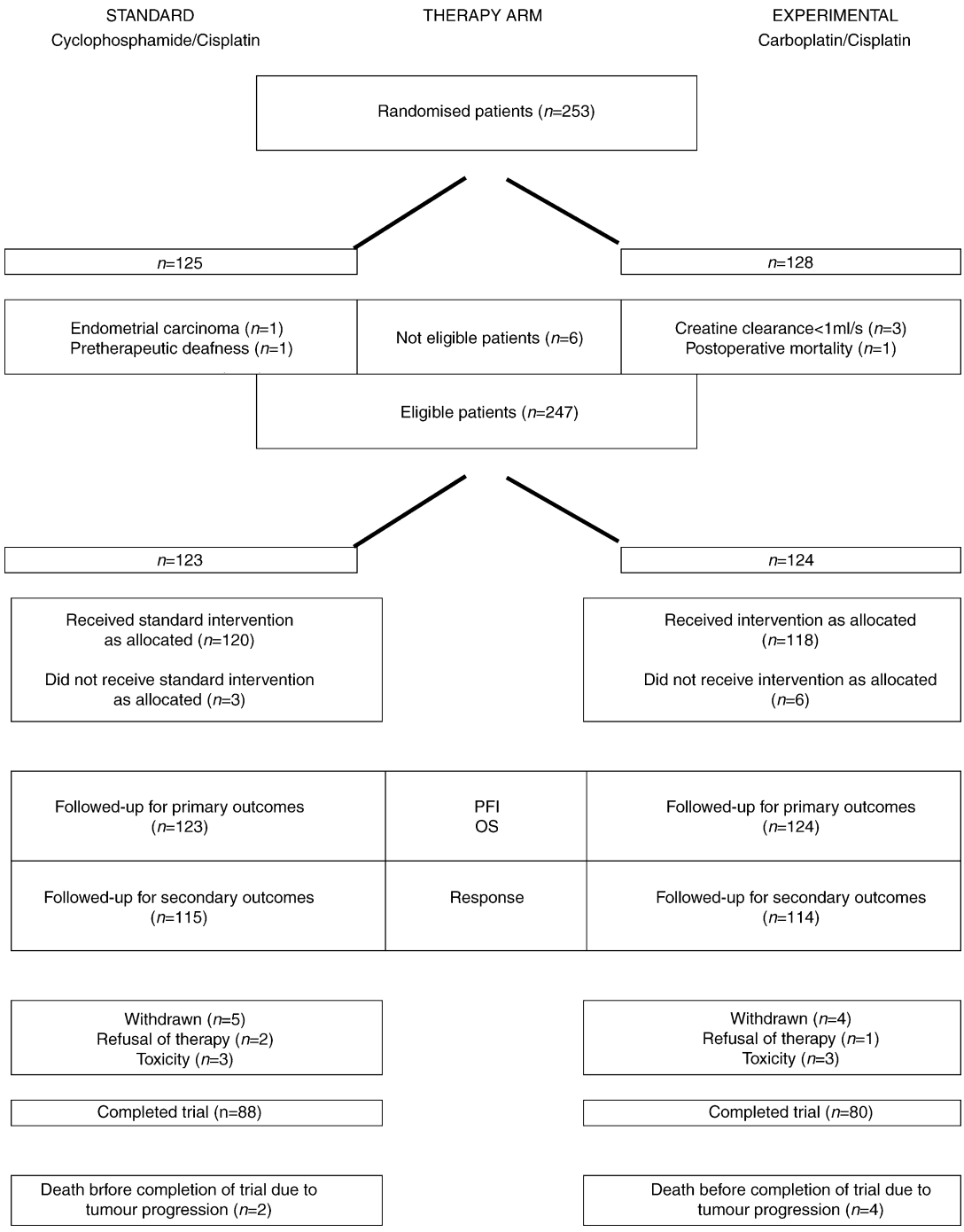

Fig. 1. Flow chart of the progress of patients through the various steps of the trial (adapted from Ref. [27]). PFI, progression-free interval; OS, overall survival.

therapy; 4 in the experimental arm, 2 in the standard arm.

The number of patients treated at each course and the interval between consecutive courses are shown in Table 2. Only slightly fewer patients (80/124; 65%) completed the platinum-intensified regimen than the standard regimen where 88 out of 123 patients completed the therapy (72%) ($P=0.236$). 38 patients (31%) in the platinum-intensified arm versus 32 patients (26%) in the standard arm did not complete all six courses due to PD/NC, death, toxicity and/or refusal of further therapy ($P=0.349$). The median number of days between courses ranged from 29 to 34 in the Carbo–Cis arm and from 29 to 33 in the Cyclo–Cis arm and did not show indication of cumulative toxicity. The number of cycles administered was 610 (82% of the planned) and 641 (87% of the planned) in the Carbo–Cis and Cyclo–Cis arms, respectively. The frequency of dose modifi-

Table 1
Characteristics of all eligible patients ($n=247$)

Variables	Carboplatin–cisplatin ($n=124$)	Cyclophosphamide–cisplatin ($n=123$)
	n (%)	*n* (%)
Age (years)		
Median (range)	56 (21–75)	55 (22–74)
Performance status (WHO)		
0	78 (63)	69 (56)
1	36 (29)	47 (38)
2	10 (8)	7 (6)
Histological type		
Serous	89 (72)	96 (78)
Mucinous	5 (4)	5 (4)
Endometrioid	11 (9)	9 (7)
Clear-cell	5 (4)	2 (2)
Other	14 (11)	11 (9)
Grade		
1	17 (14)	18 (15)
2	35 (28)	36 (29)
3	72 (58)	69 (56)
Stage		
I	11 (9)	11 (9)
II	15 (12)	11 (9)
III	83 (67)	86 (70)
IV	15 (12)	15 (12)
Residual disease (cm)		
0	46 (37)	41 (33)
<2	33 (27)	34 (28)
2–5	14 (11)	17 (14)
>5	31 (25)	31 (25)
Surgery		
TAH + BSO	104 (84)	98 (80)
Biopsies only	20 (16)	25 (20)
Ascites		
Present	46 (37)	46 (37)
Absent	78 (63)	77 (63)

TAH + BSO, total abdominal hysterectomy + bilateral salpingo-oophorectomy; WHO, World Health Organization.

cations were 67% and 23% in the Carbo-Cis and Cyclo–Cis arms, respectively. This difference was statistically significant ($P<0.0001$) (Table 3). No differences were observed for global treatment delay ($P=0.8429$) and for toxicity-related delay ($P=0.1333$). These results infer that the Carbo–Cis arm was slightly more toxic than the standard Cyclo–Cis arm.

3.2. Total dose and dose intensity

The planned total dose of Cis was the same (600 mg/m^2) for both treatment groups (Table 4). There was no statistically significant difference between the groups in the total administered dose of Cis ($P=0.0908$). When converting Carbo–platinum into Cis–platinum on the basis of an equivalence ratio of 4:1, patients in the Carbo–Cis arm received a total platinum dose 1.58 times the platinum dose of the Cyclo–Cis arm, which was only slightly below the normalised projected total platinum total dose. The normalised values shown in Table 4 facilitate a comparison of the experimental regimen and the standard regimen by indicating the projected total platinum total dose per therapy arm as 1.0 and the administered one accordingly.

Focusing on differences in the platinum dose intensities, a total platinum DI of 25 mg/m^2/week in the standard arm and one of 43.75 mg/m^2/week in the dose-intensified one was projected yielding a mean administered total platinum DI of 22 mg/m^2/week in the standard arm and one of 35 mg/m^2/week in the experimental arm, which was significantly different ($P=0.0001$). In the standard arm an average of 88% of the projected total platinum DI could be administered, whereas the degree of the drug delivery in the experimental arm was significantly reduced with an average of 80%. In order to allow a comparison of the standard regimen (Cyclo–Cis) with the experimental arm (Carbo–Cis), the values were also expressed in a normalised way, i.e. by indicating the normalised projected total platinum DI of the reference arm as 1.0 and the administered one accordingly.

In addition, DI was calculated as suggested by Levin and Hryniuk [10], using the Greco version of a CHAP regimen as a standard in order to facilitate the comparison of data from regimens not restricted to platinum only with the relevant literature [24]. In the standard CHAP regimen, ignoring schedule differences and reducing to the form of mg/m^2/week, the DIs were: Cyclo 175, hexamethylmelamine 525, doxorubicin 10, and Cis 15, respectively. The average relative DI of a regimen was calculated as follows: each of the four single drug DIs calculated as a decimal fraction of the DI of the respective drug in the standard regimen was added and this sum was divided by 4 (the number of drugs in the CHAP regimen). In regimens containing fewer than four drugs, a DI of zero was assigned to the missing drug, but the sum of the fractions was still divided by 4. Relative to the Greco standard, the average projected relative DIs of treatment for the regimens in this study were 0.63 (standard regimen: Cyclo 150 mg/m^2/week, Cis 25 mg/m^2/week) and 0.73 (platinum-intensified regimen: Carbo 75 mg/m^2/week, Cis 25 mg/m^2/week), those administered were 0.56 and 0.58, respectively.

Thus, the two regimens which were designed to yield only a 16% increase in the average projected relative DI in the experimental arm (0.73) versus the standard arm (0.63), lost even that modest difference for various reasons (i.e. delay of therapy, dose modification). In fact, only a 4% increase in DI was observed in the experimental arm (0.58) compared with the standard arm (0.56) in the final evaluation.

Table 2
Number of courses completed, application intervals and number of courses administered/cancelled

Course	Carboplatin–cisplatin ($n=124$)				Cyclophosphamide–cisplatin ($n=123$)			
	Patients treated		Days between courses		Patients treated		Days between courses	
	n	(%)	Median	90%tile	*n*	(%)	Median	90%tile
1	118	(95)	–	–	120	(98)	–	–
2	114	(92)	31	42	115	(93)	29	40
3	108	(87)	29	42	113	(92)	29	36
4	102	(82)	33	43	108	(88)	29	42
5	88	(71)	32	47	97	(79)	33	49
6	80	(65)	34	42	88	(72)	30	41
Courses	Patients (*n*)	(%)	Courses (*n*)	(%)	Patients (*n*)	(%)	Courses (*n*)	(%)
Planned	124	(100)	744	(100)	123	(100)	738	(100)
Cancelled[a]	38	(31)			32	(26)		
due to: Toxicity		17		52		14		36
PD + NC		12		27		12		30
Refusal		12		56		9		42
Administered	80	(65)	610	(82)	88	(72)	641	(87)

PD, progressive disease; NC, no change.
[a] One or more reasons for correlation as a single patient simultaneously.

Table 3
Number of courses completed and treatment delayed and/or dose modified according to treatment group

Course	*n*	Carboplatin–cisplatin ($n=124$)			*n*	Cyclophosphamide–cisplatin ($n=123$)		
		Delay		Modification		Delay		Modification
		Toxicity	No toxicity			Toxicity	No toxicity	
		n (%)	*n* (%)	*n* (%)		*n* (%)	*n* (%)	*n* (%)
1	118	0 (0)	0 (0)	0 (0)	120	0 (0)	0 (0)	0 (0)
2	114	20 (18)	9 (8)	33 (29)	115	10 (9)	10 (9)	5 (4)
3	108	21 (19)	14 (13)	34 (31)	113	11 (10)	7 (6)	6 (5)
4	102	22 (22)	18 (18)	48 (47)	108	20 (19)	6 (6)	7 (6)
5	88	16 (18)	12 (14)	44 (50)	97	18 (19)	16 (16)	10 (10)
6	80	19 (24)	8 (10)	46 (58)	88	18 (20)	7 (8)	15 (17)

3.3. Response

Response was assessed in 229 eligible patients. As detailed in Table 5, there were no statistically significant differences in the rates of objective responses, with 38% in the Carbo–Cis arm and 44% in the Cyclo–Cis arm ($P=0.308$), or in the rates of patients who were free from tumour progression, with 87% in the Carbo–Cis arm and 86% in the Cyclo–Cis arm. The percentages of patients with NC and PD were also similar. 30 (26%) out of the 114 and 115 patients in each of the two treatment arms, reached a cCR. According to the protocol, these patients, together with the patients with NED, were candidates to undergo second-look laparotomy for a more exact response assessment. Overall, only 24% (56/229) of the patients evaluable for response underwent a re-assessment by second-look laparotomy (Table 6). 27 out of 60 (45%) patients belonging to the Carbo–Cis arm and 29 out of 55 (53%) patients to the Cyclo–Cis arm could be pathologically re-assessed. Interestingly, the rate of macroscopically-positive disease did not differ between the two arms, with 41% in the Carbo–Cis arm and 34% in the Cyclo–Cis arm ($P=0.812$). Overall, the rates of 44% pCR in the Carbo–Cis arm and 45% in the Cyclo–Cis arm of all patients undergoing second-look laparotomy were almost identical.

3.4. Progression-free and overall survival

Figs. 2 and 3 display the PFI and OS curves. All eligible patients randomised were included in these analyses. The median duration of follow-up was 6 years. There were no statistically significant differences between the treatment groups in both graphs. The median PFI in the Cyclo–Cis group was 29.7 months (95% CI: 17.4–41.7); in the Carbo–Cis group this was 23.1 months (95% CI: 17.8–35.4) (relative risk: 1.03; 95% CI: 0.74–1.41; $P=0.88$). The median OS of patients treated with Cyclo–Cis was 41.2 months (95% CI: 29.2–50.7) and for those treated with Carbo–Cis it

Table 4
Total dose and dose intensity according to treatment group

	Carboplatin–cisplatin		Cyclophosphamide–cisplatin	
Total dose				
Projected TD (mg/m^2)	1800	600	3600	600
Administered TD (mg/m^2)	1400	550	3490	489
Administered/projected TD %	78	92	97	82
Projected TD with platinum conversion[a] (mg/m^2)	450	600	3600	600
Administered TD with platinum conversion[a] (mg/m^2)	350	550	3490	568
Administered TD/projected TD %	78	92	97	95
Projected total platinum[b] TD (mg/m^2)	1050	–		600
Administered total platinum[b] TD (mg/m^2)	900	–		568
Administered total platinum[b] TD %	86	–		95
Normalized[c] projected total platinum[b] TD	1.75	–		1.00
Normalized[c] administered total platinum[b] TD	1.58	–		1.00
Dose intensity				
Projected DI (mg/m^2/week)	75	25	150	25
Administered DI (mg/m^2/week)	56	21	133	22
Administered/projected DI%	75	84	89	88
Average projected relative DI	0.73		0.63	
Average administered relative DI	0.58		0.56	
Projected total platinum DI with C→P conversion (mg/m^2/week)	43.75	–		25
Administered total platinum DI with C→P conversion (mg/m^2/week)	35.00	–		22
Normalised[c] projected total platinum DI	1.75	–		1.00
Administered total platinum DI	1.40	–		0.88
Normalised[c] administered total platinum DI	1.60	–		1.00

TD, total dose: cumulative dose over all courses projected/administered; DI, dose intensity.
[a] Platinum conversion: platinum resulting from the conversion of carboplatin–platinum in 'cisplatin–platinum' based on the conversion rate of 4:1.
[b] Total platinum: platinum from cisplatin plus the platinum resulting from the conversion of carboplatin–platinum in 'cisplatin–platinum' based on the conversion rate of 4:1.
[c] Normalised: the standard is arbitrarily indicated by 1.0.

Table 5
Clinical response according to treatment group

Clinical response	Carboplatin–cisplatin ($n=114$)	%	Cyclophosphamide–cisplatin ($n=115$)	%
Freedom from progression	87		86	
Complete remission		26		26
Partial remission		12		18
No evidence of disease		43		37
No change		5		5
Progression	13		14	

Table 6
Results of measurement by second-look laparotomy according to treatment group

Re-assessment result	Carboplatin–cisplatin $n=27$ (%)	Cyclophosphamide–cisplatin $n=29$ (%)
Microscopically-negative	12 (44)	13 (45)
Microscopically-positive	4 (15)	6 (21)
Macroscopically-positive	11 (41)	10 (34)

was 43.0 months (95% CI: 34.3–63.2) (relative risk: 1.05; 95% CI: 0.76–1.46; $P=0.75$). An intention-to-treat analysis including all randomised patients did not alter these results appreciably (data not shown).

Table 7 lists the relative death rates (relative risks) for all patients with respect to several prognostic factors. All characteristics considered as stratification criteria kept their discriminating value on the basis of univariate regression analyses with the exceptions of therapy and grade. When all these factors were entered into a multivariate analysis, only histological type ($P=0.002$) and postoperative residual disease ($P=0.005$) kept their discriminative power and were independent prognostic factors for survival. Chemotherapies in general, and especially the platinum dose-intensified one tested, did not impact upon survival, either in the univariate or the multivariate analyses.

3.5. Toxicity

238 patients were evaluable for toxicity (Table 8). The severity of leucopenia, granulocytopenia, thrombocytopenia, anaemia, nausea and emesis was statistically significantly higher in the Carbo–Cis arm than in the Cyclo–Cis arm in an evaluation of maximal toxicities per patient. It is of interest to note that although we expected

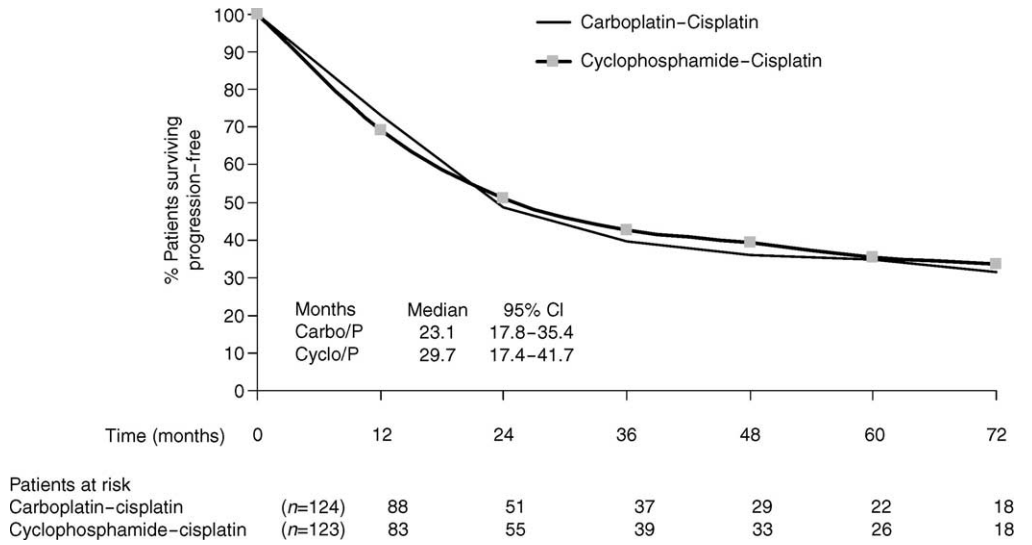

Fig. 2. Progression-free interval in ovarian cancer patients treated with carboplatin–cisplatin or cyclophosphamide–cisplatin. 95% CI, 95% Confidence Interval.

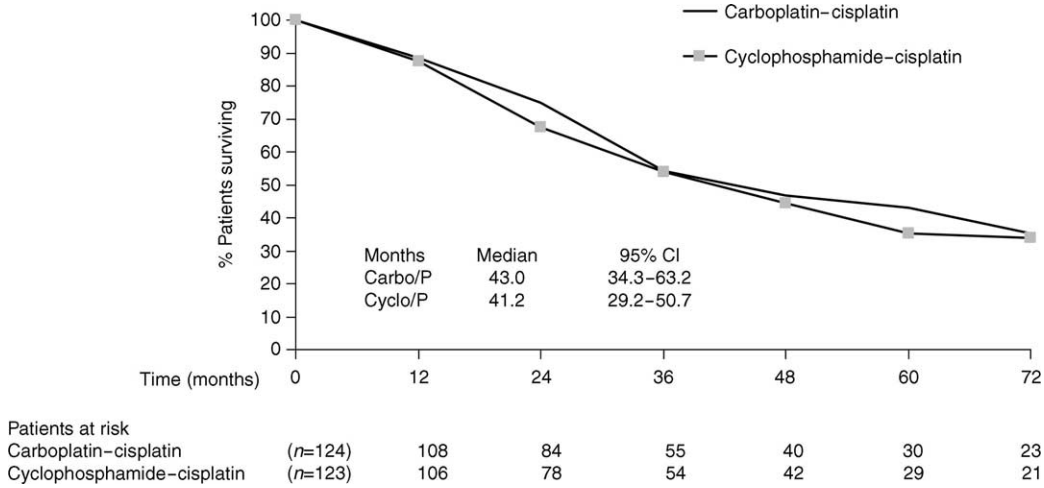

Fig. 3. Overall survival in ovarian cancer patients treated with carboplatin–cisplatin or cyclophosphamide–cisplatin.

an increase in neurotoxicity following platin dose intensification, neither the degree of peripheral neurotoxicity (Wilcoxon Rank Sum test, $P=0.40$) nor ototoxicity (Wilcoxon Rank Sum test, $P=0.120$) differed significantly between the two treatment arms. Nevertheless, when the two treatment arms were compared with regard to the ototoxicity of WHO Grade $\geqslant 2$, a statistically significant higher frequency of this toxicity ($P=0.03$) was found for the platinum dose-intensified regimen. With regard to peripheral neurotoxicity, the same categorisation (WHO Grade <2 versus $\geqslant 2$) did not reveal any statistically significant differences ($P=0.5332$).

4. Discussion

A retrospective sub-analysis of 33 clinical trials by Levin and Hryniuk, trying to assess the relationship between DI and clinical outcome in patients with ovarian cancer, revealed that only cisplatin was substantially correlated with response and contributed disproportionately to the clinical outcome when compared with other agents of combination chemotherapy [10]. This analysis suggested a positive correlation between median survival and the DI of cisplatin in a variety of non-randomised and randomised ovarian cancer trials. Therefore, we focused specifically on the comparison of the platinum DI in our study. Based on earlier described assumptions on the comparability of the two platins used, we converted the projected and administered DI of Carbo into platinum DI for this purpose. With an average of 35.0 mg/m^2/week, the administered total platinum DI of the Carbo–Cis arm was significantly higher than that of 22 mg/m^2/week reached in the Cyclo–Cis arm ($P<0.0001$). Overall, the total platinum DI of the platinum dose-intensified regimen administered was 1.6-fold that of the Cyclo–Cis standard

Table 7
Patient characteristics related to survival performing Cox regression analyses

Prognostic factor	Univariate analyses			Multivariate analyses		
	Relative risk	95% Confidence Interval	*P* value	Relative risk	95% Confidence Interval	*P* value
Age (years)			0.021			0.094
Increase by 10 years	1.20	1.03–1.40		1.16	0.98–1.37	
Performance status (WHO)			0.0009			0.326
0	1.00			1.00		
1	1.13	0.80–1.60		0.99	0.68–1.43	
2	2.82	1.64–4.86		1.59	0.84–2.99	
Histological type			0.040			0.002
Serous	1.00			1.00		
Mucinous	2.31	1.17–4.57		4.69	2.15–10.26	
Endometrioid	0.83	0.43–1.58		1.71	0.84–3.49	
Clear-cell	0.33	0.08–1.34		0.91	0.21–3.87	
Other	1.31	0.81–2.14		1.43	0.83–2.46	
Grade			0.094			0.219
1	1.00			1.00		
2	1.53	0.85–2.72		1.73	0.93–3.21	
3	1.79	1.05–3.06		1.54	0.84–2.80	
Stage			0.0001			0.519
I	1.00			1.00		
II	1.00			1.00		
III	3.05	1.75–5.34		1.37	0.66–2.81	
IV	4.51	2.30–8.85		1.64	0.70–3.87	
Residual disease (cm)			0.0001			0.005
0	1.00			1.00		
<2	3.01	1.89–4.81		2.81	1.51–5.21	
2–5	3.19	1.86–5.47		2.49	1.25–4.96	
>5	4.04	2.53–6.44		3.28	1.62–6.62	
Surgery			0.0001			0.973
TAH + BSO	1.00			1.00		
Biopsies only	2.24	1.48–3.39		0.99	0.56–1.77	
Ascites			0.0003			0.367
Present	1.00			1.00		
Absent	1.96	1.37–2.82		1.21	0.80–1.81	
Chemotherapy			0.752			0.434
Cyclophosphamide–cisplatin	1.00			1.00		
Carboplatin–cisplatin	1.05	0.76–1.46		1.14	0.82–1.60	

TAH + BSO, total abdominal hysterectomy + bilateral salpingo-oophorectomy; WHO, World Health Organization.

regimen. This significant difference is also reflected by the values of the normalised converted 'total platinum' total doses administered.

The mature results of this prospective randomised trial contribute to the discussion of whether dose-intensified therapy in ovarian cancer impacts upon patients prognosis. In the late 1980s, Levin and Hryniuk assessed the relationship between outcome and DI for first-line chemotherapy in advanced ovarian cancer using a four drug regimen comprising among other agents of Cis and Cyclo as the standard therapy at that time and they were the first to find a distinct advantage for multi-agent regimens over single alkylating agents, especially when they contained Cis [10]. In a sub-analysis, only the DI of Cis was substantially correlated with response and consecutive clinical outcome. McGuire and colleagues conducted a prospective study to investigate the impact of DI of Cyclo–Cis as a standard regimen on OS, PFS and the response of patients with sub-optimally debulked ovarian cancer [25]. In this trial, patients received the same total dose of Cyclo and Cis, but 1.97 times greater DI than the standard group. Clinical and pathological response rates and survival were similar in both groups, but toxicities were significantly more common and severe in the dose-intensified group.

Although our trial design differed with regard to how the dose intensification of platinum was reached, we drew almost identical conclusions. In the original publication of Levin and Hryniuk on DI analysis of regimens in ovarian cancer, the average DI normalised to the Greco standard varied from 0.21 to 1.11 and for Cis from 0.33 to 2.22, respectively [10]. McGuire and

Table 8
Occurrence of adverse effects (%) according to maximum severity (WHO grading system) and treatment group per patient

Adverse event	Carboplatin–cisplatin						Cyclophosphamide–cisplatin						*P* value
	Grade of severity					Patients	Grade of severity					Patients	
	0	1	2	3	4	*n*	0	1	2	3	4	*n*	
Leucopenia	4	12	33	38	11	113	5	15	47	31	3	117	0.045
Granulocytopenia	4	4	11	28	51	106	8	6	28	37	21	115	<0.001
Thrombocytopenia	5	9	10	36	40	114	50	16	13	19	3	117	<0.001
Anaemia	4	25	46	22	4	114	12	45	30	11	2	117	<0.0001
Increase in creatinine	84	14	0	2	0	115	89	9	2	0	0	119	0.150
Peripheral neurotoxicity	45	37	13	4	0	115	50	36	13	1	1	119	0.400
Ototoxicity	53	24	14	9	0	115	65	24	8	3	0	119	0.120
Nausea/emesis	4	23	37	32	4	115	15	29	29	19	8	119	0.003
Mucositis	87	11	1	1	0	115	95	4	1	0	0	119	0.150
Alopecia	16	35	42	8	0	115	14	35	34	15	3	119	0.150
Infections	83	15	2	1	0	114	87	12	1	0	0	118	0.580

WHO, World Health Organization.

colleagues succeeded in a better separation of their median global relative DIs (according to Greco standard [24]) varying from 0.46 to 0.91 from that of Cis varying from 0.99 to 1.96, reflecting a dose intensification by a factor of almost 2 for both, the entire regimen as well as for Cis separately. In our prospective study, the average projected relative DIs of 0.63 for Cyclo–Cis and 0.73 for Carbo–Cis, and the average administered relative DIs of 0.56 for Cyclo–Cis and 0.58 for Carbo–Cis, did result in an uncomparable study situation due to discrepancies in the DIs. Moreover, we tried to focus on the comparison of platinum DIs since Levin and Hryniuk established a significant correlation between DI and survival exclusively for this drug. Based on the above detailed conversion of Carbo–platinum DI into total platinum DI, the following intensities were reported for the Cyclo–Cis arm and the Carbo–Cis arm, respectively: normalised projected total platinum DI: 1.0 versus 1.75; administered total platinum DI: 0.88 versus 1.40, resulting in a normalised administered total platinum DI of 1.0 versus 1.60. Although the DI factor of 1.6 is somewhat smaller than the one of 2.0 reported by McGuire and colleagues, the tendency and therefore also our conclusion are the same. That is, an increase in DI of a magnitude that is feasible by means of conventional procedures, i.e. without a built-in (and regularly needed) rescue management with bone marrow and/or peripheral stem cell transplantation, is not beneficial for patients with epithelial ovarian cancer.

If the dose-intensified therapy arm had proved to be of benefit to the patients, our study could not have differentiated whether that effect was exclusively due to an increased DI and not, or at least not also, due to increased total dosages in the dose-intensified arm. It is likely that that total platinum dose and/or the platinum intensity did not significantly impact upon the patient's prognosis in our study. This is to be said with the restriction that both the lower platinum total dose and the lower platinum DI of the standard arm may have been compensated for by the combination with Cyclo and that this is somehow reflected by the comparable average relative DIs of the two treatment arms.

Of note, until now most data in the literature refers to suboptimally debulked patients. In the study by McGuire and colleagues, 4 out of 5 patients had lesions that were larger than 2 cm left behind after the primary surgery [25]. We, for the first time, report on a patient population with 3 out of 4 patients belonging to the optimally debulked group of patients, a group for which Hoskins and colleagues claimed more profit from a dose intensification than for large-volume disease patients [26]. Based on the data presented, we conclude that platinum dose intensification within the limits of conventional procedures was not of benefit, even in patients with a high preponderance of small volume disease left behind after surgery. This even holds true after the subgroup analysis of patients with postoperative small-volume (<2 cm) and larger volume ($\geqslant 2$ cm) disease. No positive impact from the platinum dose-intensified regimen was observed with regard to PFI and OS.

Although—in general—the combination of a platin and paclitaxel is the standard of first-line therapy for ovarian cancer worldwide, we think it is still appropriate to report on the above comparisons of drug combinations. Firstly, these data are one of the few reports of mature long-term results of a prospective study; secondly, for small volume disease patients, the question of platinum dose intensification has not yet been answered and thirdly, even in the era of the taxanes, the platins are still considered most important. To our knowledge, platinum has not been substituted in any combination therapy study started in the taxane era. The question of dose-intensification up to a level where rescue has to be given, e.g. via peripheral blood

stem cell support, has been addressed, but not yet answered up.

Acknowledgements

This work was supported (in part) by a research grant from Bristol-Myers Squibb, Vienna, Austria, and Glaxo-SmithKline, Vienna, Austria.

Appendix

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References

1. Neijt JP, ten Bokkel Huinink WW, van der Burg ME, *et al.* Randomised trial comparing two combination chemotherapy regimens (CHAP-5 v CP) in advanced ovarian carcinoma. *J Clin Oncol* 1987, **5**, 1157–1168.
2. Bertelsen K, Jakobsen A, Andersen JE, *et al.* A randomised study of cyclophosphamide and *cis*-platinum with and without doxorubicin in advanced ovarian carcinoma. *Gynecol Oncol* 1987, **28**, 161–169.
3. Omura GA, Bundy BN, Berek JS, Curry S, Delgado G, Mortel R. Randomised trial of cyclophosphamide plus cisplatin with or without doxorubicin in ovarian carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol* 1989, **7**, 457–465.
4. Gruppo Interegionale Cooperativo Oncologico Ginecologia. Randomised comparison of cisplatin with cyclophosphamide/cisplatin and with cyclophosphamide/doxorubicin/cisplatin in advanced ovarian cancer. *Lancet* 1987, **2**, 353–359.
5. Dittrich C. Ovarialkarzinom. In Dittrich Ch, ed. *Angewandte Onkologie*. Wien, New York, Springer-Verlag, 1989, 80–165.
6. Neijt JP, ten Bokkel Huinink WW, van der Burg ME, van Oosterom AT. Complete remission at laparotomy: still a gold standard in ovarian cancer? *Lancet* 1986, **1**, 1028.
7. Dittrich C. *Klonieren von soliden Tumoren. Therapiesimulation, Therapieoptimierung und Prognoseerstellung am Beispiel des Ovarialkarzinoms*. Wien, New York, Springer-Verlag, 1987.
8. Wiltshaw E, Subramarian S, Alexopoulos C, Barker GH. Cancer of the ovary: a summary of experience with *cis*-dichlorodiammineplatinum (II) at the Royal Marsden Hospital. *Cancer Treat Rep* 1979, **63**, 1545–1548.
9. Ozols RF, Corden BJ, Jacob J, Wesley MN, Ostchega Y, Young RC. High-dose cisplatin in hypertonic saline. *Ann Intern Med* 1984, **100**, 19–24.
10. Levin L, Hryniuk WM. Dose intensity analysis of chemotherapy regimens in ovarian carcinoma. *J Clin Oncol* 1987, **5**, 756–767.
11. Ozols RF. Cisplatin dose intensity. *Semin Oncol* 1989, **16**(Suppl. 6), 22–30.
12. Mangioni C, Bolis G, Pecorelli S, *et al.* Randomised trial in advanced ovarian cancer comparing cisplatin and carboplatin. *J Natl Cancer Inst* 1989, **81**, 1464–1471.
13. Piccart MJ, Nogaret JM, Marcelis L, *et al.* Cisplatin combined with carboplatin: a new way of intensification of platinum dose in the treatment of advanced ovarian cancer. *J Natl Cancer Inst* 1990, **82**, 703–707.
14. Lund B, Hansen M, Hansen OP, Hansen HH. High-dose platinum consisting of combined carboplatin and cisplatin in previously untreated ovarian cancer patients with residual disease. *J Clin Oncol* 1989, **7**, 1469–1473.
15. Dittrich C, Sevelda P, Baur M, *et al.* In vitro and in vivo evaluation of the combination of cisplatin and its analogue carboplatin for platinum dose intensification in ovarian carcinoma. *Cancer* 1993, **71**, 3082–3090.
16. International Federation of Gynecology and Obstetrics (FIGO). Changes in definitions of clinical staging for carcinoma of the cervix and ovary. *Am J Obstet Gynecol* 1987, **156**, 263–264.
17. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
18. Stplan. *Calculations for Sample Size and Related Problems*, Version 20, Houston, USA, Department of Biomathematics, The University of Texas MDACC, 1987.
19. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966, **50**, 163–170.
20. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975, **31**, 103–115.
21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc* 1958, **53**, 457–481.
22. Cox DR. Regression models and life-tables. *J R Statist Soc B* 1972, **34**, 187–220.
23. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996, **17**, 343–346.
24. Greco FA, Julian CG, Richardson RL, Burnett L, Hande KR, Oldham RK. Advanced ovarian cancer: brief intensive combination chemotherapy and second-look operation. *Obstet Gynecol* 1981, **58**, 199–205.
25. McGuire WP, Hoskins WJ, Brady MF, *et al.* Assessment of dose-intensive therapy in suboptimally debulked ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 1995, **13**, 1589–1599.
26. Hoskins WJ, McGuire WP, Brady MF, *et al.* The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am J Obstet Gynecol* 1994, **170**, 974–979.
27. Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomised controlled trials: the CONSORT statement. *JAMA* 1996, **276**, 637–639.