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Risks and Benefits of Cisplatin in Ovarian Cancer. A Quality-adjusted Survival Analysis

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Abstract—*Both the efficacy and toxicity of short intensive cisplatin-based chemotherapy was established in an unselected group of patients with stage III–IV ovarian cancer. The impact of this treatment on quality of life (QOL) was assessed by the TWIST index, expressed as Time Without Symptoms of Treatment and Disease, in relation to the individual length of progression free survival (PFS). Sixty-eight patients were treated with six cycles of a combination of cyclophosphamide, Adriamycin® and cisplatin (CAP-5), every 4 weeks. Patients with a clinical response to treatment were evaluated by second look laparotomy (SLL), which could be performed in 52 patients. There were 20 pathological CR, seven microscopic disease, 17 PR and eight SD in these 52 patients. Median follow up at evaluation was 22 months. The median progression free survival (PFS) was 18 months and the median overall survival 22 months. The median duration of TWIST was 10 months, indicating that about 8 months were lost to symptoms due to treatment or hospital admissions for chemotherapy or laparotomy. Of 45 patients receiving six cycles, only eight patients had no symptoms of peripheral neuropathy, and four patients were free of nephropathy at the end of treatment.*

The overall survival for this limited duration of treatment is similar to that after more protracted treatment. Despite its limited duration, however, about 28% of the cumulative period of progression free survival is consumed by the treatment and its side-effects. Correction of PFS by TWIST may be a suitable instrument to compare the impact of different cytotoxic schedules on quality of life.

INTRODUCTION

THERE is little doubt that the survival of patients with ovarian cancer has improved by the combination of debulking surgery followed by chemotherapy. A survival advantage of cisplatin-containing combinations over schemes lacking this drug has been found [1–4]. However, the price for this advantage is the side-effects inherent to cisplatin, like protracted nausea, malaise and peripheral neuropathy. The place of less toxic cisplatin analogs like carboplatin in ovarian cancer is not yet quite settled.

The following study will try to establish the efficacy of a short induction treatment with three cycles of CAP-5 after optimal debulking followed by restaging and a limited number of three further consolidation courses. This approach was chosen with the intent to minimize eventual side-effects, maintaining an optimal cytotoxic effect. The efficacy of this treatment in relation to prognostic parameters is reported. The toxicity of the treatment was the second subject of study. We tried to measure the effect of cisplatin-based therapy on the individual quality of life by a modification of TWIST [5], the Time Without Symptoms of Treatment and Disease, subtracting the duration of all admissions and of disabling symptoms from the individual progression free survival. Furthermore, the ratio between TWIST and progression free survival, the TWIST index, indicates the impact of treatment on the time gained by the patient as a measure of her quality of life.

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PATIENTS AND METHODS

Sixty-eight patients, median age 52 years, range 29–69 years, with carcinoma of the ovary were entered in the study. They were all treated and evaluated at the University Hospital Groningen between 1 April 1981 and 1 June 1987, the final evaluation was 1 August 1988. The initial treatment was optimal tumor reductive surgery. Forty-two patients underwent a laparotomy in the referring

hospital, 36 could be debulked, in the other six optimal debulking was not possible. Of the 26 patients operated at the University Hospital, in 21 optimal debulking could be done, while five only had tumor biopsies.

All patients were staged according to the International Federation of Obstetrics and Gynecology (FIGO) classification. The bulk of residual disease was defined as the largest diameter in centimeters with the following classification; no macroscopic disease, residual tumor smaller than 2 cm, residual tumor from 2 to 5 cm, or residual disease over 5 cm in diameter.

The entry criteria were patients with ovarian cancer, FIGO stage IC, IIC, III and IV under 70 years of age. Excluded were patients with a WHO performance score of 3 or 4, creatinine clearance below 90 ml/min, bilirubin over 35 μmol/l, overt cardiac failure, infectious foci, or a second malignancy.

Combination chemotherapy was initiated with a median of 3 weeks (range 2–6 weeks) after laparotomy, and consisted of a combination of cisplatin (P) 100 mg/m^2 intravenously, divided over 5 days with adequate hydration, Adriamycin® (A) 35 mg/m^2, and cyclophosphamide (C) 500 mg/m^2 intravenously on day 1, at 28-day intervals. All patients received six cycles of combination chemotherapy, unless the tumor response after three cycles was insufficient or when WHO grade III nephro- or neuropathy occurred.

The drug dose was modified according to the following rules: There was no dose reduction for nadir blood cell counts. Full dosage was given when WBC were above 3.0×10^9/l and platelets over 100×10^9/l. For WBC $2.0–3.0 \times 10^9$/l or platelets $75–100 \times 10^9$/l, Adriamycin® and cyclophosphamide were reduced to 75% with full dose cisplatin. When WBC were below 2.0×10^9/l or platelets below 75×10^9/l, the next cycle was delayed 1 week. When delay exceeded 4 weeks, the patient went off study. Cisplatin dosage was reduced to 50% for severe neuropathy (WHO grade 2) or when creatinine clearance decreased below 60 ml/min. Neuropathy grade 3 or creatinine clearance below 30 ml/min meant discontinuation of cisplatin. The occurrence of nephropathy was graded according to WHO criteria, using the patient's own baseline values of creatinine to calculate an increase over 1.25 (grade 1) or 2.5 (grade 2). Neuropathy was graded by a neuro-oncologist.

Evaluation relaparotomy was planned after three cycles of combination chemotherapy only in patients with a clinical response and could be performed in 52 patients. The tumor response was classified according to WHO criteria. Complete response was always histologically verified by taking multiple biopsies from former tumor sites or likely sites of metastases and by cytology of peritoneal washings.

After chemotherapy and surgery all patients were followed during the first year on a 6 weekly basis, and 3 monthly thereafter. No patient was lost to follow-up during the study period.

The probability of progression free and overall survival were calculated by a log-rank test according to Kaplan–Meyer in months from the first laparotomy, and the influence of pre-existent or postoperative tumor load, tumor stage and tumor differentiation was compared by chi-square analysis.

TWIST

The toxicity of cisplatin-based chemotherapy can be divided into organ-directed toxicity, which does not have an immediate or perceivable effect on the patient's well being, and into more or less severely disabling symptoms, influencing the patient's quality of life during and after treatment. The first may comprise myelo- and nephrotoxicity, the second all usual sequelae of cytostatic treatment like loss of appetite, taste, nausea, vomiting, weakness, general malaise and psychological depression. The cisplatin-induced neuropathy is superposed on these effects.

TWIST, the Time Without Symptoms of Treatment and Disease, was calculated in the following way. All time consumed by hospital admission was subtracted from the period of progression free survival (PFS). This included admissions for treatment as well as complications such as septic fever, blood or platelet transfusions and first and second look laparotomy. For every outpatient visit one additional day was counted. All days the patients had untoward symptoms of the treatment, like general malaise, loss of appetite, nausea, weakness, fatigue or anemic symptoms between admissions were scored at the moment of admission for every cycle of chemotherapy and (an arbitrarily chosen) 50% of the duration of this symptomatic period was subtracted from PFS. The main symptoms remaining after completion of chemotherapy were those of peripheral neuropathy. The burden imposed on the patient was calculated and quantified as follows: For grade 2–3 (but not for grade 1) neuropathy remaining after treatment, again arbitrarily 50% of the period with these symptoms was deducted from the PFS. Thus, half the period with side-effects from the treatment or its complications was subtracted from the progression free survival. This way, there remained a period of 'Time Without Symptoms of Treatment and Disease' (TWIST) as a parameter of quality of life, expressed in months free of symptoms which were gained by treatment. PFS was chosen instead of the overall survival, to exclude the period of symptoms arising from tumor relapse. Finally, the symptom free period of TWIST was divided by PFS, to arrive at a TWIST/PFS ratio, relating the time consumed by

symptoms to time gained by the treatment, as a kind of cost/benefit ratio.

RESULTS

Efficacy

Sixty-eight patients were entered in the study. Optimal debulking resulted in tumor residuals smaller than 2 cm in 30 patients, and residuals over 2 cm in 38 patients (Table 1). All patients were treated with three cycles of CAP-5 and were then re-evaluated.

Fifty-two patients were considered to be in partial or complete remission clinically and could be surgically evaluated (Table 1). Twenty had achieved a pathological complete remission, seven had microscopic disease, 17 a partial remission and eight patients were stable.

Sixteen patients did not have a second look procedure. One patient had a cerebrovascular accident and died, five had clinical progressive disease and four, with large residuals initially, were stable. Three patients refused a second look, one had a partial and two a clinical complete remission. Three patients with microscopic disease were not surgically re-evaluated.

Twenty-three patients did not receive six treatment cycles. In five patients with progressive disease treatment was stopped after three cycles, and five patients with stable disease but bulky residuals became progressive over the last three cycles. Four patients stopped for persistent myelosuppression, four stopped for grade III neuro- and/or nephropathy, and four refused further treatment after second look. One patient died of a CVA after four cycles.

An analysis of the remission by tumor load is outlined in Table 2.

The median follow-up is 22 months. The median progression free interval was 18 months, with a range of 0–77+ months. The median overall survival was 22 months, with a range of 3–77+ months. Stratification for tumor load is illustrated in Fig. 1. The overall survival curves according to tumor response are shown in Fig. 2.

Table 1. Analysis of tumor response at second look laparotomy

	CR	pCR	MD	PR	SD	PD	NE	Total
Tumor residuals after primary laparotomy								
No macroscopic	3	8	—	—	4	—	1	16
<2 cm	2	7	1	3	1	—	—	14
>2 cm		5	4	15	9	5	—	38
Total	5	20	7	18	12	5	1	68
Percentage	7	30	10	27	18	7	2	100
Pathological confirmation after surgery	—	20	7	17	8	—	—	52

CR = clinical complete remission; pCR = pathological complete remission; MD = microscopic disease; PR = partial remission; SD = stable disease; PD = progressive disease; NE = not evaluable.

Table 2. Dose reduction and treatment delays resulting from myelo-, nephro- and neurotoxicity

	No. of patients (%)	No. of cycles (%)
Total number	23 (37%)	351
Dose reduction of cyclophosphamide and Adriamycin®	11 (16%)	19 (6%)
Dose reduction of cisplatin		
for nephrotoxicity	3* (6%)	4
for neurotoxicity	4 (8%)	4
Delay in administration	11 (16%)	31 (9%)
1 week		12
2 weeks		13
3 weeks		6
≥4 weeks (off study)	4† (6%)	4
Additional admission for fever or thrombocyte transfusion	12 (18%)	19 (6%)

*All three patients also had grade III neurotoxicity.
†All four patients had treatment delays on earlier occasions.

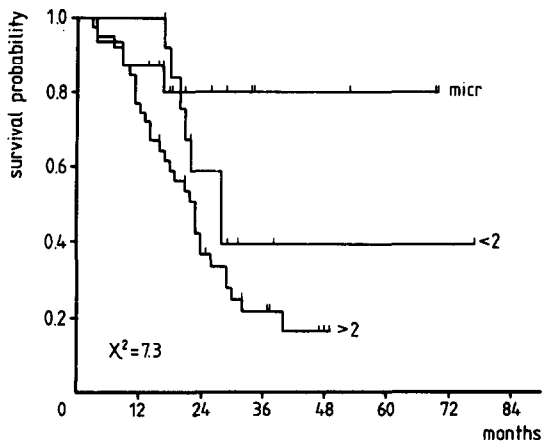

Fig. 1. Survival probability according to tumor residuals after maximal debulking.

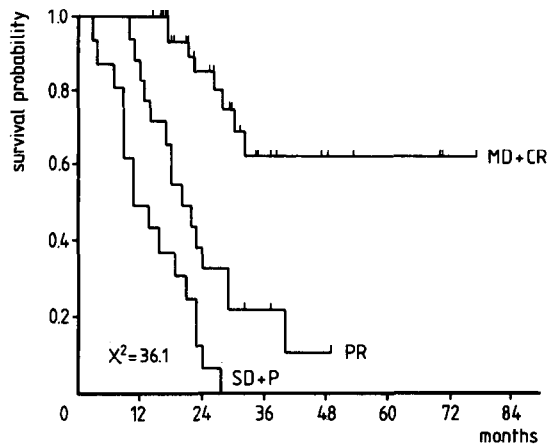

Fig. 2. Survival probability according to tumor response at second look laparotomy.

Table 3. WHO grade of neurotoxicity occurring after each treatment cycle

WHO grade/after cycle No.	1	2	3	4	5	6
0	68	64	54	27	16	8
1		3	12	25	25	27
2		1	3	4	7	15
3			1*	3*	3	7
Total	68	67	67	56	48	45

*Stopped for neurotoxicity.

Toxicity

In 26 patients (38%) insufficient bone marrow recovery caused a delay in the administration of chemotherapy in 35 cycles, on a total of 351 cycles given (10%) (Table 2). This lasted 1 week (12 cycles), 2 weeks (13 cycles) and 3 weeks (six cycles). Four patients went off study for a delay of 4 weeks or more. Twelve patients had to be readmitted for fever or platelet transfusion on 19 occasions.

Neurotoxicity was classified according to the WHO criteria (Table 3). After termination of the 6th cycle, completed by 45 patients, only eight patients (18%) were free from neurological symptoms and 10 (22%) had severe (grade 2 or 3) peripheral neuropathy. The other 27 patients (60%), who completed six cycles of combination chemotherapy, developed mild paresthesiae of fingers and toes during the courses of chemotherapy, but no patient suffered from WHO grade 4 neurotoxicity. In four patients chemotherapy had to be stopped for progressive neurotoxicity.

A rise of serum creatinine level was noted in nearly all patients; from a median of 65 μmol/l to a median of 99 μmol/l 4 weeks after termination of the 6th cycle of the CAP-5 regimen (Fig. 3). In Table 4 the steady increase in the serum creatinine level is outlined. The creatinine clearance decreased

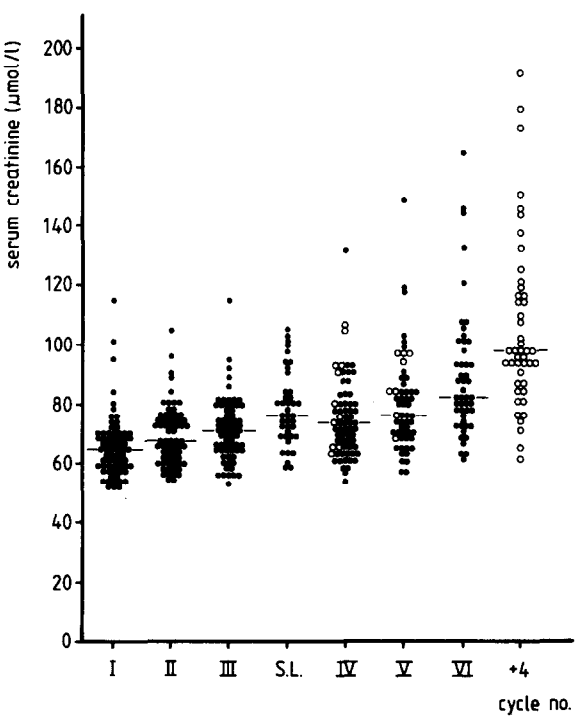

Fig. 3. Serum creatinine in patients during treatment with CAP-5. The mean values for every cycle and before the second look (S.L.) are indicated. Patients who stopped treatment are separately indicated (O), the median values are indicated.

Table 4. WHO grade of nephrotoxicity at the start of each treatment cycle*

WHO grade/after cycle No.	1	2	3	4	5	6	+1
0	68	64	61	42	26	14	4
1		3	6	14	22	31	39
2							2
Total	68	67	67	56	48	45	45

*Grade 0 = less than 1.25 times the individual base-line creatinine (BC); grade 1 = 1.26–2.5 × BC; grade 2 = 2.6–5.0 × BC. +1 gives the WHO grade 1 month after completing the last (sixth) cycle.

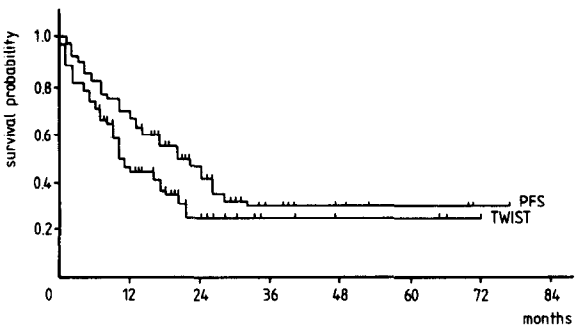

Fig. 4. Overall progression free survival and PFS corrected for TWIST.

from a median of 94 ml/min (range 46–140 ml/min) before the first cycle of combination chemotherapy to a median of 62 ml/min (range 20–125 ml/min) the day before the last cycle of combination chemotherapy. In this study no patient developed WHO grade 3 renal failure, but in three patients cisplatin dosage was reduced for nephrotoxicity, and four patients were taken off study for combined nephro- and neuropathy.

TWIST

A comparison between the progression free survival (PFS) and the progression free survival corrected for TWIST is given in Fig. 4. The median duration of TWIST amounts to 10 months, which is about 8 months less than the median PFS. Expressed in cumulative patient-months, the PFS amounts to 1448+ patient-months (120.7 patient-years) and corrected for TWIST 1036+ patient-months (86.3 patient-years or 72% of PFS). At the time of analysis, 25 patients are still free of progression, which will in the future cause a relative increase of the value for TWIST. When the duration and impact of side-effects are calculated in this way at this moment, however, 412 patient-months or 28% of the time of progression free survival studied is taken up by untoward symptoms caused by the treatment. The TWIST/PFS ratio can be calculated from the PFS curve, in relation to the survival time. This ratio consistently exceeds 50% after 20 months of follow-up (Fig. 5). Of 68 patients, 24 have a ratio of 50% or lower, indicating that in 32% of all patients the symptom-free time gained by the patient does not exceed the time consumed by the treatment and its symptoms. Calculated for subgroups, patients starting treatment with microscopic disease stand a 80% chance of approaching a 100% ratio, patients with residual disease under 2 cm 40% and over 2 cm only 20% (Fig. 1).

DISCUSSION

Treatment efficacy

In treating patients with disseminated ovarian cancer, we have chosen an approach aiming at a short, intensive induction treatment, followed by a second look and three consolidation cycles thereafter. This limited treatment duration seems to produce survival figures comparable to those of more prolonged treatment [6, 7].

Patients with microscopic residuals seem to do best, which is also reflected by the results in patients with stage I and IIC in this study. Of patients with tumor residuals over 2 cm or with disease outside the peritoneal cavity (stage IV), only a minority reaches a survival over 36 months.

The overall results of this study appear to be comparable with other reports employing cisplatin-based chemotherapy [8, 9]. The limited duration of treatment does not seem to lead to an unacceptable fall in overall survival, nor has this been reported by others [6, 7]. The effect of the duration of treatment on survival has recently been studied in a randomized fashion, with similar survival in patients treated for 6, 9 or 12 months with the same cisplatin-containing schedule [19, 20].

Myelotoxicity

Higher drug dosages and longer treatment duration have been used in other studies, but the actual amounts of drug given, the dose reduction and

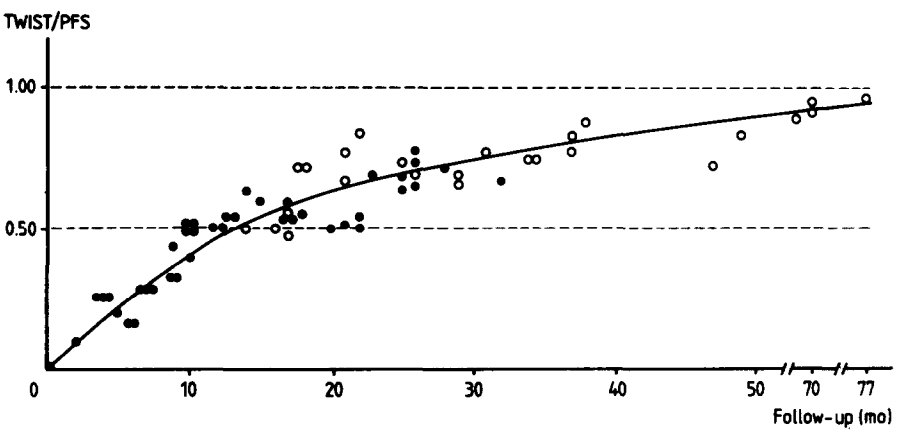

Fig. 5. The TWIST/PFS ratio expressed as a function of follow-up time. ●: Patients with a tumor relapse; ○: patients still surviving progression free.

treatment delay may differ a great deal from the projected treatment, and is not always extensively reported. The treatment delays and dose reduction, respectively 9 and 6% of cycles in this study, seem low in view of other reports stating 100% delay or reduction in the last cycle for other drug combinations [9]. Delay of treatment will have an impact on the measurement of TWIST, by increasing the days with symptoms between treatment cycles.

Nephrotoxicity

Severe renal disturbance occurred in three patients leading to dose reduction. Termination of cytostatic therapy was necessary in three cases.

This kind of toxicity will have no great impact on TWIST unless of course PFS is markedly reduced by an early abrogation of cytostatic treatment as a result of renal toxicity.

Neurotoxicity

The neurotoxicity of cisplatin, which occurred in most cases after completing cytostatic treatment, has a profound effect on the patient's well being. Only 18% of our patients were free of these symptoms after receiving six cycles, while 30% had some motoric dysfunction. This may, but does not always, recover after a number of months.

Grade 2–3 neuropathy has a profound impact on the calculation of TWIST, as these symptoms put a great strain on the patient. The quality of survival is influenced greatly, as the symptoms may last for months or even years. In our view, discounting half the symptomatic period is not exaggerated in the calculation of TWIST.

Time without symptoms of treatment and disease

We have tried to quantify disabling toxicity by measuring the cumulative time spent by the patient without symptoms of treatment or disease, the TWIST. This should give an approximation of the time gained by the patient which is not 'spoiled' by the presence of unpleasant symptoms or hospital admissions. Renal or myelotoxicities, which can easily be measured objectively, do not infer much strain on the patient as long as they do not result in symptoms of anemia or in additional admissions for blood and platelet transfusions or septic fever, which were counted in the calculation of TWIST.

The scoring of subjective toxicity measured as a function of time has earlier been reported in the evaluation of adjuvant treatment of breast cancer [5, 18]. We have chosen to avoid a quantification of the symptoms in view of its variability and subjective interpretation. The quantification by the patient herself, e.g. by repeated questionnaires according to a linear analog scale self assessment score (LASA) or a functional living index (FLIC) [10, 11], may be very variable and may diverge from the actual situation [12]. It will depend a great deal on the patient's actual condition, her mood and prospects and the extent of psychological support received. Patients are reported to overestimate their actual physical conditions and deny symptoms indicating deterioration, while repeated data collection tends to get more difficult over time [12]. In this study, the duration of untoward symptoms was stated by the patient at each visit or admission, which enabled an estimate of their duration and impact on her general well being and their influence on quality of life in the individual patient.

In the calculation of TWIST, the time consumed by all admissions (e.g. for chemotherapy, transfusions, or primary and second look laparotomy), was subtracted from RFS. During treatment with cisplatin-containing regimens, general malaise, loss of appetite and change in taste may have profound effects on the patient's condition and sense of well being. The negative impact of these side-effects on the quality of life experienced by the individual is not negligible. This prompted us to subtract 50% of the whole period of time during which the patient was symptomatic from the duration of PFS. The choice to calculate 50% as 'time lost' must evidently be arbitrary; in the future it might be possible to define a more refined estimate of individual symptoms. For the impact of neurologic symptoms on TWIST we have again chosen to subtract half the symptomatic period, which for grade 3 neuropathy might even be unrealistic in view of its profound effect on the patient's well being. In this way, an indication can be obtained of the time consumed by the symptoms resulting from cytotoxic therapy, deducting it from the time gained by instituting this therapy. A kind of cost/benefit ratio thus can be obtained, which relates the period of good quality of life gained by treatment to the period of PFS: the TWIST/PFS 'index'. For certain prognostic subgroups an estimate can then be made if the duration and severity of treatment is outweighed by the symptom-free survival gained by the patient, expressed as the TWIST/PFS ratio, which in our view should preferably be above 50%. Thus, it can be estimated if a certain treatment will be worthwhile for patients in a particular prognostic subgroup. In this manner, we should be able to withhold too demanding a treatment from patients who will not be able to enjoy its benefit, and in whom a milder therapeutic approach would be preferable. Moreover, when it is calculated in this way, TWIST may provide a more or less objective means to compare the strains imposed by different chemotherapy combinations on the same patient population.

The period of TWIST was related to the period of progression free survival and not to the overall survival. This was chosen to exclude the period of

tumor relapse with its inherent doubts and fears and varying symptoms occurring from tumor relapse and its complications.

In the future some types of toxicity may be prevented by specific measures. It may well be that duration of leukopenia and sepsis can be prevented by the use of lymphokines like GM-CSF [17]. Cisplatin nephropathy may be ameliorated by the use of certain thiol compounds like sodium thiosulfate [13] and disabling neuropathy may occur later when thiols are used [14]. Recently, the use of an ACTH(μ–g) analog has been found to delay the occurrence of platinum-induced peripheral neuropathy [15]. The advent of more effective antiemetics such as the serotonin receptor antagonists may well be a major advance in improving quality of life [16]. By these specific measures it may be possible to prevent some of these side-effects and improve the patient's well being and quality of her survival, which then can be quantified by measuring TWIST.

The substitution of cisplatin by a less toxic analog like carboplatin will prevent the neuro- and nephrotoxicity at the cost of greater myelosuppression. The efficacy of carboplatin in ovarian cancer may even be comparable to that of cisplatin, but this issue is not quite settled at present [21, 22].

Evaluation of the role of an early surgical evaluation was not the main objective of this study. We have studied this issue in a separate paper [23]. The main conclusions of that study were that early second look laparotomy is of minimal therapeutic importance, as optimal debulking is possible only in exceptional cases, and thus second look laparotomy mainly has a negative impact on quality of life and TWIST. Generally, second look laparotomy should only be performed if it is of consequence for the choice of further treatment, or in a research setting.

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