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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

*Seija Grénman[a,*], Tom Wiklund[b], Jyrki Jalkanen[c], Tapio Kuoppala[d], Johanna Mäenpää[d], Arja Kuronen[e], Arto Leminen[c], Ulla Puistola[f], Päivi Vuolo-Merilä[f], Tuula Salmi[a], Maarit Vuento[d], Merja Yliskoski[g], Maija Itälä[h], Hans Helenius[i], Heikki Joensuu[b], Pentti Lehtovirta[c]*

[a]*Department of Obstetrics and Gynaecology, Turku University Hospital, PL 52, 20521 Turku, Finland*
[b]*Department of Oncology, Helsinki University Hospital, Pl 140 00029 HYKS, Finland*
[c]*Department of Obstetrics and Gynaecology, Helsinki University Hospital, PL 140, 00029 HYKS, Finland*
[d]*Department of Obstetrics and Gynaecology, Tampere University Hospital, PL 2000, 33521 Tampere, Finland*
[e]*Department of Obstetrics and Gynaecology, Middle Finland Central Hospital, Keskussairaalantie 19, 40620 Jyväskylä, Finland*
[f]*Department of Obstetrics and Gynaecology, Oulu University Hospital, PL 22, 90221 Oulu, Finland*
[g]*Department of Obstetrics and Gynaecology, Kuopio University Hospital, PL 1777, 70211 Kuopio, Finland*
[h]*Department of Internal Medicine, Turku University Hospital, PL 52, 20521 Turku, Finland*
[i]*Department of Biostatistics, Turku University, 20014 Turun Yliopisto, Finland*

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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.



* *Corresponding author:* Tel.: +358 2 313 2300; fax: +358 2 313 2340.
E-mail address: seija.grenman@tyks.fi (S. Grénman).
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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 $0.5 \times 10^9$/L was 11 days (range, 8–17) and to platelet recovery to $20 \times 10^9$/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.

**Table 2 – Therapy outcome**

| | Group A[a] N (%) | Group B[a] N (%) |
|---|---|---|
| Alive, disease-free | 4 (20) | 5 (23) |
| Progressive disease | 16 (80) | 15 (68) |
| Alive with disease | 2 (10) | 2 (9) |
| Dead | 14 (70) | 12 (54) |

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

group A and 64.3 months among those assigned to group B (HR, 0.74; 95% CI 0.34–1.61, $P = 0.44$).

The regimen containing HDCT was more toxic than the conventionally dosed regimen (Table 3). One toxic death from renal failure and subsequent cerebral infarction took place following HDCT. The median number of days spent in hospital was 13.5 in arm A and 34.5 in arm B, and the need of red blood cell and platelet transfusions was also greater in arm B (Table 4).

**Table 3 – Grades 3 and 4 adverse events**

| | Group A[a] Number of cycles administered: 121 (Number of patients: 20) N (%) | Group B[a] Number of cycles administered: 98 (Number of patients: 22) N (%) | Group B[a] Number of high dose cycles administered: 17 (Number of patients: 17) N (%) |
|---|---|---|---|
| Anaemia | | | |
| Grade 3 | 7 (35) | 19 (86) | 7 (41) |
| Grade 4 | 0 (0) | 0 (0) | 0 (0) |
| Neutropenia | | | |
| Grade 3 | 0 (0) | 0 (0) | 0 (0) |
| Grade 4 | 20 (100) | 21 (95) | 16[b] (94) |
| Thrombocytopenia | | | |
| Grade 3 | 0 (0) | 0 (0) | 0 (0) |
| Grade 4 | 4 (20) | 16 (73) | 16 (100) |
| Infections | | | |
| Grade 3 | 2 (10) | 9 (41) | 8[b] (50) |
| Grade 4 | 0 (0) | 0 (0) | 0 (0) |
| Mucositis | | | |
| Grade 3 | 0 (0) | 2 (9) | 2[b] (13) |
| Grade 4 | 0 (0) | 0 (0) | 0 (0) |
| Diarrhoea | | | |
| Grade 3 | 1 (5) | 4 (18) | 3 (18) |
| Grade 4 | 0 (0) | 1 (5) | 1 (6) |
| Peripheral neurotoxicity | | | |
| Grade 2 | 1 (5) | 1 (5) | 0 (0) |
| Grade 3 | 1 (5) | 0 (0) | 0 (0) |

a Group A, paclitaxel and cisplatin chemotherapy; Group B, paclitaxel and cisplatin followed by high-dose chemotherapy.
b 1 patient had missing data.

**Table 4 – Supportive care given**

| | Group A[a] Number of cycles administered: 121 (Number of patients: 20) N (%) | Group B[a] Number of cycles administered: 98 (Number of patients: 22) N (%) | Group B[a] Number of high dose cycles administered: 17 (Number of patients: 17) N (%) |
|---|---|---|---|
| | Group A[a] | Group B[a] | Group B[a] |
| Number of days in hospital, median per patient (range) | 13.5 (3–39) | 34.5 (7–102) | 24 (9–80) |
| Total number of days on i.v. Antibiotics, median per patient (range) | 36 0 (0–14 ) | 292 10 (1–32) | 228 13 (8–32)[b] |
| Total number of RBC transfusions (units) | 31 | 107 | 60 |
| Total number of platelet transfusions (units) | 7 | 74 | 73 |

a Group A, paclitaxel and cisplatin chemotherapy; Group B, paclitaxel and cisplatin followed by high-dose chemotherapy.
b 1 patient had missing data.

## 4. Discussion

The current prospective, randomised study was initiated to evaluate HDCT as the front-line treatment of optimally debulked advanced ovarian cancer. The high-dose chemotherapy administered was feasible, but the study was closed prematurely due to decreasing accrual rates in the participating centres. A slow patient accrual has been a major problem in all prospective studies that have evaluated HDCT in ovarian cancer.[14–19] The reasons for this may include treatment-related toxicity, high costs and modest survival gains associated with HDCT in other cancer types.[20] Although adverse events were more frequent and one patient died of toxicity in the high-dose arm, toxicity was not considered to be a significant limiting factor for accrual in the present study.

The preliminary results of one randomised trial where HDCT was administered as the first-line treatment for ovarian cancer has been reported. A French study group randomly assigned 110 women with small-volume chemosensitive disease at second-look laparotomy to receive either carboplatin and cyclophosphamide-based HDCT or 3 cycles of conventional therapy using the same drugs.[19] After a median follow-up of 60 months, neither progression-free survival nor overall survival was significantly different between the conventional dose arm and the high-dose arm (12.2 versus 17.5 months and 42.5 versus 49.7 months, respectively). Although neither the French nor the present study detected a significant difference in survival between the HDCT and the control groups, a clinically significant survival benefit associated to HDCT cannot be excluded due to the small numbers of patients entered.

## Conflict of interest statement

None declared.

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REFERENCES

1. Benedetti-Panici P, Greggi S, Scambia G, et al. Very high-dose chemotherapy with autologous peripheral stem cell support in advanced ovarian cancer. *Eur J Cancer* 1995;**31**(12):1987–92.
2. Shinozuka T, Miyamoto T, Muramatsu T, et al. High dose chemotherapy with autologous stem cell support in the treatment of patients with ovarian carcinoma. *Cancer* 1999;**85**:1555–64.
3. Bertucci F, Viens P, Delpero JR, et al. High-dose melphalan-based chemotherapy and autologous stem cell transplantation after second-look laparotomy in patients with chemosensitive advanced ovarian carcinoma: long-term results. *Bone Marrow Transplant* 2000;**26**:61–7.
4. Salerno MG, Ferrandina G, Greggi S, et al. High-dose chemotherapy as a consolidation approach in advanced ovarian cancer: long-term results. *Bone Marrow Transplant* 2001;**27**:1017–25.
5. Ledermann JA, Herd R, Maraninchi D, et al. High-dose chemotherapy for ovarian carcinoma: Long-term results from the Solid Tumor Registry of the European Group for Blood and Marrow Transplantation (EBMT). *Ann Oncol* 2001;**12**:693–6.
6. Bengala C, Guarneri V, Ledermann J, et al. High-dose chemotherapy with autologous haemopoietic support for advanced ovarian cancer in first complete remission: retrospective analysis from the Solid Tumour registry of the European Group for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* 2005;**36**:25–31.
7. WHO Handbook of Reporting Results of Cancer Treatment. Geneva: Who Offset Publication; 1979. p. 48.
8. Mulder PO, Sleijfer DT, Willemse PH, et al. High-dose cyclophosphamide or melphalan with escalating doses of mitoxantrone and autologous bone marrow transplantation for refractory solid. *Tumors Cancer Res* 1989;**49**:4654–8.
9. Stiff P, Bayer R, Camarda M, et al. A phase II trial of high-dose mitoxantrone, carboplatin, and cyclophospamide with autologous bone marrow rescue for recurrent epithelial ovarian carcinoma: Analysis of risk factors and clinical outcome. *Gynecol Oncol* 1995;**57**:278–85.
10. Rustin GJS, Nelstrop AE, Tuxen MK, et al. Defining progression of ovarian carcinoma during follow-up according to CA 125: A North Thames Ovary Group study. *Ann Oncol* 1996;**7**:361–4.
11. Vergote I, Rustin GJ, Eisenhauer EA, et al. Re: new guidelines to evaluate the response to treatment of solid tumors [ovarian cancer]. *Gynecologic Cancer Intergroup. J Natl Cancer Inst* 2000;**92**:1534–5.
12. Rustin GJ, Quinn M, Thigpen T, et al. Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. *Gynecologic Cancer Intergroup. J Natl Cancer Inst* 2004;**96**:487–8.
13. Rustin G, Timmers P, Nelstrop A, et al. Comparison of CA-124 and standard definitions of progression of ovarian cancer in the intergroup trial of cisplatin and paclitaxel versusus cisplatin and cyclophophamide. *J Clin Oncol* 2006;**24**:45–51.
14. Grénman S, Rantanen V, Salmi T. High-dose chemotherapy with autologous stem cell support in advanced ovarian cancer. *Ann Med* 1996;**28**:151–8.
15. Ozols R, Gore M, Trope C, Grenman S. Intraperitoneal treatment and dose-intense therapy in ovarian cancer. *Ann Oncol* 1999;**10**:S59–64 (Supplement).
16. Pujade-Lauraine E, Cure H, Battista C, et al. High dose chemotherapy in ovarian cancer. *Int J Gynecol Cancer* 2001;**11**(Suppl. 1):64–7.
17. Rosti G, Ferrante P, Ledermann J, et al. High-dose chemotherapy for solid tumors: results of the EBMT. *Crit Rev Oncol/Hematol* 2002;**41**:129–40.
18. Schilder RJ, Brady MF, Spriggs D, et al. Pilot evaluation of high-dose carboplatin and paclitaxel followed by high-dose melphalan supported by peripheral blood stem cells in previously untreated advanced ovarian cancer: A Gynecologic Oncology Group Study. *Gynecol Oncol* 2003;**88**:3–8.
19. Cure H, Battista J, Guastalla J, et al. Phase III Trial of high-dose chemotherapy (HDC) and peripheral blood stem cell (PBSC) support as consolidation in patients (pts) with responsive low-burden advanced ovarian cancer (AOC): 5-year follow-up of a GINECO/FNCLCC/SFGM-TC Study. In: Proceedings of the American Society of Clinical Oncology (abstr 5006), vol. 23, 2004. p. 449 .
20. Nieboer P, de Vries EGE, Mulder NH, van der Graaf WTA. Relevance of high-dose chemotherapy in solid tumours. *Cancer Treat Rev* 2005;**31**:210–25.