Adjuvant chemotherapy with carboplatin and taxane compared with single drug carboplatin in early stage epithelial ovarian carcinoma

INGIRÍDUR SKÍRNISDÓTTIR[1], KATARINA LINDBORG[1] and BENGT SORBE[2]

[1]Department of Women's and Children's Health, Obstetrics and Gynecology, University Hospital, Uppsala;
[2]Department of Gynecological Oncology, Örebro University Hospital, Örebro, Sweden

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Abstract. The objective of the present study was to compare recurrence-free survival (RFS) in early stages (FIGO stages I-II) of epithelial ovarian cancer after adjuvant chemotherapy with carboplatin and a taxane (113 patients) and with carboplatin alone (27 patients). The distribution of clinical and pathological prognostic factors as well as type of primary surgery were comparable in the two groups. Recurrence rate was 21% and RFS was 79% in the series of patients treated with taxane-based chemotherapy and 19% and 81%, respectively, in the series of patients who received single drug carboplatin. Thus, no significant differences were recorded. The major toxicities in the present study were myelosuppression (46%) and neuro-toxicity (26%). Neuro-toxicity was more frequently (P=0.007) recorded and of higher grade (P=0.011) for patients in the carboplatin-taxane series compared with patients in the carboplatin series. RFS for patients in FIGO-stage I was 85% and for patients in FIGO-stage II only 47%. In a multivariate logistic regression analysis of predictive factors for tumor recurrence in the complete series (n=140) the FIGO stage was the only independent and significant (P=0.0006) predictive factor with an odds ratio of 6.4 (95% CI: 2.2-18.9) for stage II versus IA-C. Age, tumor grade and type of adjuvant chemo-therapy (± taxane) were not significant predictive factors. In the present study, although based on a limited number of patients, we could not find any improvement in recurrence rate or recurrence-free survival for patients treated with a carboplatin-taxane combination regimen compared with patients treated with carboplatin monotherapy. The spectrum of side effects was also in favor of the monotherapy regimen. Further, larger randomized studies are needed to give a final and fully conclusive answer to this question.

Correspondence to: Dr Ingirídur Skírnisdóttir, Department of Women's and Children's Health, Obstetrics and Gynecology, University Hospital, Akademiska sjukhuset, SE-751 85 Uppsala, Sweden
E-mail: ingiridur.skirnisdottir@kbh.uu.se

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Introduction

At diagnosis <30% of women with epithelial ovarian cancer (EOC) have early-stage (FIGO I-II) disease. In the early stages, 10-50% of patients who receive adjuvant treatment after the primary surgery will have a recurrence. The high recurrence rate explains the many attempts to use different types of adjuvant therapy (1). Platinum-based adjuvant chemotherapy seems to be effective in treatment of occult residual tumor in supposed early stage ovarian cancer after non-optimal surgical staging (EORTC-ACTION and ICON1 trials). However, for optimally staged patients, the ACTION trial suggests that adjuvant chemotherapy is of doubtful benefit (2,3). In these EORTC-ACTION/ICON1 trials the recurrence rate was 24% for patients treated with platinum-based chemo-therapy versus 35% in the no-treatment arm (4,5). Ideally, a new randomized trial in non-optimally staged patients could answer the question of whether the recurrence rate could be improved for the non-optimally staged patients by comparing restaging with adjuvant chemotherapy. However, randomized trials are difficult to perform in the patients with early-stage ovarian cancer due to the small patient population, an imprecise surgical staging, and the relatively good prognosis (6-8).

To date, only the FIGO substage and the tumor grade have been identified as reliable and useful predictive factors for identifying women at high risk of recurrence after primary surgery (9,10). In patients with ovarian cancer, carboplatin has been demonstrated to be one of the most useful and well-tolerated cytotoxic agents available, especially because of its relative lack of nephrotoxicity and neurotoxicity (11). Based upon data from two other studies, GOG (Gynecologic Oncology Group) chose the standard chemotherapy with the combination of carboplatin and paclitaxel used for advanced ovarian cancer for a randomized phase III trial of three versus six cycles of adjuvant carboplatin-paclitaxel in early stage epithelial ovarian cancer (GOG 175) (12-14). In this study, it was concluded that compared to 3 cycles, 6 cycles of carboplatin and paclitaxel did not significantly change the

recurrence rate in high-risk early stage EOC, but were associated with more toxicity (14).

In the present study of early stage epithelial ovarian cancer, the outcome (recurrence rate and recurrence-free survival) after adjuvant chemotherapy with a taxane and carboplatin versus single drug carboplatin was compared and treatment related toxicity was evaluated and compared for the two chemotherapy regimens.

Patients and methods

Patients. A total of 140 patients with FIGO-stage I-II epithelial ovarian cancer, who underwent primary surgery and adjuvant chemotherapy in the Örebro-Uppsala Medical Region during the 5-year period from January 1, 2000 to December 31, 2004, were entered into this study. The total series consisted of 113 patients who received carboplatin-taxane chemotherapy in the Örebro-Uppsala Medical Region and of 27 patients who underwent single drug carboplatin (AUC=7) chemotherapy in the Uppsala Medical Region. The records were reviewed for clinical and pathological data of each patient. Patient characteristics, e.g. age, performance status (WHO), FIGO-stage, histology, and FIGO-grade are presented in Table I. The FIGO grading system cannot normally be applied to clear cell carcinomas and was therefore excluded from grading by the FIGO (15) and WHO (16) classification systems.

Surgery. The primary surgery was performed at nine different gynecological departments and the staging procedure was done at the time of the primary surgery. The standard surgical procedure included abdominal exploration through a midline incision, pelvic and abdominal washings, manual exploration of all serosal surfaces with multiple peritoneal biopsies, total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy and appendectomy. Pelvic lymph node sampling or lymphadenectomy, mostly without paraaortic node dissection, was included in the standard surgical procedure at three of the gynecological departments. Thus, modified surgical staging according to the EORTC surgical staging categories in early ovarian cancer (3) was undertaken in 38 (27%) out of the 140 women, and in the remaining 102 (73%) patients surgical staging was regarded as minimal or inadequate according to the same guidelines.

Postoperative chemotherapy and follow-up. All patients in the study met the criteria of WHO performance status ≤2 and of adequate function of bone marrow and kidney. The median time between primary surgery and the first course of chemotherapy in the complete series of 140 patients was 40 days (range: 12-125 days). In the taxane series 4 courses of paclitaxel 175 mg/m^2 and carboplatin (AUC=5) at 3-week intervals was the standard treatment. However, 6 patients received docetaxel 60 mg/m^2 and carboplatin (AUC=5), and 4 patients received paclitaxel 175 mg/m^2, epirubicin 75 mg/m^2 and carboplatin (AUC=5). The majority of the patients (n=81) received 4 courses of taxane-carboplatin. However, 3 patients had only one course of taxane because of severe hypersensitivity reactions, 2 patients received 2 courses, one patient had 3 courses, 4 patients received 5 courses and 16 patients underwent 6 courses of taxane-carboplatin. Finally, 2 patients received 8 courses and one patient received 9 courses of taxane-carboplatin. All patients who underwent less than 4 courses of taxane continued chemotherapy with carboplatin (AUC=6-7) at least up to 4 courses. The mean dose given in the study of taxane was 289 mg and of carboplatin 615 mg. The median interval between the first and the last course was 65 days. The median follow-up time for patients alive was 48 months (range 19-76 months).

Table I. Patient and tumor characteristics (n=140).

Age (mean)	59.7 years (range 25-84 years)	
WHO performance status		
0	124	(88.6%)
1	16	(11.4%)
FIGO-stage		
IA	44	(31.4%)
IB	6	(4.3%)
IC	69	(49.3%)
IIA	2	(1.4%)
IIB	1	(0.7%)
IIC	18	(12.9%)
Histopathology		
Serous	53	(37.9%)
Mucinous	23	(16.4%)
Endometrioid	43	(30.7%)
Clear cell[a]	19	(13.6%)
Anaplastic	2	(1.4%)
FIGO-grade		
Grade 1	35	(25.0%)
Grade 2	44	(31.4%)
Grade 3	42	(30.0%)
Not graded[a]	19	(13.6%)

[a]Clear cell carcinomas were not graded.

In the parallel carboplatin series of 27 patients the standard treatment given was single drug carboplatin (AUC=7) with 4 courses at 3-week intervals. Thus, 19 patients received 4 courses, 2 patients 5 courses, 5 patients 6 courses and one patient was treated with 7 courses. The mean dose given of carboplatin was 589 mg (range: 325-875 mg). The median interval between the first and the last course was 84 days. The median follow-up time for patients alive was 39 months (range: 20-67 months).

Statistical analyses. The Pearson's Chi-square test was used for testing proportional differences in univariate analyses. The survival curves were generated by using the Kaplan-Meier technique (17), and differences between these curves were tested by the log-rank test. For multivariate analyses the logistic regression model was used with recurrence as the end point. All tests were two-sided and the level of statistical significance was $P \leq 0.05$. The Statistica 7.0 (StatSoft™) statistical package for personal computers was used for the analyses.

Table II. FIGO stages versus clinicopathological features (n=140).

FIGO stages	IA No (%) 44 (31)	IB No (%) 6 (4)	IC No (%) 69 (49)	IIA No (%) 2 (1)	IIB No (%) 1 (1)	IIC No (%) 18 (13)
Histopathology						
Serous	10 (23)	4 (67)	32 (46)	0	1 (100)	6 (33)
Mucinous	17 (39)	0	4 (6)	0	0	2 (11)
Endometrioid	12 (27)	2 (33)	21 (30)	2 (100)	0	6 (33)
Clear cell	4 (9)	0	12 (17)	0	0	3 (17)
Anaplastic	1 (2)	0	0	0	0	1 (6)
						P=0.012[a]
Tumor grade						
G1	17 (43)	1 (17)	16 (28)	0	0	1 (7)
G2	16 (40)	1 (17)	23 (40)	1 (50)	0	3 (20)
G3	7 (18)	4 (67)	18 (32)	1 (50)	1 (100)	11 (73)
						P=0.015[a]
Nineteen clear cell carcinomas were not graded						
Recurrences						
Recurrence	4 (9)	2 (33)	11 (16)	0	1 (100)	11 (61)
No recurrence	40 (91)	4 (67)	58 (84)	2 (100)	0	7 (39)
						P=0.00005[a]

[a]Pearson Chi-square test.

Table III. Recurrences versus clinicopathological factors (n=140).

	Patients with recurrent disease n=29 (20.7%)	Patients without recurrent disease n=111 (79.3%)	P-value
Age (mean)	62.8 years	58.8 years	0.137[a]
FIGO-stage			
Stage IA	4 (13.8%)	40 (36.0%)	
Stage IB	2 (6.9%)	4 (3.6%)	
Stage IC	11 (37.9%)	58 (52.3%)	
Stage IIA	0	2 (1.8%)	
Stage IIB	1 (3.5%)	0	
Stage IIC	11 (37.9%)	7 (6.3%)	0.00005[b]
Histology			
Serous	13 (44.8%)	40 (36.0%)	
Mucinous	4 (13.8%)	19 (17.1%)	
Endometrioid	9 (31.0%)	34 (30.6%)	
Clear cell	3 (10.3%)	16 (14.4%)	
Anaplastic	0	2 (1.8%)	0.839[b]
Tumor grade			
G1	4 (15.4%)	31 (32.6%)	
G2	8 (30.8%)	36 (37.9%)	
G3	14 (53.9 %)	28 (29.5%)	0.021[b]
Nineteen clear cell carcinomas were not graded			
Node sampling status			
Node sampling	5 (17.2%)	33 (29.7%)	
No node sampling	24 (82.8%)	78 (70.3%)	0.178[b]

[a]Student's t-test; [b]Person Chi-square test.

Results

C*linical outcome*. The recurrence rate of the complete series of 140 patients with early stage epithelial ovarian cancer after primary surgical staging and adjuvant chemotherapy was 21% and the 5-year recurrence-free survival was 80%. The 5-year recurrence-free survival (RFS) rate for all 113 patients with ovarian cancer receiving adjuvant chemotherapy carboplatin-taxane after primary surgery was 79% and for the 27 patients receiving adjuvant chemotherapy with single drug carboplatin was 81%. The recurrence rate was 21% and 19% for the series of 113 patients with taxane-based chemotherapy and for the 27 patients with single drug carboplatin, respectively. However, the median time of follow-up for the patients treated with carboplatin-taxane was 48 months and for the patients treated with single-drug carboplatin 39 months. The recurrence rate for clear cell carcinomas was only 10% and the recurrence-free survival was 84%.

Clinicopathological features. In the complete series of 140 patients, histopathology, tumor grade and recurrent disease were all related to the FIGO stages (Table II). Thus, 17 out of the 23 (74%) mucinous tumors were in stage IA, and 15 out of the 19 (79%) clear cell tumors belonged to tumor stages IC or IIC. For tumor grade it was noted that 13 out of the 21 (62%) stage II tumors were poorly differentiated compared to 39 out of 119 (33%) tumors in stage I. Furthermore, for the 21 tumors in stage II, all grades, the recurrence rate was 57% compared to 15% for the 119 tumor in stage I. The recurrence rate of tumors in stage IIC, all grades, was 61%. None of the patients in the series had evidence of disease (NED) after primary surgery and adjuvant chemotherapy.

Recurrent disease. Recurrent disease was recorded in 29 out of the 140 patients (21%) and the median time to recurrence was 19 months (range: 3-72). Fourteen patients died of their disease and 15 patients were still alive. Four patients (two in stage IA and two in stage IC) succumbed due to other diseases without recurrence. Site of recurrence was in the pelvic and/or the abdominal cavities in 15 out of the 29 patients (52%), and distant metastases were detected in 6 patients (21%). Eight patients (27%) had disseminated disease. In univariate analyses recurrent disease was associated with both FIGO-stage and tumor grade (Table III). The most striking finding was 12 recurrences among the 21 stage II patients (57%) compared to 6 recurrences among the 50 patients (12%) with stage IA-B disease. Furthermore, recurrent disease was recorded in 14 out of the 42 patients (33%) with poorly differentiated tumors compared to 4 out of 35 patients (11%) diagnosed with well-differentiated tumors. Recurrent disease was not associated

Table IV. Type of chemotherapy versus clinicopathological factors (n=140).

	Patients treated with carboplatin + taxane n=113 (80.7%)	Patients treated with carboplatin single-drug n=27 (19.3%)	P-value
Age (mean)	58.7 years	63.7 years	0.088
FIGO-stage			
Stage IA	35 (31.0%)	9 (33.3%)	
Stage IB	5 (4.4%)	1 (3.7%)	
Stage IC	55 (48.7%)	14 (51.9%)	
Stage IIA	2 (1.8%)	0	
Stage IIB	1 (0.9%)	0	
Stage IIC	15 (13.3%)	3 (11.1%)	0.970[a]
Histology			
Serous	43 (38.1%)	10 (37.0%)	
Mucinous	20 (17.7%)	3 (11.1%)	
Endometrioid	33 (29.2%)	10 (37.0%)	
Clear cell	15 (13.3%)	4 (14.8%)	
Anaplastic	2 (1.8%)	0	0.821[a]
Tumor grade			
G1	32 (32.7%)	3 (13.0%)	
G2	31 (31.6%)	13 (56.2%)	
G3	35 (35.7%)	7 (30.4%)	0.055[a]
Nineteen clear cell carcinomas were not graded			
Node sampling status			
Node sampling	34 (30.1%)	4 (14.8%)	
No node sampling	79 (69.9%)	23 (85.2%)	0.109[a]
Recurrences			
No recurrence	89 (78.8%)	22 (81.5%)	
Recurrence	24 (21.2%)	5 (18.5%)	0.754[a]

[a]Person Chi-square test.

Table V. Treatment-related adverse events versus type of chemotherapy (n=140).

	Patients treated with carboplatin + taxane n=113 (80.7%)	Patients treated with carboplatin single-drug n=27 (19.3%)	P-value
Dose reduction			
Reduction	20 (17.7%)	3 (11.1%)	
No reduction	93 (82.3%)	24 (88.9%)	0.407[a]
Myelosuppression			
Yes	52 (46.0%)	12 (44.4%)	
No	61 (54.0%)	15 (55.6%)	0.883[a]
Myelosuppression Grade			
G1	26 (23.0%)	6 (22.2%)	
G2	16 (14.2%)	6 (22.2%)	
G3	8 (7.1%)	0	
G4	2 (1.8%)	0	0.508[a]
Neurotoxicity			
Yes	38 (33.6%)	2 (7.4%)	
No	75 (66.4%)	25 (92.6%)	0.007[a]
Neurotoxicity Grade			
G1	29 (25.7%)	0	
G2	9 (8.0%)	2 (7.4%)	0.011[a]

[a]Person Chi-square test.

with age, histological type or status of node-sampling (Table III). Recurrent disease in univariate analyses was not associated with ascitic fluid (P=0.793), malignant cells in ascitic fluid or peritoneal washings (P=0.801) or with cyst rupture (P=0.484) at the surgical staging laparotomy. On the other hand, recurrent disease was associated with preoperative cyst rupture (P=0.021), where 4 recurrences were recorded among the 7 tumors (57%) with preoperative rupture compared to 8 recurrences among the 45 tumors (8%) with intra-operative cyst rupture.

Clinicopathological factors versus type of chemotherapy. The distribution of the clinicopathological factors (Table IV) with regard to the type of chemotherapy was comparable in the two treatment groups (113 patients in the carboplatin-taxane series and 27 patients in the carboplatin series). Thus, no differences were found for FIGO-stage, histology, grade, node sampling status or recurrences for the two groups with different types of chemotherapy. There was a trend for older patients in the carboplatin series, but the difference was not statistically significant (P=0.088). There was also a trend for more grade 1-2 tumors in the carboplatin group when compared with the carboplatin-taxane series. However, the poorly differentiated tumors (grade 3) were rather equally represented in the tumors in the taxane series (36%) as in the tumors of the carboplatin series (30%), and the difference in distribution did not reach statistical significance (P=0.055).

Adjuvant postoperative chemotherapy. Adjuvant treatment with carboplatin and a taxane was given every 3-weeks in 4-6 courses in most of the patients (95%) in the carboplatin-taxane series. More courses were administered to patients in higher FIGO-stages (P=0.002). Thus, all 6 patients treated with more than 6 courses were in stage II. Among the 6 patients with less than 4 courses of treatment with carboplatin-taxane, 3 patients had severe hypersensitivity reactions during or after the first course and they were all treated with further 3 courses of single drug carboplatin. Adjuvant treatment with single drug carboplatin (AUC=7) was given every 3-weeks in 4-6 courses in all patients (96%) with exception for one patient who

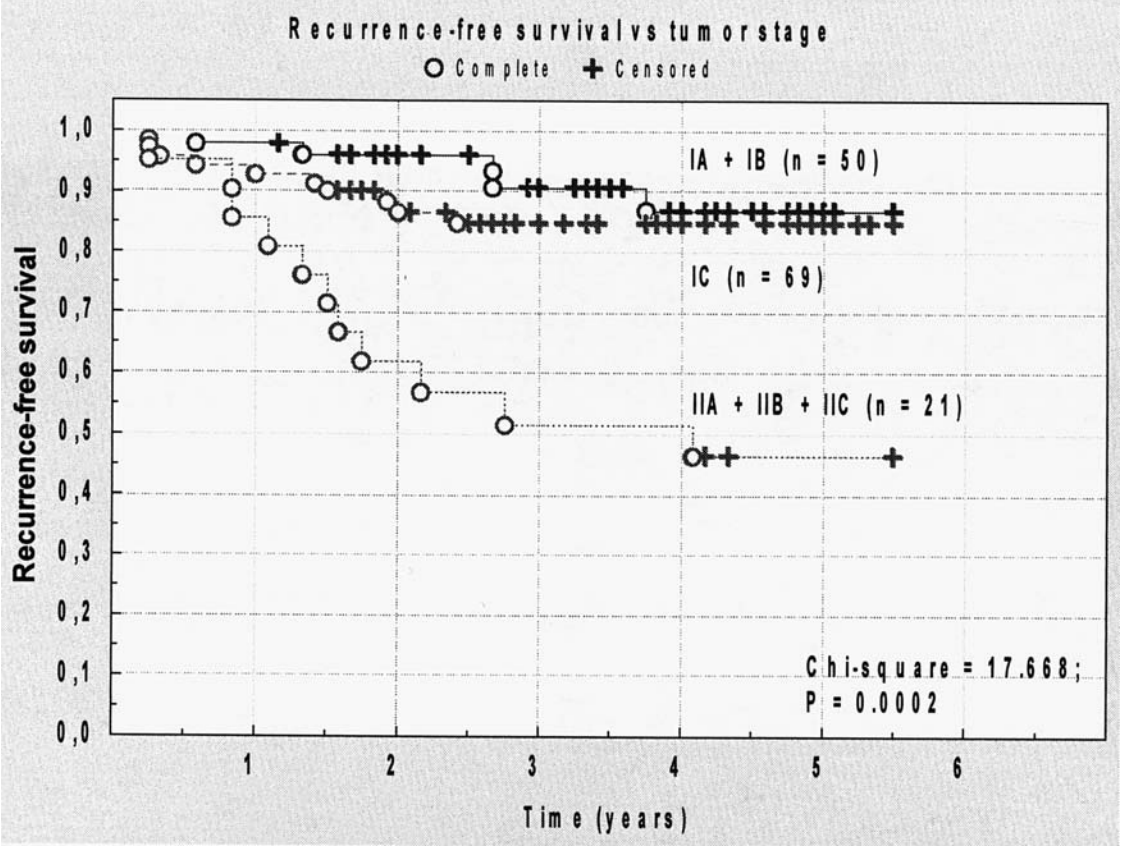

Figure 1. Recurrence-free survival (RFS) versus FIGO stages in the complete series (n=140). Kaplan-Meier survival curves and Chi-square statistics were used for test of differences.

Table VI. Predictive factors for tumor recurrences. Logistic regression analysis of the complete series (n=140).

Factor	ß	SE	OR[a]	95% CI[b]	P-value
Age	0.023	0.020	1.023	0.984-1.064	0.248
Stage (II vs. IA-C)	1.863	0.543	6.442	2.200-18.860	0.0006
Grade (3 vs. 1-2)	0.511	0.510	1.667	0.607-4.574	0.317
Type of chemotherapy (carboplatin-taxane vs. carboplatin)	0.167	0.610	1.181	0.354-3.946	0.785

[a]Odds ratio; [b]95% confidence interval of the odds ratio.

received 7 courses. Higher number of courses were administered to patients in higher FIGO-stages (P=0.03). No carboplatin-related hypersensitivity reactions during or after treatment with single-drug agent were recorded.

Treatment-related adverse effects. Treatment-related adverse effects of carboplatin-taxane versus single drug carboplatin were compared (Table V). The major toxicities in the present study were myelosuppression and neurotoxicity. Forty-two patients experienced grade 1-2 myelosuppression, 8 patients experienced grade 3 and 2 patients grade 4 myelosuppression in the carboplatin-taxane series. Twelve patients experienced grade 1-2 myelosuppression in the carboplatin series, and no grade 3 or grade 4 myelosuppression were registered. The difference was not statistically significant. Neurotoxicity was recorded in 38 out of the 113 patients (34%) in the carboplatin-taxane series compared to 2 out of the 27 patients (7%) in the carboplatin series (P=0.007). The neurotoxicity was of grade 1 in 29 out of the 38 patients (76%) and of grade 2 in the remaining 9 patients (24%) belonging to the carboplatin-taxane series and of grade 2 for both patients in the carboplatin series (P=0.011). WHO-performance status during the period of treatment was recorded as 0-1 in 89 out of the 113 patients (79%) in the taxane-carboplatin series. Nineteen patients (17%) had performance status evaluated as grade 2, and finally 5 patients (4%) as grade 3 in the carboplatin-taxane series compared to WHO-performance status of 0-1 in 22 out of the 27 patients (81%), and grade 2 in the 5 remaining patients (19%) in the carboplatin series. No statistically significant (P=0.438) differences in WHO-performance status during treatment were found for the two groups of different chemotherapy. Treatment at recurrence included in most cases a platinum agent, paclitaxel, gemcitabin or topotecan.

Survival and prognostic factors. Kaplan-Meier plots of recurrence-free survival (RFS) by tumor stage are shown in Fig. 1 and by type of chemotherapy in Fig. 2. Patients in FIGO-stages IA + B and IC had RFS of 85% and 86%, respectively. However, RFS for patients in FIGO-stage II was only 47%. In a logistic regression analysis of the complete series (n=140) predictive factors for tumor recurrences were evaluated (Table VI). FIGO-stage was the only

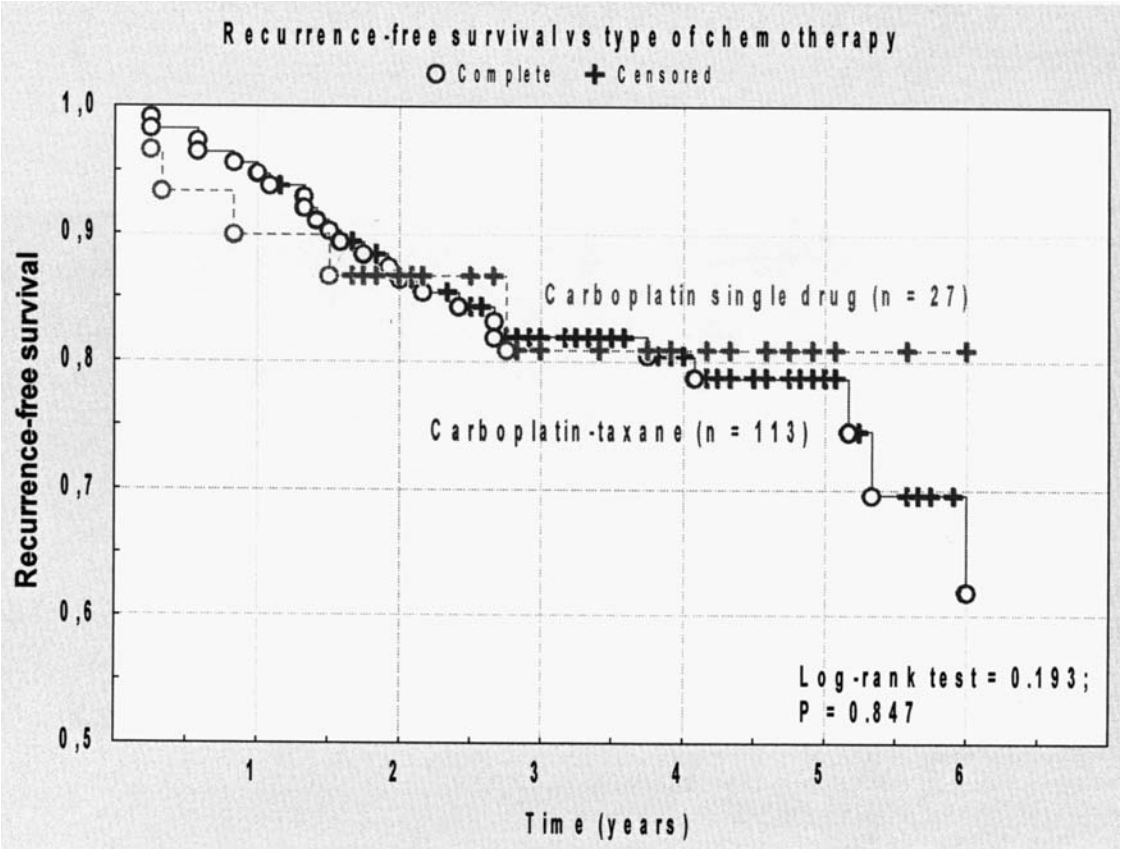

Figure 2. Recurrence-free survival (RFS) versus type of postoperative adjuvant chemotherapy. Combination chemotherapy with carboplatin-taxane (n=113) was compared with single drug carboplatin (n=27). Kaplan-Meier survival curves and log-rank test were used to analyze differences between the survival curves.

independent and significant (P=0.0006) prognostic factor. However, an odds ratio (OR) of 1.7 for tumor grade (grade 3 versus grade 1-2) demonstrated a 70% increased risk for tumor recurrence for a patient diagnosed with a grade 3 tumor compared to a patient with a grade 1-2 tumor. An OR of 1.2 for type of chemotherapy indicates a 20% increased risk for recurrence for patients who underwent carboplatin-taxane chemotherapy compared with single drug carboplatin after primary surgery. These factors were not statistically significant in the multivariate analysis (Table VI).

Discussion

Recurrence rate for the complete series of 140 patients with early stage epithelial ovarian cancer after primary surgery and adjuvant chemotherapy was 21% and the 5-year recurrence-free survival was 80%. Recurrence rate and 5-year recurrence-free survival was similar in the series of 113 women treated with adjuvant carboplatin-taxane chemotherapy and in the series of 27 women treated with adjuvant single drug carboplatin. The recurrence-free survival rate of 80% in this series of 140 patients is comparable with the results presented by Young *et al* (18). In that study they concluded that platinum-based adjuvant therapy can reduce the risk of relapse in patients belonging to a high-risk group, resulting in disease-free survival of ~80%. Furthermore, the recurrence rate of 21% and the 5-year recurrence-free survival of 80% in our study are comparable with a recurrence rate of 24% and a 5-year recurrence-free survival rate of 76% in patients treated with platinum-based chemotherapy in the ICON-1 and EORTC-ACTION trials (5). However, the main aim of the present study was to find out if the addition of a taxane (paclitaxel or docetaxel) to a platinum agent (carboplatin) will reduce the risk of recurrences and increase the recurrence-free survival rate in early stage epithelial ovarian cancer. No significant differences in recurrence rate and recurrence-free survival rate were noted in this study neither in univariate nor in multivariate analyses. There are a number of limitations in this study, however, e.g. the retrospective design, the number of patients treated with carboplatin alone, and the surgical staging procedure which was minimal or inadequate in 102 out of 140 patients (73%) according to the EORTC surgical staging guidelines (3).

In a retrospective study from Spain (19) undertaken to determine the role of paclitaxel in addition to platinum-based chemotherapy in early stage (I-II) ovarian cancer patients no difference was found between patients receiving or not receiving paclitaxel, resulting in a 5-year disease-free survival of 76%. Results from a GOG randomized phase III trial comparing 3 versus 6 cycles of carboplatin and paclitaxel showed a cumulative 5-year recurrence rate of 25% after 3 courses and 20% after 6 courses. However, the recurrence rate was 24% lower in the 6-cycle arm after adjustment for FIGO-stage and tumor grade. However, the difference was not statistically significant and it was concluded that three additional cycles of carboplatin-paclitaxel chemotherapy

provide a modest reduction in the absolute risk of recurrence and are associated with increased toxicity (14).

The major toxicities in the GOG study (14) were myelosuppression and neurotoxicity. Neurotoxicity of grade 3 or 4 occurred in 2% of the patients in the 3-cycle arm and in 11% in the 6-cycle arm. Myelosuppression (granulocytopenia grade 4 and anemia grade ≥2) also occurred in a higher frequency in the 6-cycle arm. In our study there were no recorded cases with neurotoxicity of grade 3 or 4, but neurotoxicity of grade 1 or 2 (34%) occurred mainly in the carboplatin-taxane series. Myelosuppression of grade ≥2 was found in 32 out the 140 patients (23%). All the 10 patients with myelosuppression of grade 3 or 4 belonged to the carboplatin-taxane series. It should be mentioned that carboplatin in the GOG study was dosed at AUC 7.5 compared to AUC 5 in our study. On the other hand, the dose of paclitaxel of 175 mg/m^2 by 3-h infusion was not different from the GOG study. In our study the mean dose given of carboplatin in the carboplatin-taxane series was 615 mg compared to 589 mg in the series of single drug carboplatin. The relatively lower mean dose of carboplatin given in the single drug series could probably be explained by the trend of older patients in that series.

Adjuvant therapy is used with the aim of reducing recurrences due to occult residual disease and the outcome is dependent on whether or not the patient has been adequately staged and whether or not the adjuvant therapy is effective. Since FIGO-stage is used to select patients for adjuvant therapy, and since ≤30% of the patients with apparent stage I-disease have occult metastases, complete surgical staging is very important. Otherwise, a true adjuvant therapy for early-stage disease may not be given due to undetected stage III-disease in many cases (20,21). Various prognostic factors are used to select patients for adjuvant treatment and both FIGO-stage and tumor grade are often used as such selection criteria (22). In the current study, FIGO-stage was the only significant and independent prognostic factor. Tumor grade was a prognostic factor only in a univariate analysis in the present study. However, tumor grade is the most powerful prognostic factor in the early stages of epithelial ovarian cancer and it is confirmed by many authors (23-27). However, since all patients in our study received postoperative adjuvant chemotherapy, neither FIGO-stage nor tumor grade were used to select patients to adjuvant treatment.

Taken into account that the primary issues for the outcome of adjuvant therapy are both the completeness of surgical staging and the effectiveness of the given therapy, the secondary issue is the biological nature of the tumor. This means that stage-for-stage the intrinsic features of the tumor have prognostic importance. Thus, tumor grade and DNA-ploidy may be surrogates for genetic instability, which may be the principal determinant of prognosis, while apoptotic competence required for radiosensitivity and chemosensitivity may require prospective studies for evaluation of different types of gene expression (28). Tumors of clear cell histology had a favorable outcome after taxane-based adjuvant chemotherapy with a recurrence rate of 10% and recurrence-free survival of 84% compared to a recurrence rate of 38% and a recurrence-free survival of 61% after adjuvant cisplatin plus cyclophosphamide in a previous study from our institution (29).

In a study from Australia on patients with clear cell ovarian carcinomas who received carboplatin and paclitaxel after complete surgical staging, the recurrence rate was 33% and the overall survival rate 82% in stage I patients (30). In a further study on clear cell carcinomas from Japan, the 5-year progression-free survival were 95% in stage IA, 84% in stage IC and 62% in stage II after adjuvant taxane-based chemotherapy (31). In a published retrospective multicenter study (24) on 1,545 patients with epithelial ovarian carcinoma in FIGO stage I, rupture of the tumor before surgery was a powerful predictive factor for recurrent disease with a hazard ratio (HR) of 2.65 (95% CI: 1.53-4.56). These findings were confirmed in our study by the fact that recurrent disease was associated with preoperative rupture in univariate analysis.

In our study, the outcome after adjuvant chemotherapy with a carboplatin-taxane combination versus single drug carboplatin in the early stages of epithelial ovarian cancer was compared and no differences were found with regard to recurrence rate or the 5-year recurrence-free survival rate in univariate and multivariate analysis. The combination regimen was associated with increased toxicity, especially neurotoxicity and myelosuppression. A prospective, randomized multicenter trial of combination versus single drug chemotherapy in early stage epithelial ovarian cancer with the aim to compare recurrence-free survival and treatment-related toxicity is still warranted. Due to the high recurrence rate and the associated death rate following tumor recurrences in early stages of ovarian carcinomas, it is a primary issue to offer every patient the optimal primary surgical and oncological treatment.

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