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Short Communication

A randomised phase III study comparing high-dose chemotherapy to conventionally dosed chemotherapy for stage III ovarian cancer: The Finnish Ovarian Cancer (FINOVA) study

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ABSTRACT

Women with stage III ovarian cancer and with ⩽2 cm residual tumour were randomly assigned to receive either conventionally dosed chemotherapy (group A) or HDCT (group B). Patients allocated to group A received 6 cycles of paclitaxel (T) 135 mg/m^2 and cisplatin (P) 75 mg/m^2 every 3 weeks, and those allocated to HDCT received 3 TP cycles followed by peripheral blood stem cell mobilisation with cyclophosphamide (C) 3000 mg/m^2 and T 175 mg/m^2, and subsequently HDCT with carboplatin 1500 mg/m^2, C 120 mg/kg, and mitoxantrone 75 mg/m^2. The trial was closed early after 42 patients were entered due to slow accrual. The median follow-up time of patients who were alive was 81 months. The median progression-free survival time was 15.9 and 16.6 months (hazard ratio, HR 0.83; 95% CI 0.41–1.69, $P = 0.61$) and the median overall survival time was 43.7 and 64.3 months (HR, 0.74; 95% CI 0.34–1.61, $P = 0.44$) in groups A and B, respectively. Although one patient died of HDCT-related toxicity, the regimen was otherwise relatively well tolerated. We conclude that the HDCT regimen used was feasible, but did not result in significantly improved survival in this prematurely closed trial. A clinically important survival benefit cannot be excluded due to the small sample size.

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1. Introduction

Patients diagnosed with ovarian carcinoma and who have a low tumour burden following surgery, chemosensitive disease, and who are treated at the first remission might benefit from high-dose chemotherapy (HDCT) supported by autologous stem cell transplantation (ASCT).[1–6] However, none of the gynaecologic oncology collaborative groups has as yet succeeded in performing a well-powered randomised trial comparing efficacy and safety of HDCT with modern conventionally dosed chemotherapy regimens. The purpose of the present study was to evaluate whether a clinically relevant improvement in the outcome can be achieved when HDCT is added to a combination of paclitaxel and cisplatin as a part of the first-line therapy of patients with optimally debulked ovarian cancer.

2. Patients and methods

This prospective, randomised, phase III, open-label, multicenter study was designed to compare conventionally dosed chemotherapy (group A) to the same chemotherapy followed by HDCT (group B) as the first systemic therapy for ovarian cancer. The study was conducted in five University Hospitals of Finland between May 1997 and June 2000. The inclusion criteria were histologically confirmed stage III ovarian cancer, presence of a residual tumour mass 2 cm or smaller at the time of surgery, age 65 years or less at randomisation, the World Health Organization (WHO) performance status 2 or less, and no prior cancer chemotherapy. Renal, hepatic, cardiac and haematologic functions were required to be adequate for chemotherapy. The study was approved by the National Agency for Medicines in Finland and by an Institutional Review Board of the participating hospitals. All patients provided a written informed consent before study entry.

All study participants first received 3 cycles of paclitaxel (T) 135 mg/m^2 and cisplatin (P) 75 mg/m^2 at 3-week intervals; the first response evaluation was performed after the third TP cycle. The patients who had progressive disease were removed from the study. In case of stable disease or response as defined by the WHO,[7] patients allocated to group A received 3 further cycles of TP, and those allocated to group B (HDCT) received cyclophosphamide 3000 mg/m^2 followed by paclitaxel 175 mg/m^2 to mobilise bone marrow stem cells followed by one cycle of HDCT. The HDCT regimen consisted of carboplatin 1500 mg/m^2, cyclophosphamide 120 mg/kg, and mitoxantrone 75 mg/m^2.[8,9] Patients who had either a partial remission or stabilised disease were treated with 3 cycles of carboplatin at the AUC 5, and those who had progressive disease received second line chemotherapy at the discretion of the treating physician. Protocol-defined follow-up visits took place at 2-month intervals during the first 2 years following randomisation, and subsequently at 4-month intervals. The median follow-up time of the patients who were still alive was 81 months (range, 27–99 months).

The primary end-point was overall survival and the secondary end-point was progression-free survival (PFS). In cases with no measurable residual disease, clinical response evaluation and detection of recurrent disease were based on the CA-125 criteria.[10–13]

Analyses of survival and PFS were done according to the intention-to-treat principle. Survival was estimated using the Kaplan–Meier method, and survival between groups was compared using the log-rank test. Hazard ratios and confidence intervals are based on Cox's regression analysis. All P values are 2-sided.

3. Results

Forty-two patients were randomly assigned to the study between May 1997 and June 2000 (Table 1). All 17 patients who received mobilisation treatment underwent successful peripheral blood stem cell collection. The median number of days needed to neutrophil recovery to 0.5×10^9/L was 11 days (range, 8–17) and to platelet recovery to 20×10^9/L was 12 days (range, from 6–17). Sixteen patients assigned to group A and 15 of those assigned to group B were diagnosed with progressive cancer, and 14 patients in group A and 12 patients in group B died (Table 2). The median progression-free survival time was 15.9 months in group A and 16.6 months in group B (hazard ratio, HR 0.83; 95% CI 0.41–1.69, $P = 0.61$). The median overall survival time did not differ significantly between the groups, and was 43.7 months among women assigned to

Table 1 – Characteristics of the patients and reasons for therapy discontinuation

	Group A[a] ($n = 20$) N (%)	Group B[a] ($n = 22$) N (%)
Median age (range)	54 (24–65)	52.5 (35–64)
FIGO stage		
III A	1 (5)	1 (5)
III B	4 (20)	2 (9)
III C	15 (75)	19 (86)
Histological type of cancer		
Serous	12 (60)	15 (68)
Mucinous	3 (15)	0 (0)
Endometrioid	2 (10)	3 (14)
Clear cell	0 (0)	2 (9)
Undifferentiated	3 (15)	2 (9)
Histologic grade		
1	2 (10)	7 (32)
2	6 (30)	7 (32)
3	9 (45)	7 (32)
0 = not known	3 (15)	1 (5)
Residual tumour		
Microscopic	6 (30)	8 (36)
Macroscopic, <2 cm	14 (70)	14 (64)
Reasons for treatment discontinuation		
As per protocol	17 (85)	17 (77)
Progressive disease	1 (5)	2 (9)
Adverse event	1 (5)	1 (5)
Consent withdrawn	0 (0)	2 (9)
Other	1	0 (0)

a Group A, paclitaxel and cisplatin chemotherapy; Group B, paclitaxel and cisplatin followed by high-dose chemotherapy.