Ann Med 1996 Apr;**28(2)**:151-158

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MeSH Terms:

- Antineoplastic Agents, Combined/therapeutic use*
- Antineoplastic Agents, Combined/administration & dosage
- Clinical Trials
- Combined Modality Therapy
- Dose-Response Relationship, Drug
- Female
- Hematopoietic Stem Cell Transplantation*
- Human
- Ovarian Neoplasms/therapy*
- Ovarian Neoplasms/pathology
- Survival Rate
- Transplantation, Autologous

Substances:

- Antineoplastic Agents, Combined

PMID: 8732644, MUID: 96309481

High-dose Chemotherapy with Autologous Stem Cell Support in Advanced Ovarian Cancer

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Since 1981, over 300 patients reported with advanced or refractory ovarian cancer have been treated with high-dose chemotherapy supported by autologous bone marrow or peripheral blood stem cell transplantation. Partial or complete clinical response has been reported in 54–100% of the cases, but the median duration of the response in the majority of patients has been only a few months. It is obvious from the available data that high-dose regimens supported by autologous stem cell transplantation (ASCT) are not capable of inducing long-term survival in patients with heavy tumour burden or chemoresistant ovarian cancer. Recent reports on nearly 100 patients have described results of the use of high-dose chemotherapy as first-line treatment for patients with optimally debulked disease or negative second-look laparotomy. Response rates and survival have been better when compared to historical controls, but the efficacy of this treatment modality in inducing durable remission has not been tested in randomized trials. Most of the ongoing trials presented briefly in this review have been designed to evaluate the potential of high-dose therapy as first-line treatment in preventing the development of resistant tumour clones and recurrence. The role of sequential high-dose chemotherapy with ASCT as a part of primary treatment or as salvage therapy for chemosensitive recurrent disease is also under investigation.

Key words: autologous stem cell transplantation; high-dose chemotherapy; ovarian carcinoma; peripheral blood stem cell transplantation.

(Annals of Medicine 28: 151–158, 1996)

Introduction

Cancer of the ovary is the sixth most common cancer in women (1) and affects 1–2% of women during their lifetime (2). Because of the lack of early symptoms, 75–80% of the patients present with stage III or IV disease (3) and systemic chemotherapy plays a significant role in the treatment of these patients. Approximately 60–80% of the patients with advanced ovarian cancer will have objective responses with platinum-based chemotherapy, and 50% of the patients will achieve clinically complete remission (CR). However, pathologically proven CR is obtained only in 28–35% (4), and no more than half of these patients will obtain durable remission (5). Thus, 5-year actuarial survival of stages III and IV are 23% and 14%, respectively (3). The contrast of high response rates with major reduction in tumour burden and low numbers of durable complete remissions indicate the presence or development of resistant subpopulations of cells causing relapse of the disease.

The somatic mutation theory explains failure to cure a malignancy as a result of failing to eradicate all drug-sensitive cells because of insufficient dose intensity, or as the emergence of cells that are resistant to the drug regimen (6). The potential benefit of dose-intensive therapy lies in its ability to overcome relative drug resistance and prevent recurrence. Randomized studies evaluating the role of conventional cisplatin-based high-dose chemotherapy in improving survival of advanced ovarian cancer have given contradictory results (7, 8) and currently it is widely agreed that dose escalation by a factor of 2 does not offer a therapeutic benefit in advanced cases (9, 10).

For over 15 years high-dose chemotherapy with autologous stem cell transplantation (ASCT) has been tested in a variety of clinical situations for the treatment of ovarian cancer. In the early trials autologous stem cell support was given as bone marrow transplantation (ABMT), whereas more recent trials have used

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peripheral blood stem cells (PBSC). The heterogenous group of treated patients can be divided into three groups: (i) those who have failed to respond to primary therapy; (ii) those who have had either macroscopic or microscopic residual disease after some response to primary therapy; and (iii) those who have relapsed at various times after CR to primary therapy. The available data show that the patients with low tumour burden have achieved the best response to high-dose therapy with ASCT (11). The initial studies on dose-intensive first-line therapy have given encouraging results (12–15). Consequently, the current ongoing trials have focused on testing the potential of this treatment modality in inducing long-term disease-free survival in patients with low tumour burden and chemosensitive disease. This paper reviews the main results of the available data on high-dose therapy with ASCT in the treatment of advanced ovarian cancer and presents some of the ongoing trials.

Drug Resistance

Drug resistance is still an unsolved obstacle to the successful treatment of ovarian cancer. Changes in cellular detoxification pathways, such as glutathione (GSH), result in a resistance restricted to groups of drugs that have similar reactive species. GSH plays a critical role in cellular detoxification pathways with its ability to bind cytotoxic agents or to facilitate their metabolism and transport. GSH also appears to facilitate DNA repair (16). Studies with drug-resistant human ovarian cancer cell lines have shown that resistance to cisplatin and alkylating agents is associated with increased levels of GSH as well as an increased capacity of tumour cells to repair DNA damage (16–18). Changes in target enzymes or membrane transporters for the drug cause a resistance specific to a small group of structurally related analogues. Classical multidrug resistance is mediated by mdr-1 gene product, P-glycoprotein, causing enhanced efflux of natural products (e.g. doxorubicin, vinca alkaloids and taxanes) in drug-resistant tumour cells (19). Immunohistochemical P-glycoprotein staining or mdr-1 mRNA expression have been detected in 48–63% of ovarian cancer biopsies (20, 21). These findings have correlated with the clinical response to chemotherapy. Some clinical pilot studies have tested the possibility of modulating factors causing platinum resistance in ovarian cancer. These studies have demonstrated inhibition of glutathione synthesis with buthione sulfoximin (BSO) during melphalan chemotherapy (22), decrease of glutathione s-transferase activity after administration of ethacrynic acid to patients receiving thiotepa (23) and inhibition of DNA repair capacity with aphidicolin (24). However, none of these agents has been accepted for wider clinical use.

Many chemotherapeutic agents, irrespective of their mechanism of action, appear to kill cells, with apoptosis being a common final pathway. Mutation of p53 (25) and overexpression of bcl-2 (26) are reported to be associated with impaired ability of programmed cell death. An interesting chemotherapeutic approach to be developed in the future may be agents that mimic p53 function or inhibit bcl-2 activity.

Dose Intensity and Current Practice with Conventional Doses

The rationale for high-dose therapy in ovarian cancer is based on *in vitro* studies showing a deep dose–response curve for cytostatic agents (27, 28) as well as on the classical meta-analysis by Levin and Hryniuk suggesting correlation between cisplatin dose intensity and response to treatment ovarian carcinoma (29). Subsequent evaluation of this meta-analysis indicates that the dose–response relationship of cisplatin is seen to a level of 15 and 25 mg/m^2/week and higher doses do not improve treatment results (30). A recent meta-analysis including 4118 patients evaluated whether increasing cisplatin/carboplatin alone or in combination with other drugs would improve median survival in advanced ovarian cancer. No significant correlation could be demonstrated between dose intensity (mg/m^2/week) or total dose intensity (mg/m^2/week × number of courses) of platinum compounds and median survival. However, total dose intensity of all drugs together with the percentage of optimally debulked patients correlated with median survival (31).

Two frequently cited prospective randomized trials evaluating the relationship of dose intensity and outcome in advanced ovarian cancer have shown no advantage in a doubling of cisplatin dose intensity over ranges from 16 to 33 mg/m^2/week (8) and from 24 to 50 mg/m^2/week (4). In contrast, the study by the Scottish Gynaecological Cancer Study Group, using a dose range from 16 to 33 mg/m^2/week, was closed early because an interim analysis showed significantly better survival in the high-dose arm, 125 vs. 69 weeks (7). The first two studies gave the same total dose of drug in both arms but a 2-fold difference in the dose intensity between the two regimens. In the Scottish trial the high-dose arm received a 66% greater total dose of cisplatin and almost one-third of the patients had stage I or II disease, whereas all patients included in the Gynecological Oncology Group (GOG) and Italian studies were stages III and IV. Detailed reviews of available prospective randomized trials have agreed that no firm evidence exists yet to prove that dose escalation by a factor of two offers any therapeutic benefit in advanced cases (9, 10, 32). This is not surprising because *in vitro* data suggest that a greater than 5-fold increase in dose is desirable (33). The role of conventional high-dose therapy in the treatment of patients with a low tumour burden has not yet been clarified.

The current standard conventional chemotherapy for epithelial ovarian cancer is cisplatin 50–75 mg/m^2 and cyclophosphamide 500–750 mg/m^2 every 3 weeks (10, 34). Mature data from the GOG study, which compares cisplatin plus cyclophosphamide vs. cisplatin plus paclitaxel in the treatment of 385 patients with sub-

optimally debulked stages III and IV ovarian cancer, have been presented recently. Median survival was 24.4 months in the cisplatin group and 37.5 months in the paclitaxel group (35). The potential of paclitaxel

Table 1. Summary of studies on high-dose chemotherapy with autologous stem cell transplantation (ASCT) support in ovarian cancer.

Ref.	Total number of patients	Number of prior regimens	Disease status prior to ASCT*	High-dose treatment†	Clinical responses (%)	Pathological responses (%)	Median response duration (months)	Median survival (months)
38	14	1	mac 9 mic 9	MEL	ND	ND	43	ND
41	11	1	mac 3 mic 8	CTX, VP-16	CR 6/11 (55)	CR 5/11 (46)	15	23
42	12	ND	ND	CBDCA	CR 1/11 (9) PR 5/11 (45)	ND	ND	ND
43	12	median 3 range: 1–5	mac	CDDP i.p., CTX, THIO	CR 1/9 (11) PR 6/9 (67)	PR 6/8 (75)	6	ND
39	35	1	mac 26 mic 9	MEL	CR 4/12 (33) PR 5/12 (42)	ND	ND	ND
44	24	median 2 range: 1–4	mac 19 mic 5	CBDCA IFO VP-16/VM-26 } ×2	CR 2/14 (14) PR 9/14 (64)	ND	ND	ND
12	13	§	mac	CDDP CBDCA VP-16	CR 7/12 (58) PR 5/12 (42)	CR 4/9 (44) PR 5/9 (56)	ND	>10
45	12	1	mac 7 mic 5	CBDCA VP-16	ND	ND	ND	>7
46	14	ND	ND	CTX THIO (+CBDCA)	CR 3/7 (43) PR 1/7 (14)	ND	8.5	ND
47	37	1	no 8	variable	ND	ND	ND	32
40	31	1	no 9	MEL or CBDCA CTX	ND	ND	27	47
48	8	>2	mac 7 mic 1	CBDCA i.p., VP-16 THIO	CR 4/7 (57) PR 2/7 (29)	ND	ND	ND
49	32	ND	ND	CBCDA VM-26 IFO } ×2	CR 2/16 (13) PR 7/16 (43)	ND	ND	ND
50	9	median 2 range: 1–3	ND	CBDCA IFO	CR 5/8 (63) PR 2/8 (25)	ND	6	ND
13	42	0	mac 20 mic 22	CDDP CTX ADR } ×2	ND	ND	ND	‡
14	20	§	mac	CDDP CBDCA VP-16	CR 19/20 (95)	CR 7/19 (37) PR 9/19 (47)	>24	>42
15	16	¶	ND	CBDCA CTX } ×4	ND	CR 5/13 (39) PR 8/13 (61)	ND	ND
51	30	median 2 range: 1–4	mac 27 mic 1 no 2	CBDCA CTX MX	CR 16/27 (59) PR 8/27 (30)	ND	7	29

*mac, macroscopic; mic, microscopic; no, no disease.
ND, no data.
†CDDP, cisplatin; CBDCA, carboplatin; CTX, cyclophosphamide; VP-16, etoposide; VM-26, tenoposide; MEL, melphalan; THIO, thiotepa; ADR, doxorubicin; IFO, ifosfamide; MX, mitoxantrone; PAC, paclitaxel; ABMT, autologous bone marrow transplantation; ASCT, autologous stem cell transplantation; i.p., intraperitoneal.
‡ABMT was performed as adjuvant therapy in 22 patients with a 5-year survival rate of 77.7% and as therapeutic in 20 patients with a 5-year survival rate of 26.3%.
§Two cycles of induction chemotherapy (CDDP, CTX).
¶Two cycles of induction chemotherapy (CTX, PAC).

combined with cisplatin as the first-line treatment for ovarian cancer is currently being studied in a multicentre trial including the European Organization for Research and Treatment of Cancer (EORTC), the National Institute of Canada and several institutions from Scotland and Scandinavia. The optimal dose, schedule, and combination for paclitaxel have not yet been definied (36).

High-dose Therapy with ASCT in Refractory or Recurrent Ovarian Cancer

Patients who progress during treatment, who have stable disease in response to the initial platinum-based regimen, or who relapse within 6 months are considered to have platinum-refractory disease. Patients who respond and have a progression-free interval greater than 6 months off treatment are defined as platinum-sensitive. Response rates of 0–19% have been achieved with conventional salvage therapy in platinum-refractory ovarian cancer. Response rates in platinum-sensitive cases have been 17–100%. The duration of response has been less than 9 months in the majority of studies including both platinum-sensitive and -resistant tumours (37).

The first experiences of the use of high-dose therapy supported by ABMT in the treatment of ovarian cancer were obtained in the early 1980s (38–40). The results from the majority of trials currently available, including over 350 patients with ovarian cancer, are summarized in Table 1. Over two-thirds of the reported patients have been treated for refractory disease. Clinical CR or partial remission (PR) has been seen in 54–100% of the patients. The mean duration of the response has varied between 6 and 43 months, but in most studies it has been less than 9 months. Pathologically proven CR has been reported in 0–46% of evaluable patients. However, detailed response data is missing in several reports and the numbers given are suggestive.

The three largest studies, with over 35 patients each, have been reviewed recently by de Vries and coworkers (11). Altogether, 122 patients with stages III or IV disease had been treated with 6–8 cycles of cisplatin-based chemotherapy after cytoreductive surgery. For 57 patients high-dose therapy was given as consolidation, and 65 patients had either macroscopic disease at follow-up or recurrent disease. In the consolidation group, the median progression-free survival was 32 months and the 5-year progression-free survival was 30%. The median progression-free survival in the salvage group was only 8.7 months and the 5-year overall survival was 25%. Two recent studies have shown similar results. Shpall and coworkers have reported results on 35 patients with bulky or refractory disease. The patients had been treated with high-dose cyclophosphamide, thiotepa and either intravenous (i.v.) or intraperitoneal (i.p.) cisplatin. Also in this series a high response rate of 75% was followed by a short median duration of 6 months (52). Stiff et al. treated 22 patients with ≥ 1 cm residual disease and eight patients with ≤ 1 cm disease at the time of ASCT. The median survival was nearly double in the patients with ≤ 1 cm disease compared to the patients with bulky disease (51). Due to the small number of patients it was concluded that it is too early to determine whether patients with low tumour burden at the time of high-dose therapy have a survival advantage. In the same study platinum-resistant and platinum-sensitive patients were analysed separately. It was obvious that patients with platinum-resistant disease do not benefit significantly from high-dose platinum-containing regimen, as the median progression-free survival was 5.1 months and the overall survival was 10.4 months (51). These data are not different from those reported for single-agent paclitaxel therapy (53).

High-dose Therapy with ASCT as the First-line Treatment

According to the latest FIGO (Fédération Internationale de Gynécologie et d'Obstetrique) Annual Report the actuarial 5-year survival of stages Ia–IIIa ovarian cancer varies from 84 to 52%, whereas that of stages IIIb–IV is 29–14% (3). A meta-analysis of randomized trials for advanced stage patients treated with conventional platinum-based chemotherapy has shown less than 30% 4-year survival (54). However, it is to be noted that patients receiving conventional platinum-based chemotherapy for microscopic disease after cytoreductive surgery have a 50–60% change of 5-year survival (54).

Data on the use of high-dose therapy with ASCT support as the first-line therapy in the treatment of ovarian cancer is limited. However, the first published trials including almost 100 patients have given promising results (12–15). In three out of four studies patients have been treated with a few courses of postoperative induction chemotherapy before high-dose treatment (12, 14, 15). Patients in the study reported from the Tokai University underwent primary cytoreductive surgery but received no prior chemotherapy before entering the trial (13). The study included 42 stages Ic–IV patients who had <1 cm residual disease after cytoreduction. Twenty-two patients received adjuvant therapy for microscopic disease, and 20 patients were treated for small volume residual disease. Chemotherapy consisted of two cycles of high-dose cyclophosphamide (1600–2400 mg/m^2), doxorubicin (80–100 mg/m^2) and cisplatin (100–150 mg/m^2) with AMBT given twice with a median interval of 6 weeks. No additional maintainance chemotherapy was applied. The adjuvant setting group had an overall 5-year survival of 77.7%, whereas the 5-year survival of the patients with macroscopic residual disease after cytoreductive surgery was 26.3%. In their recent updated report with 49 patients, the study group reported a 5-year survival of 75% for stage II, of 60% for stage III and of 33% for stage IV patients (56).

A recent study from the Catholic University in Rome reported a 4-year survival of 62% and a progression-free survival of 57% survival in a group of 20 stages III–IV

patients treated with high-dose therapy supported by ASCT. Sixteen patients were left with 0.5–2.0 cm residual disease after primary cytoreductive surgery and the remaining four patients underwent intervention surgery to achieve similar tumour burden before high-dose therapy. Within 2 weeks from the primary surgery the patients were treated with two courses of induction chemotherapy including cisplatin 160 mg/m^2 and cyclophosphamide 1500 mg/m^2. High-dose chemotherapy consisted of cisplatin 100 mg/m^2, etoposide 650 mg/m^2 and carboplatin 1800 mg/m^2. One fatal treatment-related candida sepsis was reported in this series but the remaining 19 patients were in clinical CR 3 months after the treatment and underwent second-look laparotomy. Pathologically proven CR was seen in seven (37%), PR in nine (47%) and no change in three (16%) patients. All patients with pathologically proven CR or microscopic disease in the lymph nodes before ASCT were disease free at the time of the report (14).

Fenelly and coworkers used cyclophosphamide and escalating doses of paclitaxel for mobilization of PBSC, whereafter the patients were treated with four courses of rapidly cycled high-dose carboplatin and cyclophosphamide with PBSC support (15). Ten out of 16 patients entered into the study had suboptimally debulked (>1 cm) disease after primary cytoreduction. The median interval between paclitaxel/cyclophosphamide courses was 14 days and that of high-dose carboplatin/cyclophosphamide was 17 days. Thirteen patients were evaluable for response and underwent second look operation. Overall response rate was 100% with five patients showing pathologically proven CR, six microscopic residual disease and two PR. Duration of response was not reported from this phase I study.

Open and Future Trials

The role of high-dose therapy with ASCT in the treatment of ovarian cancer is studied widely at the moment. Some of the ongoing or planned trials are summarized in Table 2. Most of the studies test the efficacy of this treatment modality as part of primary treatment in patients with low tumour burden. The Dutch and Canadian trials are designed to test the role of dose-intensive therapy in the treatment of obviously platinum-sensitive recurrent disease. The South Western Oncology Group has opened a phase II study (SWOG 9106), for stages III/IV ovarian cancer with microscopic up to 3 cm residual disease following one platinum-based regimen. This study compares the feasibility of two high-dose regimens. Results obtained from this study will guide the selection of high-dose combination for a phase III trial (57).

Long-term remission of ovarian cancer may require multiple sequential high-dose courses. A mathematical model of tumour growth kinetics suggest that multiple applications rather than a single high-dose course would represent a superior strategy. The use of PBSCT to support two sequential cycles of high-dose therapy is now being explored in three trials. This approach has been shown to be feasible in ovarian cancer both with ABMT (13) and PBSCT (15). The study conducted at the Tokai University has combined two new approaches: intraperitoneal (i.p.) chemotherapy as part of preceeding treatment and tandem high-dose therapy with PBSC support. This is an interesting approach because a recent study on combined i.p. and i.v. therapy in newly diagnosed small-volume ovarian cancer has shown improved survival when compared to conventional i.v. therapy (59).

Six out of seven currently open or planned trials are based on a combination of high-dose platinum and cyclophosphamide and include patients with small volume tumour only. However, other eligibility criteria, the choice of additional third cytotoxic agent and the number of transplant courses is variable. Paclitaxel has been shown to be effective in mobilizing progenitor cells from the bone marrow (15) and escalation of paclitaxel dose up to 250–300 mg/m^2 has been reported in some recent studies (15, 60). The highest tolerated dose has been reported to be as high as 775 mg/m^2 (61). Paclitaxel exhibits dose- and schedule-dependent effects both on survival and side-effects and there is suggestive data on the importance of dose intensity (62, 60). Therefore, the inclusion of paclitaxel would be justified in high-dose regimens tested for the treatment of advanced ovarian cancer. Furthermore, paclitaxel-based combinations should be tested as a control arm in a randomized trial evaluating the survival benefit obtained with high-dose therapy supported by ASCT.

Both response to chemotherapy and long-term survival are the sum of multiple factors, including biological characteristics of the tumour and the type of available surgical and cytotoxic therapy. According to the National Institute of Health (NIH) consensus statement reproducible independent factors that prolong survival of ovarian cancer include younger age, early stage, low tumour grade, low residual tumour volume, and rapid rate of tumour response. Other prognostic factors include initial tumour volume and para-aortic lymph node involvement (63). A new development in the search for prognostic factors and prediction of the treatment outcome is the use of neural networks (64). EORTC is currently training neural networks on a large dataset to detect hidden prognostic factors that may contribute to the development of a more reliable prognostic index for ovarian cancer. This approach might be useful also for identification of patients who would benefit most from high-dose therapy supported by ASCT.

Conclusions

Although experience with the use of high-dose chemotherapy with ASCT in the treatment of advanced or refractory ovarian cancer dates back to the early 1980s the data is still limited and no clear consensus of the role of this treatment modality is available. The current data on the use of high-dose therapy with ASCT in the treatment of advanced ovarian cancer indicate

that this approach does not significantly improve survival in patients with refractory or chemoresistant tumours. On the other hand, good response rates and survival obtained with high-dose therapy in patients with low tumour burden either as first-line treatment or as salvage therapy are difficult to ignore and have stimulated wide research in this field. It seems reasonable to use dose-intensive therapy early in the course of the disease before development of resistant cell populations and preferably at a time of minimal tumour burden.

Patients with gross or measurable residual tumours after the primary operation should first be treated with a few courses of conventional chemotherapy to evaluate chemosensitivity and high-dose therapy might be given for responding patients only.

The efficacy of high-dose therapy with ASCT has not been tested in randomized trials. To our knowledge the French study (58) is the first trial comparing this treatment modality with conventional platinum-based first-line chemotherapy. Another randomized multicentre study co-ordinated by the Italian group will be started soon (S. Mancuso, personal communication). These studies and other ongoing studies will show if enhanced long-term survival can be achieved with high-dose therapy supported by ASCT and the progress of these trials will be followed with great interest.

References

1. **Parkin DM, Pisani P, Ferlay J.** Estimates of the world-wide incidence of eighteen major cancers in 1985. *Int J Cancer* 1993; 54: 594–606.
2. **Piver MS, Baker TR, Piedmonte M, Sandecki AM.** Epidemiology and etiology of ovarian cancer. *Semin Oncol* 1991; 18: 177–85.
3. **Pettersson F (Ed.)** *Annual Report on the Results of the Treatment in Gynecological Cancer.* FIGO. 1994.

Table 2. Some of the currently open or planned trials on high-dose chemotherapy supported by autologous stem cell transplantation (ASCT) for the treatment of advanced or recurrent epithelial ovarian cancer.

Institute or study group	Inclusion criteria	Randomization	Preceeding chemotherapy	High-dose chemotherapy	Reference or study co-ordinator(s)
Southwest Oncology Group, USA	Stages III–IV, microscopic up to 3 cm residual disease at second-look laparotomy	No	One platinum-based induction regimen	CDDP CTX THIO or CBDCA MX CTX	E. Shpall, et al. (57)
Gynecology Dept, Catholic University, Rome, Italy	Stages IIIB–IV, 0.5–2.0 cm residual tumour after primary surgery	No	CDDP 100 mg/m^2 + CTX 1500 mg/m^2 × 1 CDDP 100 mg/m^2 + CTX 600 mg/m^2 × 3	CBDCA 1200 mg/m^2 VP-16 900 mg/m^2 MEL 100 mg/m^2	P. Benedetti-Panici, et al. (14)
Royal Hospital for Women, Paddington, Australia	Stages IIIC–IV, negative or microscopical disease at second-look laparotomy	No	Platinum-based chemotherapy, 6 cycles	CBDCA 1500 mg/m^2 CTX 6000 mg/m^2	N. Hacker
The French GINECO Group, France	Not defined	Yes	Not defined	CBDCA 1200 mg/m^2 CTX 4500 mg/m^2	E. Pujade-Lauraine and J. M. Extra, (58)
Tokai University, Kanagawa, Japan	Stages III–IV	No	CDDP 50 mg/m^2 + ADR 50 mg/m^2 + CTX 1000 mg/m^2 × 4 CDDP 100 mg/m^2 i.p. × 1	CBDCA 1500 mg/m^2 CTX 3000 mg/m^2 twice, 5–8 weeks interval	T. Sinozuka
Daniel den Hoed Clinic, Rotterdam Cancer Institute, The Netherlands	Recurrence ≥12 months after first line platinum-based chemotherapy	No	CDDP 50 mg/m^2 days 1, 8, 15, 29, 36, 43 VP-16 50 mg/m^2 days 1–15, 29–43	CBDCA 1600 mg/m^2 CTX 6000 mg/m^2 THIO 480 mg/m^2 twice, interval not defined	M. E. L. van der Burg and R. de Wit
Tom Baker Cancer Centre, Calgary, Canada	Microscopic or ≤1 cm residual disease at second look laparotomy or recurrence ≥6 months after first-line treatment	No	Platinum-based chemotherapy, 6–9 cycles	CBDCA 1800 mg/m^2 CTX 6000 mg/m^2 VP-16 1800 mg/m^2 followed by MEL 200 mg/m^2, 6–8 weeks interval	D. Stewart

ADR, doxorubicin; CBDCA, carboplatin; CDDP, cisplatin; CTX, cyclophosphamide; MEL, melphalan; MX, mitoxantrone; THIO, thiotepa; VP-16, etoposide.

4. **Colombo N, Pittelli M, Parma G, et al.** Cisplatin dose intensity in advanced ovarian cancer: a randomized study of conventional dose vs. dose-intense cisplatin monotherapy. *Proc Am Soc Clin Oncol* 1993; 12: 255.
5. **Podczaski E, Manetta A, Kaminski P, et al.** Survival of patients with ovarian epithelial carcinomas after second-look laparotomy. *Gynecol Oncol* 1990; 36: 43–7.
6. **Coldman A, Goldie J.** Impact of dose-intense chemotherapy on the development of permanent drug resistance. *Semin Oncol* 1987; 14: 29–33.
7. **Kaye SB, Lewis CR, Paul J, et al.** Randomized study of two doses of cisplatin with cyclophosphamide in epithelial ovarian cancer. *Lancet* 1992; 340: 329–33.
8. **McGuire WP, Hoskins WJ, Brady MF, et al.** Assesment of dose-intensive therapy in suboptimally debulked ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 1995a; 13: 1589–99.
9. **Ozols RF, Thigpen JT, Dauplat J, et al.** Dose intensity. *Ann Oncol* 1993; 4 (Suppl): S49–56.
10. **Thigpen T, Vance R, Puneky L, Khansur T.** Chemotherapy in advanced ovarian carcinoma: current standards of care based on randomized trials. *Gynecol Oncol* 1994a; 55: S97–107.
11. **de Vries EGE, Hamilton TC, Lind M, Dauplat J, Neijt J, Ozols RF.** Drug resistance, supportive care and dose intensity. *Ann Oncol* 1993; 4 (Suppl): S57–62.
12. **Menichella G, Pierelli L, Foddai M, et al.** Autologous blood stem cell harvesting and transplantation in patients with advanced ovarian cancer. *Br J Haematol* 1991; 79: 444–50.
13. **Murakami M, Shinozuka T, Kuroshima Y, Tokuda Y, Tajima T.** High-dose chemotherapy with autologous bone marrow transplantation for the treatment of malignant ovarian tumours. *Semin Oncol* 1994; 21 (Suppl): 29–32.
14. **Benedetti-Panici P, Greggi S, Scambia G, et al.** High-dose chemotherapy with autologous peripheral stem cell support in advanced ovarian cancer. *Ann Med* 1995; 27: 133–8.
15. **Fenelly D, Schneider D, Spriggs, et al.** Dose escalation of paclitaxel with high-dose cyclophosphamide, with analysis of progenitor-cell mobilization and hematologic support of advanced ovarian cancer patients receiving rapidly sequenced high-dose carboplatin/cyclophosphamide courses. *J Clin Oncol* 1995; 13: 1160–6.
16. **Woodhouse JR, Ferry DR.** The genetic basis of resistance to cancer chemotherapy. *Ann Med* 1995; 27: 157–67.
17. **Lai G-M, Ozols RF, Smyth JF, Young RC, Hamilton TC.** Enhanced DNA repair and resistance to cisplatin in human ovarian cancer. *Biochem Pharmacol* 1988; 37: 4597–600.
18. **Parker RJ, Eastman A, Bostick-Bruton F, Reed E.** Acquired cisplatin resistance in human ovarian cancer cells is associated with enhanced repair of cisplatin-DNA lesions and reduced drug accumulation. *J Clin Invest* 1991; 87: 772–7.
19. **Gottesman MM, Pastan I.** Biochemistry of multidrug resistance mediated by the multidrug transporter. *Annu Rev Biochem* 1993; 62: 385–427.
20. **Kristensen G, Baekelandt M, Holm R, et al.** PGP expression as a possible marker for response to cisplatin-epirubicin as a first-line treatment in advanced ovarian cancer. *Gynecol Oncol* 1995; 56: 110.
21. **Holzmayer T, Hilsenbeck S, Von Hoff DD, et al.** Clinical correlates of MDRI (P-glycoprotein) gene expression in ovarian and small-cell lung carcinomas. *J Natl Cancer Inst* 1992; 84: 19: 1486–91.
22. **O'Dwyer PJ, Hamilton TC, Young RC, et al.** Depletion of glutathione in normal and malignant human cells *in vivo* by buthionine sulfoximin: clinical and biochemical results. *J Natl Cancer Inst* 1992; 84: 264–7.
23. **O'Dwyer PJ, LaCreta F, Nash J, et al.** Phase I study of thiotepa in combination with the glutathione transferase inhibitor ethacrynic acid. *Cancer Res* 1991; 51: 6059–65.
24. **Sessa C, Zucchetti M, Davoli E, et al.** Phase I and clinical pharmacologic evaluation of aphidicolin glycinate. *J Natl Cancer Inst* 1991; 83: 1160–9.
25. **Lowe SW, Ruley HE, Jacks T, et al.** p53-dependent apoptosis modulates the cytotoxicity of anticancer agents. *Cell* 1993; 74: 957–67.
26. **Hockenbery YD, Nunez G, Milliman C, et al.** Bcl-2 is an inner mitochondrial membrane protein that blocks programmed cell death. *Nature* 1990; 348: 334–6.
27. **Alberts DS, Young L, Mason NL, et al.** *In vitro* evaluation of anticancer drugs against ovarian cancer at concentrations achievable by intraperitoneal administration. *Semin Oncol* 1985; 12 (Suppl): 38–42.
28. **Skipper HE.** Dose intensity vs. total dose of chemotherapy: an experimental basis. In: De Vita VT, Hellman S, Rosenberg SA, eds. *Important Advances in Oncology.* New York: JB Lippincott, 1990: 43–64.
29. **Levin L, Hryniuk WM.** Dose-intensity analysis of chemotherapeutic agents in ovarian cancer. *J Clin Oncol* 1987; 5: 756–67.
30. **Levin L, Simon R, Hryniuk W.** Importance of multiagent chemotherapy regimens in ovarian cancer: dose intensity analysis. *J Natl Cancer Inst* 1993; 85: 1732–42.
31. **Ben-David Y, Rosen B, Franssen E, et al.** Meta-analysis comparing cisplatin total dose intensity and survival. *Gynecol Oncol* 1995; 59: 93–101.
32. **Caldas C, Morris LE, McGuire WP.** Salvage therapy in epithelial ovarian cancer. *Obstet Gynecol Clin North Am* 1994; 21: 179–94.
33. **Behrens BC, Hamilton TC, Masuda H, et al.** Characteristics of *cis*-diamminedochloroplatinum (II)resistant human ovarian cell line and its evaluation of platinum analogues. *Cancer Res* 1987; 47: 414–8.
34. **Bertelssen K.** Optimal chemotherapy of ovarian cancer with an old regimen. *Ann Med* 1995; 27: 121–5.
35. **McGuire WP, Hoskins WJ, Brady MF, et al.** Taxol and cisplatin (TP) improves outcome in advanced ovarian cancer (AOC) as compare to cytoxan and cisplatin (CP). *Proc Am Soc Clin Oncol* 1995b: 14: 275.
36. **Trimble EL, Arbuck SG, McGuire WP.** Options for primary chemotherapy of epithelial ovarian cancer: Taxanes. *Gynecol Oncol* 1994; 55: S114–21.
37. **Christian MC, Trimble EL.** Salvage chemotherapy for epithelial ovarian carcinoma. *Gynecol Oncol* 1994; 55: S143–50.
38. **Dauplat J, Legros M, Condat P, Ferrieri JP, Ben Ahmed S, Plagne R.** High-dose melphalan and autologous bone marrow support for treatment of ovarian carcinoma with positive second-look operation. *Gynecol Oncol* 1989; 34: 294–8.
39. **Viens P, Maraninchi D, Legros F, et al.** High-dose melphalan and autologous marrow rescue in advanced epithelial ovarian carcinomas: a retrospective analysis of 35 patients treated in France. *Bone Marrow Transplant* 1990; 5: 227–33.
40. **Legros M, Fluery J, Cure H, et al.** High dose chemotherapy (HDC) and autologous bone marrow transplant (ABMT) in 31 advanced ovarian cancers: long term results. *Proc Am Soc Clin Oncol* 1992; 11: 222.
41. **Mulder POM, Willemse PHB, Aalders JG, et al.** High-dose chemotherapy with autologous bone marrow transplantation in patients with refractory ovarian cancer. *Eur J Cancer Clin Oncol* 1989; 25: 645–9.
42. **Shea TC, Flaherty M, Elias A, et al.** A phase I clinical and pharmacokinetic study and carboplatin and autologous bone marrow support. *J Clin Oncol* 1989; 7: 651–61.
43. **Shpall EJ, Clarke-Pearson D, Soper JT, et al.** High-dose alkylating agent chemotherapy with autologous bone marrow support in patients with stage III/IV epithelial ovarian cancer. *Gynecol Oncol* 1990; 38: 386–91.

44. **Lotz JP, Machover D, Malassagne B, et al.** Phase I-II study of two consecutive courses of high-dose epipodophyllotoxin, Ifosfamide, and Carboplatin with autologous bone marrow transplantation for treatment of adult patients with solid tumours. *J Clin Oncol* 1991; 9: 1860–70.
45. **Rebollo JH, Martin AS, Fernandez HO, et al.** High dose combination of carboplatin (CBDCA) and etoposide (VP-16) followed by peripheral blood stem cell (PBSC) transplantation in the treatment of ovarian carcinoma. *Proc Am Assos Cancer Res* 1991; 32: 172.
46. **Collins RH, Pineiro L, Fay JW.** High-dose chemotherapy and autologous bone marrow transplantation for advanced ovarian cancer. *Proc Am Soc Clin Oncol* 1992; 11: 233.
47. **Extra JM, Dieras W, Giacchetti S, et al.** High-dose chemotherapy (HCT) with autologous bone marrow reinfusion (ABMR) as consolidation therapy for patients (PTS) with advanced ovarian adeno carcinoma (AO). *Proc Am Soc Clin Oncol* 1992; 11: 234.
48. **Shea TC, Storniolo AM, Mason JR, et al.** High-dose intravenous (IV) and intraperitoneal (IP) combination chemotherapy with autologous stem cell rescue for patients with advanced ovarian cancer. *Proc Am Soc Clin Oncol* 1992; 11: 236.
49. **Lotz JP, Machover D, Bellaiche A, et al.** Tandem high-dose (HD) chemotherapy (CT) with VM-26, ifosfamide (IFM), and carboplatin (CBDCA) with autologous bone marrow transplantation (ABMT) for patients with stage III C – IV ovarian cancer (OC). *Proc Am Soc Clin Oncol* 1993; 12: 257.
50. **Broun ER, Belinson JL, Berek JS, et al.** Salvage therapy for recurrent and refractory ovarian cancer with high-dose chemotherapy and autologous bone marrow support: a Gynecologic Oncology Group pilot study. *Gynecol Oncol* 1994; 54: 142–6.
51. **Stiff P, Bayer R, Camarda M, et al.** A phase II trial of high-dose mitoxantrone, carboplatin, and cyclophosphamide with autologous bone marrow rescue for recurrent epithelial ovarian carcinoma: analysis of risk factors for clinical outcome. *Gynecol Oncol* 1995; 57: 278–85.
52. **Shpall EJ, Cagnoni PJ, Bearman SI, et al.** High-dose chemotherapy with autologous hematopoetic cell support (AHCS) for the treatment of epithelial ovarian cancer. *Am Soc Clin Oncol Educational Book* 1995a; 360–4.
53. **Thigpen JT, Blessing JA, Ball H, Hummel SJ, Barrett RJ.** Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group study. *J Clin Oncol* 1994b; 12: 1748–53.
54. **Williams CJ, Stewart L, Parmar M, et al.** Meta-analysis of the role of platinum compounds in advanced ovarian cancer. *Semin Oncol* 1992; 19: 120–8.
55. **Neijt JP, Bokkel Huinink WW, et al.** Long-term survival in ovarian cancer. Mature data from The Netherlands Joint Study Group for Ovarian Cancer. *Eur J Cancer* 1991; 27: 1367–72.
56. **Muramatsu T, Shinozuka T, Hirasawa T, et al.** High-dose chemotherapy (HDC) with autologous bone marrow transplantation (ABMT) in epithelial ovarian cancer. *Int J Gynecol Cancer* 1995; 5 (Suppl 1): 44.
57. **Shpall EJ, Jones RB, Bearman SI, Purdy MP.** Future strategies for the treatment of advanced epithelial ovarian cancer using high-dose chemotherapy and autologous bone marrow support. *Gynecol Oncol* 1994; 54: 357–61.
58. **Pujade-Lauraine E, Extra JM.** Place of intensive therapy in ovarian cancer. *Eurocancer* 95, Paris 1995; 217–8.
59. **Alberts D, Liu P, Hannigan E, et al.** Phase III study of intraperitoneal (IP) cisplatin (CDDP)/intravenous (IV) cyclophosphamide (CPA) vs. IV CDDP/IV CPA in patients with optimal disease stage III ovarian cancer: a SWOG-GOG-ECOG intergroup study (INT 0051). *Proc Am Soc Clin Oncol* 1995; 13: 273.
60. **Kohn EC, Sarosy G, Bicher A, et al.** Dose-intense taxol: high response rate in patients with platinum resistant ovarian cancer. *J Natl Cancer Inst* 1994; 86: 18–24.
61. **Cagnoni PJ, Stemmer SM, Matthes S, et al.** Phase I trial of high dose paclitaxel (Taxol), cyclophosphamide and cicplatin with autolougs hematopoetic progenitor cell rescue. *Proc Am Soc Clin Oncol* 1995; 14: 477.
62. **Swenerton K, Eisenhauer E, ten Bokkel Huinink W, et al.** Taxol in relapsed ovarian cancer: high vs. low dose and short vs. long infusion. A European Canadian study coordinated by the NCI Canada Clinical Trials Group. *Proc Am Soc Clin Oncol* 1993; 12: 256.
63. **National Institutes of Health Consensus Development Conference Statement.** Ovarian cancer: screening, treatment, and follow-up. *Gynecol Oncol* 1994; 55: S4–14.
64. **Forsström J, Dalton KJ.** Artificial neural networks for decision support in clinical medicine. *Ann Med* 1995; 27: 509–17.