DOXORUBICIN-MELPHALAN WITH AND WITHOUT CISPLATIN IN ADVANCED OVARIAN CANCER

Ten-year survival results from a prospective randomized study by the Swedish Cooperative Ovarian Cancer Study Group

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In a controlled prospective randomized study the regimen doxorubicin (A) 40 mg/m^2 + melphalan (M) 0.4 mg/kg was compared with A + M + cisplatin (C) 50 mg/m^2 given every four weeks in advanced ovarian cancer, FIGO stage III or IV and with serous or anaplastic histology. From 1981 to 1983, 300 patients entered the study and 295 patients were evaluable for response, toxicity and long-term survival. All patients were followed for at least 10 years. The majority of patients had large residual tumours >2 cm. Patients treated with MAC had a higher response rate compared with patients treated with MA (76% vs. 50%, $p < 0.01$) and treatment with MAC resulted in significantly more pathological complete responders than MA. There was a significant difference in median duration of response (19 months vs. 13 months, $p < 0.006$) and in median survival time (26 months vs. 19 months, $p = 0.05$). After 5- and 10 years a significant difference in progression-free and overall survival was found. The independent prognostic factors in this study were residual tumour after primary surgery, treatment with MAC, tumour grade, ascites, and stage. Objective and subjective side effects were significantly worse with MAC, although tolerable. In conclusion, this study shows that incorporating C into MA improves the duration of progression-free survival and overall survival in women with incompletely resected Stage III or Stage IV ovarian epithelial cancer. A 5- and 10-year survival of 25% and 18%, respectively, is impressive.

The Swedish Cooperative Ovarian Cancer Study Group (SCOG) was founded in 1978. Despite the widespread use of most available chemotherapeutic agents, the death-rate for advanced ovarian cancer was at that time approximately the same as it had been 20 years earlier (1). Soon after its foundation SCOG performed a controlled prospective randomized study to determine whether increased response rate with doxorubicin (A) combined with melphalan (M) resulted in better long-term survival than treatment with M alone in advanced ovarian cancer patients with serous or anaplastic histology (2). In this study (Study 1) 168 patients with FIGO Stages III and IV (residual tumour >10 cm) entered the study, and 148 were evaluable after five years or longer. The combination MA produced significantly more clinical complete remissions than single agent M therapy ($p < 0.001$). Median duration of response and median survival time were significantly longer for MA ($p < 0.005$ and $p < 0.0001$, respectively).

In 1978 cisplatin (C) was not available in Sweden, but when this active agent (3) became available in 1980, SCOG

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sought to improve long-term survival in advanced ovarian cancer patients from Study I by adding C to MA in a prospective, randomized study. We here report our long-term results. All the patients were followed for at least 10 years, without any patient losses during follow-up.

Material and Methods

Patients

To compare the effects of MA with or without C a randomized prospective study was carried out at 7 gynaecologic oncology departments in Sweden between May 1981 and December 1983. The women studied were aged 15–70 years, with histologically proven ovarian carcinoma (well (G1) to moderately (G2) differentiated serous, poorly differentiated (G3) serous or anaplastic/undifferentiated tumours), diagnosed as the International Federation of Gynecologic and Obstetrics (FIGO) optimal and suboptimal Stages III and IV and who had no previous chemotherapy. Suboptimal Stage III was defined as those Stage III patients with residual palpable lesions after primary surgery of >2 cm in diameter. Stage IV disease was defined as histologically proven liver metastases, inguinal or axillary lymph node metastases or positive pleural cytology. They could have clinically measurable or unmeasurable disease, and should be able to be evaluated by second-look surgery. Exclusion criteria were previous treatment with chemotherapy or radiotherapy. Patients with haematopoietic depression at the start of the study (leukocyte count below 3.0×10^9/L and the platelet count below 100×10^9/L), Karnofsky index <50 or other severe disease or other cancer were also excluded.

Before chemotherapy was started, the extent of disease was assessed clinically and/or surgically and by chest x-ray, i.v. urography, and fine-needle aspiration biopsy of available metastases. When indicated, these examinations were supplemented with other appropriate methods such as isotope scanning of the whole abdomen, computerized tomography (CT) and barium contrast examination of the bowel and stomach. Laboratory examinations included measurement of haemoglobin concentration, leukocyte count, platelet count, serum electrolytes, creatinine and liver function tests. When indicated, electrocardiography was performed.

All patients were stratified after surgery according to stage (III or IV), histological type (serous or anaplastic) and whether debulking surgery had been performed or not (only biopsy). Randomization was accomplished by selecting sealed randomized cards one to three weeks after primary surgery.

Chemotherapy

The patients were randomized to combination chemotherapy consisting of either MA or MAC. On day 1 the first group received A 40 mg/m^2 with flush drip technique for about 20 min, then M 0.4 mg/kg body weight, for 1–3 h. On day 1 the second group received MA as described above. On day 2 hyperhydration technique was used in the morning followed by C 50 mg/m^2 for 30 min followed by further hyperhydration. The treatments in both arms were given 4 times at intervals of 4 weeks (28-day cycles) and thereafter 6 cycles at intervals of 6 weeks (42-day cycles). In case of objective remission the treatment continued to maximum doses of A 500 mg/m^2.

Before each chemotherapy course leukocyte and platelet counts, haemoglobin level and the Karnofsky performance index were carried out and the patients were examined clinically. Dosage was adjusted according to the degree of haematologic toxicity, assessed by leukocyte and platelet counts on the same day as drug administration. If the leukocyte count was below 3.0×10^9/L or the platelet count was $<100 \times 10^9$/L, the dose was reduced by 50%. If the leukocyte count was $<2.0 \times 10^9$/L or the platelet count was $<75 \times 10^9$/L, the next cycle was delayed week by week until the leukocyte count was at least 2.0×10^9/L and platelet counts were at least 100×10^9/L. The treatment was stopped if repeated severe side effects necessitated prolonging the interval between courses to more than three times the normal. At progressive disease or relapse the patients were treated with second-line therapy decided by the individual cancer centres.

Toxicity was reported according to the recommendations of the World Health Organization (WHO) (4). The results of therapy were evaluated as follows: Before each course, a gynaecologic examination was performed. During weeks 8 and 24, intravenous urography or renography; chest x-ray and examination such as liver scintigram, ultrasound, and CT were performed; and during weeks 24 and 42, palpation under anaesthesia. The results of treatment were defined as follows: 1) Clinical complete remission: total disappearance of all clinical or radiologic signs of disease for at least three months; 2) clinical partial remission: at least 50% reduction in the maximum diameter of a palpable tumour, or control of an effusion for three months; 3) clinical stationary disease: Less than 50% decrease of measurable tumour volume and no new lesion for at least three months; 4) clinical progressive disease: 25% increase in volume of tumour or new lesions during treatment. Second-line treatment results were defined as above, except that remission time requirement was only one month.

Primary surgical treatment

Two different primary surgical approaches were used: 1) No primary surgery (only biopsies) or explorative surgery with only biopsy or with less than total hysterectomy or bilateral salpingo-oophorectomy and omentectomy; 2) debulking laparotomy with at least total hysterectomy, bilateral salpingo-oophorectomy and omentectomy.

In both groups second laparotomy was planned for responders 7.5 months after primary surgery (6 weeks after the 6th course).

Statistics

Our randomization was documented in the study protocol and in the medical records. The Wilcoxon rank sum test or χ^2-test was used for analysis of difference between the two groups. Progression-free survival (PFS) was based on the first sign of tumour progression. Survival time was calculated from the onset of chemotherapy. Survival was calculated as corrected survival due to ovarian cancer death. The survival probability was calculated following the method of Kaplan & Meier (5). Observed differences were examined by the Mantel logrank test (6) and Cox analysis (7) (SPSS for WINDOWS RELEASE 6.1.2). A significance level of 0.05 was used. All p-values are two-sided. The Cox proportional hazard analysis was used to identify independent prognostic factors. Factors of significance in the univariate analysis were included simultaneously and then a backward selection was performed with stepwise exclusion of insignificant variables until the model contained only significant variables.

Results

Out of 300 patients who entered the study, 295 were evaluable for response, toxicity, PFS and survival. Five patients were excluded because they did not fulfil the inclusion criteria. Two of these patients had previously received chemotherapy, two had a Karnofsky index <50 and one had mucinous histology. Of the patients included in the study, three were over 70 years of age and one was given M instead of MA. These four patients were included in the final analysis. Nine patients, 5 in the MA-group and 4 in the MAC-group were tumour-free after primary laparotomy. However, the number of patients was too low to be analyzed in separate groups as planned, and therefore these patients were included in the total analysis which was not influenced by this inclusion. In Tables 1 and 2 the main characteristics of the two treatment groups in Stages III and IV patients are summarized. There was no imbalance in major prognostic factors between the two groups.

As indicated in Figs. 1 and 2, the median PFS and the median overall survival were significantly longer for the MAC-group compared with the MA-group ($p < 0.0001$ and $p < 0.004$, respectively). The median PFS and the median overall survival for MAC were 19 months and 26 months compared with 13 months and 17.9 months for MA. The 10-year survival for MAC patients was 18% and for MA patients 10%. The median cumulative survival rates for progression-free (PFS) and overall survival in Stages III and IV are presented in Figs. 3 and 4. The

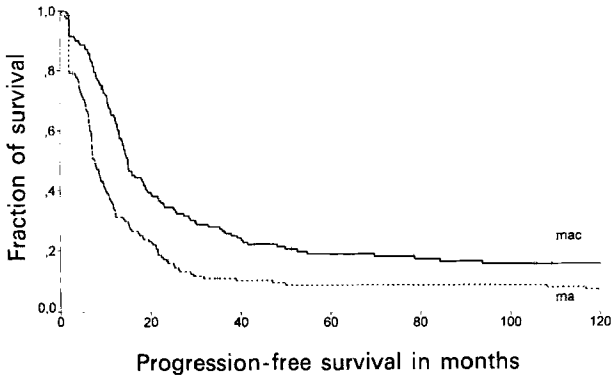

Fig. 1. Progression-free survival according to the type of chemotherapy. MA: 153 entered, 139 observed, 104.5 expected. MAC: 143 entered, 118 observed, 152 expected, $p < 0.0001$.

differences were significant only for Stage III patients. In patients with residual tumour <2 cm, MAC gave an improved cumulative survival rate compared with MA ($p = 0.0007$), in contrast to patients with residual tumour >2 cm ($p = 0.22$) (not shown). Patients with serous adenocarcinoma had a longer median survival than those with anaplastic carcinoma (24 months vs. 18 months). A difference in cumulative survival between MAC and MA chemotherapy was found only for patients with serous adenocarcinoma grade III ($p = 0.003$). Regarding age of the patients, a survival advantage was found for MAC compared with MA for patients of <40 years ($p = 0.01$) and 40-50 years ($p = 0.04$), but not for those >50 years ($p = 0.11$).

Of the 295 randomized patients 121 had Stage III bulky disease (corresponding to Stage IIIC according to the new FIGO classification) and of these, 60 patients had upfront explorative laparotomy (EL) with biopsies (residual tumour >10 cm) and 61 patients had debulking surgery (DS) (residual tumour >2 cm—<5 cm). There was no statistical difference in corrected survival between patients with no residual tumour (9 patients) and those with resi-

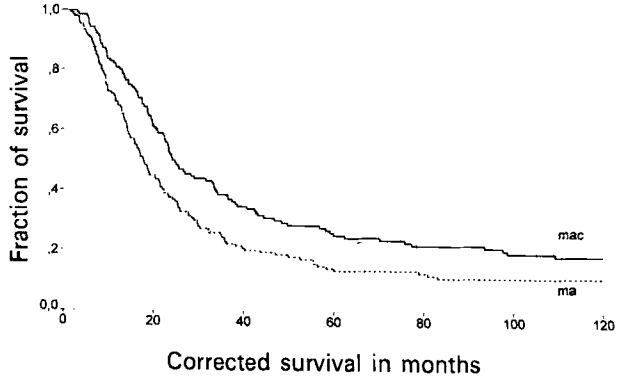

Fig. 2. Survival according to the type of chemotherapy. MA: 153 entered, 131 observed, 109 expected. MAC: 143 entered, 111 observed, 133 expected, $p = 0.004$.

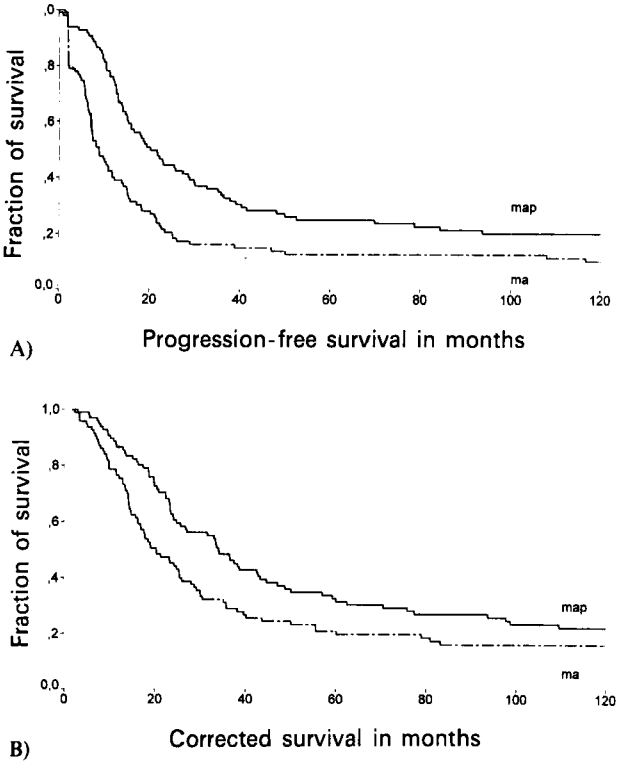

Fig. 3. A) Progression-free survival in Stage III patients. MA: 95 entered, 83 observed, 60 expected. MAC: 97 entered, 76 observed, 99 expected, $p = 0.0001$. B) Survival according to Stage III patients. MA: 95 entered, 78 observed, 64 expected. MAC: 97 entered, 73 observed, 87 expected, $p = 0.02$.

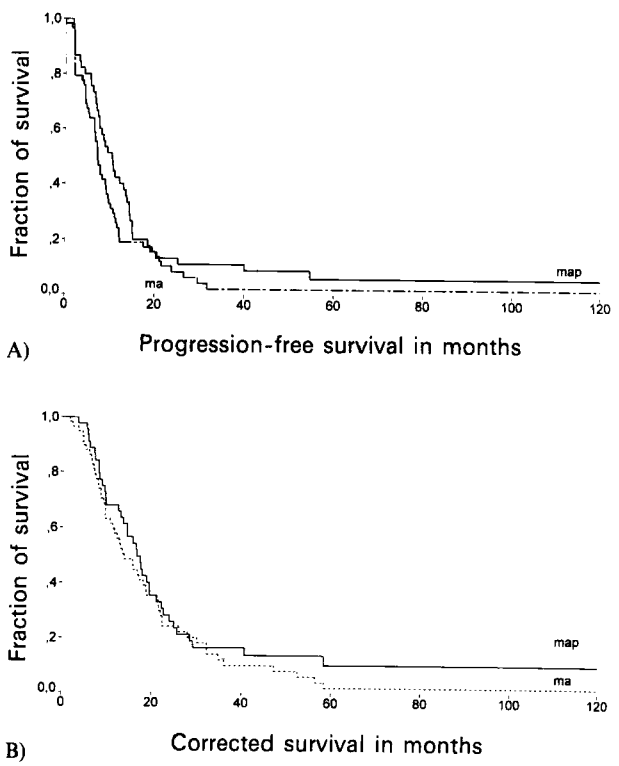

Fig. 4. A) Progression-free survival in Stage IV patients. MA: 58 entered, 56 observed, 48 expected. MAC: 46 entered, 42 observed, 50 expected, $p = 0.12$. B) Survival in Stage IV patients. MA: 58 entered, 53 observed, 48 expected. MAC: 46 entered, 38 observed, 43 expected, $p = 0.31$.

dual tumour <2 cm after primary surgery (32 patients), but a highly statistic significance between patients with residual tumour >2 cm compared with the other two groups (not shown). There was no significant difference (except for larger residual tumour in the EL-group) between the two groups concerning major prognostic factors. There was a statistical significance difference in 5-year and 10-year PFS and overall survival for the DS-group, $p < 0.001$ and $p < 0.003$, respectively, compared with the EL-group.

In Stage III, 76% of the patients receiving MAC had a clinically objective, tumour regression lasting for 3 or more months in comparison to 50.5% in the MA-group ($p < 0.0002$). Thirty-one percent of MAC patients had a microscopic and macroscopic complete remission compared with 16% in the MA-group, $p < 0.0008$ (Table 1). In stage IV, 71% of the patients receiving MAC had an objective tumour regression lasting for 3 or more months compared with 50% in the MA-group, ($p = 0.074$). Thirteen percent had macroscopic and microscopic complete remission in the MAC-group compared with 2% in the MA-group, $p = 0.06$ (Table 2).

There was no statistical difference between pathological complete responders in Stage III in long-term survival between the two treatment arms. After 10 years 59% were still alive in both groups.

In the MAC-group 26 patients with clinically objective response, but with tumour masses found at second-look operation, tumour could be reduced to <2 cm in 11 patients but in 15 patients it was impossible to perform a radical operation, compared with 8 and 5 patients respectively in the MA-group. Patients who underwent secondary tumour reduction had a survival superior to that of patients with macroscopic residual disease at second look and no secondary tumour reduction. Survival at 10 years was 8% vs. 3% ($p = 0.05$). For patients in Stage IV no difference in survival could be found for secondary debulking. A 40% overall 5-year survival was found in radically operated patients in both treatment groups. There was a significant difference in long-term survival when comparing the true pathologically complete responders with the clinically complete responders in whom tumour mass was found at second-look operation and in women where the tumour could be reduced to less than 2 cm ($p = 0.04$).

In 67 patients with Stages III and IV disease who failed treatment with MA, second-line single C was given. Twenty-six patients (63%) in Stage III and 13 patients (70%) in Stage IV obtained an objective response. In 22

Table 1

Patients' characteristics FIGO Stage III

	Group MA		Group MAC		p-value
No. of patients	95		97		
Histological type					
Serous	75		82		NS
Undiff.	19		15		
Tumour grade					
Well diff.	16		13		
Mod. diff.	11		10		
Poorly diff.	49		59		
Undiff.	19		15		NS
Ascites					
No	22		23		
Yes	73		74		NS
Age					
20–30	1		2		
31–40	5		8		
41–50	25		24		
51–60	35		35		
61–70	28		28		
>70	1				NS
Primary surgery					
None	2	2.1%	2	2.0%	
Expl. laparotomy	35	36.8%	25	25.8%	
<Hit + BSO + O	43	45.3%	51	52.6%	
Hit + BSO + O	15	15.8%	19	19.6%	NS
Residual tumour					
Tumour-free	4	4.2%	4	4.2%	
<2 cm	15	15.8%	14	14.4%	
>2 cm	76	80.0%	79	81.4%	NS
Clinical response					
CR	29	30.5%	46	47.4%	
PR	19	20.0%	28	28.94%	0.0002
SD	20	21.1%	11	11.34%	
PD	23	24.9%	6	6.2%	
Not evaluable	4	4.2%	6	6.2%	0.001
Second-look oper.					
None	51	53.7%	31	32.0%	
Expl. lap.	23	24.2%	32	33.0%	
<Hit + BSO + O	12	12.6%	24	24.7%	
Hit + BSO + O	9	9.5%	10	10.3%	0.006
Pathologic response					
Micro CR	11	11.6%	23	23.7%	
Macro CR	4	4.2%	7	7.2%	0.0008
PR	14	14.7%	22	22.7%	
SD	5	5.3%	7	7.2%	
PD	10	10.5%	6	6.2%	0.0004

Hit = Total abdominal hysterectomy. BSO = Bilateral salpingo-oophorectomy. O = Omentectomy. CR = Complete remission. PR = Partial remission. SD = Stationary disease. PD = Progressive disease. Micro CR = Microscopic complete remission. Macro CR = Macroscopic complete remission.

Table 2

Patients' characteristics FIGO Stage IV

	Group MA		Group MAC		p-value
No. of patients	58		46		
Histologic type					
Serous	39		33		
Undiff.	19		13		NS
Tumour grade					
Well diff.	1				
Moderately diff.	11		7		
Poorly diff.	27		26		
Undiff.	19		13		NS
Ascites					
No	7		3		
Yes	51		43		NS
Age					
36–40	2		2		
41–50	6		5		
51–60	24		23		
61–70	26		14		
>70			2		NS
Primary surgery					
None	6		10		
Expl. laparotomy	23		17		
<Hit + BSO + O	23		19		
Hit + BSO + O	6		0		NS
Residual tumour					
Tumour-free	1		0		
<2 cm	3		0		
>2 cm	52		46		NS
Clinical response					
CR	7	12.1%	11	23.9%	
PR	22	37.96%	20	43.2%	0.074
SD	16	27.6%	5	10.9%	
PD	13	22.4%	8	1.7%	
Not evaluable			2	4.3%	NS
Second-look operation					
None	50	86.2%	28	60.96%	
Expl. laparotomy	4	6.9%	4	8.7%	
<Hit + BSO + O			11	23.9%	
Hit + BSO + O	4	6.2%	3	6.5%	0.001
Pathologic response					
Micro CR	1	1.7%	5	10.9%	
Macro CR			1	2.2%	0.06
PR	6	10.6%	9	19.6%	
SD			1	2.2%	
PD	1	1.7%	2	4.3%	0.0156

Hit = Total abdominal hysterectomy. BSO = Bilateral salpingo-oophorectomy. O = omentectomy. CR = Complete remission. PR = Partial remission. SD = Stationary disease. PD = Progressive disease. Micro CR = Microscopic complete remission. Macro CR = Macroscopic complete remission.

patients in Stages III and IV who failed to respond to treatment with MA, second-line therapy with non-C chemotherapy and external irradiation was given, but an objective response was obtained in only three of these patients. Sixteen patients who failed treatment with MA and who were not treated with second-line therapy were compared with the C- and non-C-groups. There was no difference in recurrence localization, primary response duration, grade, stage and age between the three groups. The median survival of complete clinical responders in Stage III for the C-group was 38 months (range 10–96), for the non-C treatment group 8.5 months (range 3–5) and only 2.2 months for patients with no further treatment. The difference between second-line or not was $p < 0.0001$ and

0.03, respectively. In Stage IV the median survival for C treatment was 12 months, range 3–32.

Second-line non-C chemotherapy and external irradiation was given in 67 patients with Stages III and IV who failed to respond to treatment with MAC. A clinically objective response rate in Stage III was achieved in 4 patients (15%) and in Stage IV in one patient (5%). Second-line C chemotherapy was given to 12 patients in Stages III and IV who recurred after treatment with MAC. Only two patients responded again to C, both in Stage III. Thirty patients who recurred after MAC did not receive any second-line treatment. In this group there were more patients under 50 years of age compared with the other MAC failure groups. The other important prognostic factors: recurrence localization, primary duration of response, clinical response rate, grade and stage were equally distributed among the three groups. The median survival for the non-C chemotherapy group was 21 months (range 5–136) compared with 8.5 months (range 1–80) in the external irradiation group and only 3.6 months in the non-treatment group ($p < 0.001$ and 0.03, respectively).

Toxicity was reported in accordance with the recommendation of the WHO organization (4) (Table 3). Dose reduction in chemotherapy was necessary in 22% of the MA courses compared with 53% in the MAC-group. Five percent of the patients in the MA-group had to stop treatment because of side effects, 18% in the MAC-group. Two patients in the MA-group developed leukaemia compared with 4 patients in the MAC-group. Univariate analysis followed by the Cox multivariate analysis was done in order to analyse the dose effects and cycle duration on the treatment results. Neither interval between the different treatment cycles nor dose reduction influenced treatment outcome in the two treatment groups. Objective and subjective side effects were more pronounced in the MAC-group, although tolerable.

In the univariate analysis, stage, rest tumour after primary surgery, chemotherapy treatment, ascites, tumour grade differentiation and age were all of prognostic significance for median PFS and median overall survival. Using the Cox stepwise backward multivariate analysis and the Cox proportional hazard model (6) the various prognostic factors for PFS and overall survival were assessed in the whole material. The ranking according to the relationships with favourable prognosis was as follows:

For progression-free survival (Table 4) residual tumour was followed by ascites, treatment with MAC and tumour grade differentiation. For overall cumulative survival (Table 5) residual tumour after primary surgery was followed by tumour grade differentiation, treatment with MAC, ascites and stage.

Table 3

Toxicity, WHO-grade related to treatment groups

	MA				MAC			
	1	2	3	4	1	2	2	4
Cardiotoxicity	1	–	–	–	–	–	–	1
Neurotoxicity	–	–	–	–	1	–	–	1
Nephrotoxicity	–	1	1	–	3	5	2	3
Ototoxicity	–	–	–	–	1	1	1	–
Anaemia	1	1	–	–	3	2	–	–
Leukopenia	25	20	1	1	16	14	8	5

Table 4

Independent prognostic variables according to the Cox stepwise, backward multivariate analysis and the Cox proportional hazard model for progression-free survival for the whole material

	Relative hazard	95% confidence interval	p-value
1. Residual tumour			
None	1		
<2 cm	2.60	1.9–3.2	0.007
>2 cm	3.99	2.1–5.01	
2. Ascites			
None	1		
Yes	2.38	2.1–3.8	0.00001
3. Randomization			
MA	1		
MAC	0.46	0.3–0.5	0.00001
4. Tumour grade			
G1	1		
G2	2.04	1.8–2.1	
G3	2.21	1.9–3.2	0.05
Anaplastic	2.03	1.8–2.2	

Table 5

Independent prognostic variables according to the Cox stepwise, backward multivariate analysis and the Cox proportional hazard model for overall survival for the whole material

	Relative hazard	95% confidence interval	p-value
1. Residual tumour			
None	1		
<2 cm	2.36	1.8–3.2	0.004
>2 cm	3.56	2.0–4.1	
2. Tumour grade			
G1	1		
G2	1.85	1.6–1.9	
G3	2.42	2.2–3.0	0.003
Anaplastic	2.67	2.2–3.1	
3. Randomization			
MA	1		
MAC	0.66	0.5–0.9	0.003
4. Ascites			
None	1		
Yes	1.97	1.6–2.2	0.0004
5. FIGO			
Stage III	1		
Stage IV	1.37	1.1–3.2	0.03

Discussion

The present study is a continuation of the first randomized prospective SCOG trial which showed that the MA chemotherapy regimen gave a significantly better response rate than M alone (54.7 vs. 26.7%, $p < 0.0001$). When using the 3 months criterion for response duration, a highly significant difference in PFS (13.0 vs. 7.3 months, $p < 0.0057$) and in long-term survival (18.5 vs. 10.5 months, $p < 0.0001$) was found. At 60 months 10 patients were alive and tumour-free, compared with 3 patients treated with M (2).

The 5-year results from the present second prospective randomized study in advanced Stages III and IV ovarian cancer by SCOG adding C to MA showed that the MAC regimen achieved a significantly higher clinical and pathological complete response rate with a slight significant increase in PFS survival and median survival compared with MA (8). After at least 10 years of follow-up there is a highly statistical significant difference in PFS and long-term survival for MAC, $p < 0.0001$ and $p < 0.004$, respectively, compared with MA (Figs. 1, 2). At 60 months 32 patients in the MAC-group (25%) and 19 patients (13%) in the MA-group were still alive. At 120 months the figures were 18 (18%) and 13 (10%), respectively. When comparing Stages III and IV, there is a highly statistical significant difference in Stage III in PFS and long-term survival for MAC, $p < 0.0001$ and $p = 0.0001$, respectively, but not in Stage IV (Figs. 3, 4). Concerning histology type, the patients with serous cystadenocarcinomas had significantly better PFS and long-term survival than patients with anaplastic tumours. Histological types were, however, not an independent prognostic factor.

The tumour grade was found to be an important independent prognostic factor for both PFS and overall survival with a relative risk of dying of 2.42 for G3 and 2.67 for anaplastic tumours compared with G1 tumours. In the univariate analyses age was a significant prognostic factor with best survival for patients under 40 years compared with patients over 50 years. However, age lost its significance in the multivariate analysis.

Multivariate analysis for PFS showed that residual tumour after primary surgery followed by ascites, treatment with MAC and tumour grade were independent prognostic variables. For long-term overall survival residual tumour after primary surgery, tumour grade, ascites, treatment with MAC and stage were independent prognostic variables. Other authors have also reported that residual tumour after primary surgery, performance status and tumour grade are independent prognostic factors (9–13). The number of true pathologic responders and long-term survivors in the MAC-treated group of patients with high-risk histology and residual tumour >2 cm after primary surgery is impressive. The long-term survival results in this study and in the study by Gaducci et al. (9), where the majority of patients had residual tumour >2 cm, compare favourably with data from other papers reporting on long-term survival in advanced ovarian cancer (10, 14, 15).

At the time when the present study was performed second-look laparotomy was the only reliable method of identifying true pathologic complete responders. Our methods to evaluate clinical complete responders, CT, ultrasound and palpation and anaesthesia missed the pathologic true, complete responders in more than 50% of the patients. Patients scored as clinically complete responders, but who were not tumour-free at second look had a significantly shorter survival time than the true complete responders. Today we define optimal primary tumour reduction as debulking to residual tumour ≤ 1 cm in diameter according to the paper by Hoskins et al. (11). The frequency of patients having optimal cytoreductive surgery varies with type of department. Bertelsen et al. (16) have shown that optimal tumour debulking at different Danish gynaecologic departments varied significantly. In specialized gynaecologic oncologic centres 24% had optimal tumour reduction, in gynaecologic departments 15% and in the surgical departments only 6%. Nevertheless, there was no difference between the various types of departments concerning long-term survival, despite the finding that survival was significantly related to residual tumour and primary surgery. In Sweden and Denmark at that time (1981–1983) Högberg (17) and Bertelsen et al. (16) found in their material that only 24 and 23% of the patients were optimally debulked. In centres with a more aggressive attitude to primary debulking surgery, the optimal debulking rate increases to 70–90% (18, 19). However, the 3-year survival result (29%) is not better than in other centres that do not include aggressive primary debulking.

Beyond any doubt there is a correlation between residual tumour after primary surgery and long-term survival (16). Large tumour masses with poor blood supply are less likely to receive adequate doses of chemotherapy (20). There is little doubt that primary surgical debulking also represents a keystone in improving quality of life in patients in the advanced FIGO stage (16, 20, 21). However, it has not been proved whether this is caused by the procedure per se or whether the patients that could be optimally debulked represent a favourable prognostic subgroup (16). Hoskins et al. (20) analysed 349 patients in Stage III with residual tumour <1 cm. Survival for patients presenting primary tumour <1 cm was superior to that of patients presenting larger tumour and cytoreduced to residual tumour <1 cm. On a second look at this study, although this protocol was not desgined to assess debulking surgery, it appears that primary debulking surgery to <2 cm has had a beneficial effect on survival, compared with patients who were not debulked at all (>10 cm). This is in contrast to Hacker et al. (22) who have shown that patients with abdominal metastases >10 cm in diameter before surgery had a poor prognosis in spite of having

their tumour reduced to 1 or 2 cm. Hunter et al. (23) did a meta-analysis including 6.962 patients. This analysis revealed that the 10% increase of optimally cytoreduced patients improved median survival time by 4.1% (not significant). Hunter et al. also showed that addition of cisplatinum chemotherapy increased the median survival by 53%. There is agreement throughout the world that the diagnostic value of primary cytoreduction can only be examined in a randomized prospective trial. EORTC and GOG have tried to perform such randomized studies, but it was impossible to recruit patients, probably because no surgeon is willing to randomize an operable patient to no tumour reduction surgery. We think that for advanced stages primary DS should be performed when possible, and surgery should preferably be performed by experienced gynaecologic oncologists (21).

Intervention cytoreduction has been examined in a randomized study conducted by the EORTC group (24). After three cycles of chemotherapy, patients without progression were randomized to intervention surgery or non-intervention surgery. Patients who had interval debulking surgery after the three courses of chemotherapy survived longer than those who did not have interval debulking (27 months vs. 19 months). It is interesting that intervention surgery improves survival. This is in contrast to primary aggressive surgery, but before it can be recommended we need a confirmative study, which is at present ongoing in GOG.

This study was performed in patients in whom primary optimal debulking surgery was not successful. All patients with the exception of 41 (9 tumour-free, 32 residual tumour 1 cm– <2 cm), had residual tumour >2 cm and the majority of the patients had larger residual tumours (>5 cm). In spite of this, there was a significant difference in favour of MAC in eradicating bulky disease. The 5- and 10-year PFS and survival for MAC and MA in our series of pathologically complete responders is encouraging for patients who had palpable tumour masses before chemotherapy with a 10-year survival of 59% for both groups. This means that the most important factor for PFS and long-term survival is to achieve a pathologically complete response. It is in bulky disease that MAC is superior to MA in this study. When dividing our patient groups into different sizes of residual tumours, <2 cm, 2–5 cm, >5 cm and >10 cm, the relative risk of relapse and dying of disease increased with larger size (cut-off point 10 cm), which is partly in contrast with Hoskins et al. (25).

Outside clinical trials, second-look laparotomy can only be justified if secondary debulking has an impact on prognosis or if treatment after second-look laparotomy can change the outcome of the disease. Prognostic values of second-look laparotomy have been stated in several series (26–29). Complete pathologic response is, however, not equivalent to cure (16). In this study and in the study by Sutton et al. (30) 65% of patients with pathologic complete response at second look were alive after 5 years. It has been debated whether the distinction between complete pathologic response and microscopic disease has a clinical relevance (16). In an early analysis of patients included in the Dutch ovarian cancer study group, Nejt et al. (31) found that patients with microscopic disease had a survival similar to that of patients with complete pathological response. However, a long-term survival analysis of the Dutch study showed that the proportion of patients with complete pathologic response was 60%, compared with 25% for patients with microscopic disease (31). This is partly in agreement with the Danish ovarian cancer study group (16) and with the Swedish/Norwegian ovarian cancer study group (32).

Like Bertelsen et al. (33), we found that patients who underwent secondary debulking surgery had a survival superior to that of patients with macroscopic residual tumour at second look and who could not be debulked. The long-term overall survival result is not inferior in the debulked patients compared with second-line chemotherapy, in contrast to what was found by Luesly et al. (34).

Second-line chemotherapy has been considered to result in lower response rates and shorter survival than primary chemotherapy treatment (35). Second-line treatment with C in MA-failure patients in Stage III with a response rate of 63% and a median survival for responders of 20 months compared with 2.2 months for the patients with no treatment at all show that C is not cross-resistant to M and A. The same was true for Stage IV, as MA-failure patients achieved a 70% response rate with a median survival of 12 months. In the MAC-failure group the response rate for second-line non-C treatment in Stage III patients was only 15%, but with a median survival of 21 months. These results show that second-line treatment is significantly better than just palliative, symptomatic, non-active treatment. Even external irradiation is better than no treatment at all in these situations. It would be interesting to investigate the role of secondary debulking surgery and/or second-line chemotherapy in relapsing ovarian cancer patients in a prospective randomized study.

The platinum, doxorubicin, cyclophosphamide (PAC) regimen has proved to be superior to cisplatinum plus cyclophosphamide (CP) in the ovarian cancer meta-analysis group (36). In Sweden, with SCOG 1 and SCOG 2 we have systematically tested one drug treatment by M up through a 2-drug combination with MA to a 3-drug combination with MAC. The corner-stone has been A in the SCOG studies because we have always had the impression that A adds positive effects to long-term survival and not only toxicity, which has been the standpoint of the United States and the United Kingdom. This role of A is supported by the recently updated Gruppo Interregionale Cooperative Oncologico Ginecologico (GICOG) (10). A'Hern & Gore have re-evaluated the overall role of adding A by conducting a review of the data from the

above-mentioned ovarian cancer meta-analysis and from the Advanced Ovarian Cancer Trialist Group (37), and they were able to show that the addition of A had a highly significant beneficial effect on survival and that this effect was equal to adding C. In conclusion, adding C to MA improves the duration of PFS (relative risk for MAC relapsing 0.46, 95% confidence interval (0.3–0.6), $p = 0.0001$ and overall survival (relative risk of dying after MAC: 0.66, 95% confidence interval 0.5–0.9), $p = 0.003$). The 5- and 10-year survival rates of 25% and 18% respectively for these high-risk patients are to our knowledge the best results so far reported, and therefore, the gold standard in the treatment for advanced epithelial ovarian cancer in Sweden is the 3-drug combination MAC or PAC. The Nordic Ovarian Cancer Study Group (NOCOVA) is now planning to test the GOG's new gold standard treatment: Taxol + C (38) with MAC in a prospective, randomized study in patients with ovarian cancer Stages III and IV, suboptimally debulked.

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