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Original article

Treatment of ovarian cancer with surgery, short-course chemotherapy and whole abdominal radiation

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Summary

Background: The primary aim was to induce a high number of pCR in early (FIGO IC, IIB + C) – and advanced (FIGO III–IV) – stage ovarian cancer with a surgery plus 4 cycles of cisplatin and melphalan (PAMP) regimen. The second objective was to prevent relapse with WAR in patients in remission after chemotherapy.

Patients and methods: 218 eligible patients were treated after staging laparotomy with cisplatin 80 mg/sqm i.v. on day 1 and melphalan 12 mg/sqm i.v. on day 2 q 4 weeks. Response was verified by second-look laparotomy. WAR was carried out with the open field technique on a linear accelerator (daily dose: 1.3 Gy, total dose: 29.9 Gy) in patients with pathological or clinical CR or pathological PR with microscopical residual disease.

Results: 146/218 patients (67%, 95% CI: 61%–73%) responded to PAMP: 56 (26%) achieved pCR, 24 (11%), cCR, 56 (26%) pPR and 10 (5%) cPR (c = clinical, p = pathological). Multivariate analyses revealed that in advanced stages (92 cases in remission), the achievement of pCR was the most important factor for longer time to failure (TTF) and survival. Only 51/118 (43%) patients in remission received WAR. Early-stage patients <= 55 years were more likely to have WAR than patients older than 55 years (77% vs. 23%; p = 0.02). Advanced-stage patients with cCR were less likely to be irradiated than patients with pCR or pPR (10% vs. 51%; p = 0.003). Toxicity of PAMP was acceptable with 10% of WHO grade 4 hematologic toxicity. Acute hematological toxicity of WAR caused interruption (33%) or incompleteness (33%) of irradiation in the majority of patients.

Conclusions: PAMP is an effective treatment for advanced ovarian cancer with a 67% response rate after 4 cycles. For the majority of patients in remission, WAR as a consolidation treatment was hardly feasible. For these patients new treatment modalities to consolidate remission are needed.

Key words: advanced ovarian cancer, chemotherapy, cisplatin, melphalan, second-look surgery, whole abdominal radiation

Introduction

Ovarian cancer is currently the second most common cause of death from malignancies in the female genital tract in the Western world. Refined surgical techniques and platinum combinations have increased the number of patients achieving complete remission and a prolonged progression-free interval, but only around 20% will survive in the long run [1]. Preliminary reports of patients with early-stage and poor prognostic features (grade III, positive peritoneal washing, ascites) support the use of chemotherapy [2]. The standard chemotherapy for advanced (stage III–IV) ovarian cancer consists of 6 cycles of cisplatin or carboplatin plus cyclophosphamide. With these two regimens, similar pathologically proven response rates can be obtained [3]. Cisplatin and melphalan are equally effective. In a large single-arm study conducted by the SAKK (Swiss Group for Clinical Cancer Research), a pathological response rate of 59% was achieved with 6 cycles of this combination [4].

Whole-adominal radiotherapy (WAR) was mainly used for palliation until the reports by Dembo et al. proved its usefulness for improving survival in patients with small or no residual disease after the first operation [5]. The open field technique became the standard approach and proved to be equally effective but less toxic and easier to apply than the moving-strip [6]. Several single-arm studies of sequential multimodality therapy including chemotherapy, second-look surgery and radiotherapy [4, 7–8] have been published since the report of Dembo. It remains difficult to draw conclusions from these non-randomized studies.

In the previous SAKK trial [4], the actuarial 3-year time to progression after second-look operation for patients who achieved complete remission and underwent radiotherapy for consolidation of response was 83% vs. 49% for patients without radiation.

We therefore decided in 1985 to study the feasibility and efficacy of WAR after short-course chemotherapy. Our aims were to induce a high number of pathologically verified complete remissions with surgery plus 4 cycles of cisplatin and melphalan and to prevent relapse with WAR in a target population of patients in remission (pathologically and clinically complete remissions and patients with microscopic residual disease).

Patients and methods

Eligibility

The eligibility criteria included: histologically confirmed epithelial carcinoma of the ovary (with the exception of rare clear cell carcinoma and malignant mixed Mullerian tumors); International Federation of Gynecology and Obstetrics (FIGO) stage IC, IIB–C, III or IV; no prior treatment; upper age limit of 70 years; ECOG performance status <3; adequate bone marrow, hepatic and renal function; no history of prior malignancy other than basal or squamous cell skin cancer or adequately treated squamous cell cancer of the cervix in situ.

Patients were classified after initial surgery as having unresectable residual disease <= 2 cm or >2 cm. Lymph node and gastrointestinal involvement were judged by either histology or obvious intraoperative presentation.

A pathology review of histological diagnosis was performed by a central panel after completion of the study. The histological typing of the epithelial tumors was done in accordance with the WHO classification of ovarian tumors (1973). The histological grading of the primary tumors was analogous to the FIGO grading for endometrial carcinomas.

Baseline examinations included a complete physical examination, blood count, urine test, measurement of CA-125, chest X-ray and computed tomography. Oral informed consent was obtained from all patients before initiation of therapy.

Treatment

Chemotherapy

Patients received 4 cycles of PAMP: cisplatin (P) 80 mg/m^2 intravenously (i.v.) on day 1 with prehydration and forced diuresis, melphalan (PAM) 12 mg/m^2 i.v. on day 2. The treatment started within 10–30 days after surgery and was repeated every 28 days. Antiemetics were administered at the discretion of the treating physician.

Toxicity was graded according to the WHO classification [9].

Response evaluation was performed after 4 cycles. Patients with no signs of disease or with partial remission in whom debulking could be performed underwent a restaging laparotomy. It was planned for patients with partial remission or no change to receive an additional 2–3 cycles. Patients with clinically or pathologically complete remission or with microscopical residual disease after 4–6 cycles were scheduled for WAR.

Radiotherapy

WAR was carried out by means of the open field technique with the entire abdomen as a target volume on a linear accelerator with the recommended energy of 8 MeV (energies from 6–16 MeV were allowed). A daily prescription point dose of 1.3 Gy was administered by opposed fields in 5 fractions per week up to a total dose of 29.9 Gy.

Radiotherapy was to begin within a maximum of 6 weeks after second-look laparotomy. WAR was interrupted if WBC were $<2.5 \times 10^9$/l or platelets $<70 \times 10^9$/l. WAR was reintroduced after interruption if WBC were $>3.5 \times 10^9$/l and platelets 150×10^9/l. In instances of interruption <= 5 days, 23 fractions were still applied, and in instances of interruption of >5 days, 24 fractions were applied. If the interruption was >10 days, 25 fractions were given. If the interruption lasted longer than 20 days, continuation of radiotherapy was left to the judgment of the therapist.

Documentation of the treatment was sent to a central quality review institution.

Response

WHO criteria were adopted [9] for clinical response evaluation. Clinically assessed response was, whenever possible, documented by second-look surgery.

Patients

Two hundred sixty-two patients were registered from 15 July 1985 to 22 November 1991. Forty-four patients were excluded from this analysis. They were: 7 ineligible cases (clear cell carcinoma, FIGO stage IB, tuba carcinoma, previous breast cancer, PS = 3 and age >70 years), 34 patients identified by the central review as having borderline tumors or other histologies and 3 'major' protocol violations.

Table 1 reports the patient characteristics. Displayed histological type and tumor grading are as assessed by the central pathology review. Unclassified epithelial carcinomas are included in the group of undifferentiated tumors. About 80% of the patients started PAMP within 1 month after surgery; the maximum delay was 2 months.

Table 1. Eligible patients characteristics and features of disease.

	Frequency	Percent
Histology		
Serous	142	65%
Endometrioid	13	6%
Undifferentiated	52	24%
Mucinous	6	3%
Unknown at review	5	2%
Grade		
1	12	6%
2	43	20%
3	135	62%
Unknown at review	28	13%
FIGO stage		
IC	17	8%
IIB and C	17	8%
III	146	67%
IV	38	17%
Performance status		
0	94	43%
1	99	45%
2	25	12%
Type of surgery		
Incomplete	75	34%
Complete	143	66%
Residual tumor after first surgery		
0	43	20%
<= 2 cm	90	41%
>2 cm	85	39%
Total	218	

Statistics

All patients entered into the study were followed until death or at least August 1993. The median follow-up was 5 years (range: 20–93 months). The end points were: remission rate, pCR rate, progression-free survival, time to failure (TTF), overall survival, toxicity and morbidity of PAMP and of WAR. Allocation to WAR was not based on randomization but on the choice of the treating physician. Results concerning efficacy based on comparisons between outcome of WAR vs. no WAR have therefore be interpreted with caution.

Progression-free survival and survival time were calculated from the first day of treatment. TTF was defined as the time from second-look to the first sign of progression, second cancer or death. For patients without second-look, the earliest data of achieving best response was considered. The distributions of progression-free survival, TTF and survival were estimated by the method of Kaplan and Meier [10]. The prognostic importance of variables was assessed using both univariate and multivariate methods [11, 12]. Hazard ratio (HR, failure/death) values >1 (<1) indicate an increased (reduced) risk of failure/death as compared to the appropriate reference group. Logistic regression was used to simultaneously adjust for the effects on WAR completion of several explanatory variables. All reported p-values are for 2-sided tests.

Results

Two hundred eighteen patients were assessed for response to chemotherapy, progression-free and overall survival. The median progression-free survival was 17 months. At 3 years 28% (95% CI: 22%–34%) and at 5 years 17% (11%–23%) were alive and progression free. The median overall survival was 30 months. 148 patients died (146 of disease and 2 of myocardial infarction before relapse). At 3 years 43% (36%–50%) and at 5 years 26% (19%–33%) were still alive.

Overall response

Overall, 146/218 patients (67%, 95% CI: 61%–73%) showed response to chemotherapy. The estimated overall CR rate (pCR and cCR) was 37% (95% CI: 31%–43%). Seven patients reached pCR and 3 reached cCR after more than 4 cycles. Table 2 summarizes the responses by early- (FIGO I–II) and advanced-stage (FIGO III–IV) groups.

Table 2. Response by stage groups.

	Early stages (FIGO I–II)		Advanced stages (FIGO III–IV)	
Response	Frequency	Percent	Frequency	Percent
CR	25	74%	55	30%
pCR	19	56%	37	20%
cCR	6	18%	18	10%
PR	1	3%	65	35%
NC	4	12%	29	16%
PD	4	12%	35	19%
Total	34		184	

In a total of 147/218 (67%) patients response was pathologically verified (12 of them had second-look after >4 cycles). In the remaining 71 cases (33%) response was only clinically evaluated. As expected, the comparison between the 2 methods confirmed that clinical assessment did not always reflect the actual situation, as 30% of the pathologically verified responses were inferior to those clinically documented.

For further analyses of WAR and prognostic factors, 118 patients in remission (56 pCR, 27 cCR and 35 pPR with microscopic residual disease) were considered. Their characteristics according to stage group and WAR are displayed in Table 3. Radiotherapy was performed only in 51/118 (43%) patients in remission despite the protocol indication. The main reasons were refusal and recommendation of the treating physician. The rate of irradiation was similar in the two stage groups: 13/26 (50%) in early vs. 38/92 (41%) in advanced-stage, respectively ($p = 0.50$). However, young (<55 years) early-stage patients were more likely to be irradiated: 10/13 (77%) received WAR and 3/13 (23%) did not receive it ($p = 0.02$). Moreover, advanced-stage patients with clinical evaluation alone (i.e., cCR) were less likely to be irradiated than patients with pathological evaluation: 10% vs. 51% ($p = 0.003$) (see Table 3).

Table 3. Characteristics of patients in remission by stage and WAR.

	Early stages (FIGO I–II)		Advanced stages (FIGO III–IV)	
	Not irradiated	Irradiated	Not irradiated	Irradiated
Performance status				
0	8	9	21	19
1–2	5	4	33	19
Age (years)				
<= 55	3	10	21	15
>55	10	3	33	23
Histology				
Serous	9	9	31	25
Non-serous	4	4	23	13
Grade				
1–2	5	6	9	8
3	8	7	38	27
Unknown at review	0	0	7	3
Residual after first surgery				
<= 2 cm	12	11	33	29
>2 cm	1	2	21	9
Lymph node involvement				
No	10	7	18	14
Yes or unknown	3	6	36	24
Pathological response				
pCR	9	10	17	20
pPR	0	1	18	16
Not evaluated (cCR)	4	2	19	2
Total	13	13	54	38

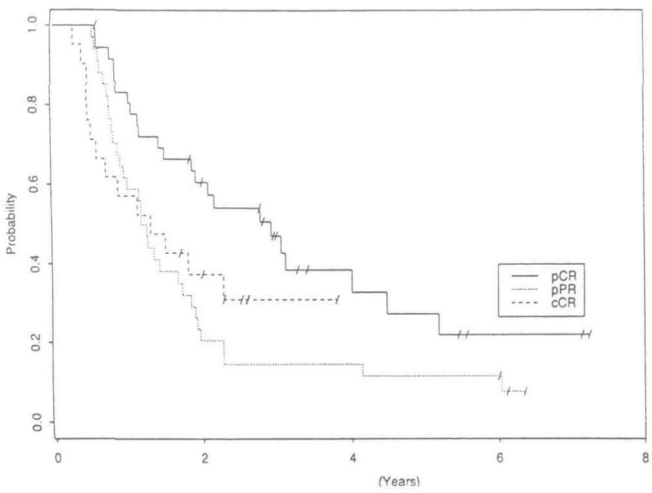

Fig. 1. Advanced stage, TTF by pathological response.

Patients in remission: Time to failure

The median TTF of all patients in remission was 23 months with 76/118 recurrences thus far. At 3 years 38% (95% CI: 28%–48%) and at 5 years 29% (19%–39%) were still in remission. No second cancers have been observed thus far. The low number of recurrences [8] did not allow a reliable evaluation of TTF in early stages.

Advanced stage (FIGO III–IV). The most important factors in predicting prolonged TTF were residual disease after first surgery <= 2 cm, no lymph node involvement at diagnosis and achievement of pCR. TTF curves by response are displayed in Fig. 1. Three-year percentages (95% CI) were: 47% (29%–65%) for pCR, 31% (10%–42%) for cCR and 15% (3%–27%) for pPR with microscopically residual disease. No significant effect of WAR could be observed. The multivariate analysis adjusted for age, grade and residual disease confirmed the role of achievement of pCR (HR = 0.48, 95% CI: 0.28–0.82, p = 0.007) and that WAR did not significantly predict TTF.

Seventy-six/118 patients in remission have relapsed so far. Sixty-one were found to have diffuse peritoneal carcinosis +/− distant metastases (23 with WAR and 38 without). In 13 patients relapse occurred in the pelvis +/− distant metastases (7 with WAR and 6 without); for 8 of them, pelvic relapse was verified by laparotomy. Two patients had distant metastases without sign of disease in their abdomen (1 with WAR and 1 without). There was no significant difference in relapse sites between irradiated and non-irradiated patients.

Patients in remission: Survival

The median survival for all patients in remission was 50 months. Fifty-nine patients died of tumor and 1 died without relapse of myocardial infarction. At 3 years 63% (95% CI: 53%–73%) and at 5 years 43% (31%–55%) were still alive. As for TTF, the low number of events did not allow a reliable evaluation in early stages.

Advanced stage (FIGO III–IV). The most important factors in predicting prolonged survival were low grade, no lymph node involvement at diagnosis and achievement of pCR. Three-year percentages (95% CI) were: 76% (62%–90%) for pCR, 53% (31%–75%) for cCR and 43% (25%–61%) for pPR with microscopically residual disease. No significant effect of WAR could be observed. The multivariate analysis adjusted for age, grade and lymph node involvement confirmed the role of achievement of pCR (HR = 0.31, 95% CI: 0.16–0.61, p = 0.0004) and that WAR did not significantly predict survival.

Radiotherapy

WAR was performed in 51/118 (43%) patients in remission. It was completed for 34 patients (67%); 17 of them had interruptions. WAR was not completed, mainly due to hematological toxicity, in 17 patients (33%). One of them received only irradiation of the pelvis (protocol violation). Advanced stages had a lower completion rate (61%) than early stages (85%; p = 0.18). Median doses were: 29.9 Gy (complete), 31.2 Gy (complete with interruptions) and 15.6 Gy (incomplete). The two stage groups received the same doses. Forty-one patients were irradiated after 4 cycles and 10 after 6–7 cycles of PAMP. A logistic regression analysis was performed to assess the effect of various factors on completeness (with or without interruptions) of WAR. Significantly higher WAR completion rates were obtained for early-stage (I–II), small (<= 2 cm) residual disease at diagnosis and previous higher doses of cisplatin. Significantly lower WAR completion rates were found for patients experiencing toxicity (nausea/vomiting and neurological) during chemotherapy. Previous second-look surgery was not significantly related to the WAR completion rate.

Toxicity and side effects

Chemotherapy

Two hundred fifty-two patients started chemotherapy and were evaluated for toxic effects of PAMP for a total of 960 cycles. Two hundred twenty-four patients (89%) received a minimum of 4 cycles of PAMP. Sixteen minor protocol violations occurred (6%) and were mainly due to: fewer cycles because of refusal, substitution of cisplatin with carboplatin after 1–2 cycles and substitution of melphalan by cyclophosphamide because of toxicity.

The median dose of cisplatin was 78 mg/m^2 (range 20–106 mg/m^2). In 62% of the cycles cisplatin was given at a dosage of >75% of the planned dose. The

median dose of Melphalan was 12 mg/m^2 (range 10–63 mg/m^2). In 75% of the cycles melphalan was given at a dosage >75% of the planned dose. Five patients erroneously received overdosages of melphalan: they received more than 30 mg/m^2 and developed transient severe myelosuppression but all eventually recovered.

Hematological toxicity was the major acute toxicity. Leukocyte counts had a median nadir of 2.1×10^9/l (range: $1.0–4.2 \times 10^9$/l). The leukocyte count was less than 4.0×10^9/l at least once for 248/250 patients. The median platelet nadir was 86×10^9/l (range: $2–269 \times 10^9$/l). Platelet counts were $<10 \times 10^9$/l for 10 patients (3 of them had received overdosages of melphalan). The median hemoglobin nadir was 9.5 g/dl (range, 5.2 to 12.3 g/dl).

Radiotherapy

Acute side effects. 17/51 patients temporarily interrupted WAR mainly because of transient hematotoxic side effects. In addition, another 15 patients were unable to complete WAR due to hematological toxicity. The median hemoglobin nadir was 10.8 (range: 9.1–13.3) g/dl, and the median leukocyte count nadir was 2.4×10^9/l (range: $1.2–4.3 \times 10^9$/l). The median platelet nadir was 85×10^9/l (range: $19–172 \times 10^9$/l). Seventeen percent of the patients had grade 2–3 diarrhoea and 20% grade 2–3 nausea. No important skin reactions were observed.

Long term side effects. Twelve patients developed side effects with delayed onset. Ten patients developed gastrointestinal side effects: 4 patients complained of chronic 'mild' constipation and 1 of chronic 'mild' diarrhoea; 3 patients developed chronic 'moderate' subtotal bowel obstruction many months before a relapse was documented; 1 patient developed bowel occlusion needing surgery (no evidence of recurrence); and 1 patient suffered from disabling bowel bleeding after additional pelvic irradiation for first relapse. Repeated colonoscopies demonstrated enteropathy due to radiation damage. In another 2 patients basal lung tissue changes were documented in repeated chest X-rays and attributed to previous irradiation.

Discussion

This study was designed to address the role of short-course cisplatin-based chemotherapy in patients with early and advanced ovarian cancer and the feasibility and role of WAR in patients in remission. The overall response rate was 67% with 26% of the patients achieving pCR. This is comparable to other data in the literature for cisplatin-based chemotherapies delivered over 6–12 cycles [4, 13]. Sixty-seven percent of the responses were pathologically evaluated. Interestingly, few patients reached pCR or cCR after more than 4 cycles. The data showed that best response with platinum regimens was obtained in an early phase of treatment and that further cycles did not necessarily eradicate persistent disease. Hainsworth suggested that, after 6 cycles, patients should be considered for investigational approaches [14]. We would recommend this approach even after 4 cycles. Toxicities observed with PAMP were mild to moderate and well manageable. Hematological toxicity grade 4, which may be attributed to melphalan, occurred in about 7%–10% of the cases, which is also a rather low rate.

The median overall progression-free survival of the 218 patients and the median overall survival were favorable compared to results for 8 cycles of platinum-based chemotherapies [15]. A direct comparison of outcome, however, may be misleading as we included early stages and the planned cisplatin dose (80 mg/m^2) was higher than in other trials.

At 5 years 29% of the 118 patients in remission were without relapse and 43% were alive. In stage III–IV, we observed a longer TTF for those achieving pCR, with residual disease <= 2 cm at first surgery and without lymph node involvement. With the limitations of prognostic variables analysis [16] in mind, we observed that in stage III–IV, the achievement of pCR was an independent predictor for TTF as well as for survival. Patients in pPR with microscopic residual disease had a worse prognosis than patients in CR, as in the long-term analysis of Neijt et al. [1]. In our study, residual disease after first surgery could not be identified as an independent prognostic variable. Its importance has already been diminished in the overview of Levin et al. [16].

The second aim of this trial was to study the feasibility and role of WAR in patients in remission (pCR, cCR and PR with pathologically documented microscopic residual disease) after the PAMP regimen. Whereas WAR has proven to be useful as adjuvant therapy in early ovarian cancer, its role in advanced stage remains controversial. More recently published results have even disclaimed a benefit for WAR in patients with residual disease after intensive chemotherapy and second-look surgery [17, 18]. A randomized trial in a small number of patients showed no difference in survival [19]. The fact that only one randomized trial has been published illustrates the difficulties of prospectively planned multimodality treatments.

In our study WAR was hardly feasible for the majority of the patients in remission, even after short-course chemotherapy. This poor tolerance of WAR was in contrast to reports from other authors who used doses ranging between 22.5 and 27.5 Gy [17, 18]. We believe that our dose and the restrictive rules defined by the protocol in 1985 were the major reasons for poor tolerance/feasibility. The importance of the dose has been confirmed by the findings of Rothenberg et al., who employed a dose of 30 Gy and observed severe enteropathy [8]. The recommendation of Thomas to limit abdominal radiotherapy to <25 Gy after first surgery, chemotherapy and second-look seems therefore rea-

sonable [20]. Another factor that may have influenced the tolerance of WAR could be the use of melphalan, which is known to be a potential stem cell killer enhancing myelosuppression. We note that about 2/3 of the irradiated as well as non-irradiated patients in remission relapsed. The majority of relapsing patients were found to have diffuse peritoneal carcinosis. We therefore believe that the addition of a pelvic boost, as has been described by others, may not substantially help to prevent relapse but may increase toxicity [20]. These results show that WAR as a consolidation treatment cannot efficiently prevent relapse in patients with pCR or cCR, nor can it be used as an efficient salvage treatment for patients with microscopic residual disease after PAMP.

From these results we conclude that 4 cycles PAMP were an effective treatment in early and advanced ovarian cancer. WAR was hardly feasible as a consolidation treatment for the majority of the patients in remission, even after short-course chemotherapy. The data allow no definitive conclusions about the role of WAR because no randomization took place and a selection bias may have influenced the data. The total dose delivered to the whole abdomen should probably be below 29.9 Gy and previous chemotherapy should be short. The current evaluation adds certainty to the conclusions drawn in our first report. For the majority of patients, especially those with advanced disease, new treatment modalities are needed.

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