

ORIGINAL ARTICLE

Phase I/II trial of multicycle high-dose chemotherapy with peripheral blood stem cell support for treatment of advanced ovarian cancer

N Frickhofen¹, WE Berdel², F Opri³, R Haas⁴, A Schneeweiss⁵, M Sandherr⁶, W Kuhn⁷, DK Hossfeld⁸, C Thomssen⁹, H Heimpel¹, R Kreienberg¹⁰, A Hinke¹¹ and V Möbus¹⁰, on behalf of the German Study Groups Arbeitsgemeinschaft Internistische Onkologie (AIO) und Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)

¹Department of Hematology/Oncology, Universitätsklinikum Ulm, Ulm, Germany; ²Department of Hematology/Oncology, Charité, Universitätsmedizin Berlin, Klinikum Benjamin-Franklin, Berlin, Germany; ³Department of Gynecology, Charité, Universitätsmedizin Berlin, Klinikum Benjamin-Franklin, Berlin, Germany; ⁴Department of Hematology/Oncology, Universitätsklinikum Heidelberg, Heidelberg, Germany; ⁵Department of Gynecology, Universitätsklinikum Heidelberg, Heidelberg, Germany; ⁶Department of Hematology/Oncology, Technische Universität München, Klinikum rechts der Isar, München, Germany; ⁷Department of Gynecology, Technische Universität München, Klinikum rechts der Isar, München, Germany; ⁸Department of Hematology/Oncology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; ⁹Department of Gynecology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; ¹⁰Department of Gynecology, Universitätsklinikum Ulm, Ulm, Germany and ¹¹Wissenschaftlicher Service Pharma, Langenfeld, Germany

Ovarian cancer is chemosensitive, but most patients with advanced disease die from tumor progression. As 25% of the patients can be cured by chemotherapy, it is reasonable to evaluate high-dose chemotherapy (HDCT). Forty-eight patients with untreated ovarian cancer were entered in a multicenter phase I/II trial of multicycle HDCT. Median age was 46 (19–59 years); International Federation of Gynecology and Obstetrics-stage was III in 79% and IV in 21%; 31% had residual disease > 1 cm after surgery. Two courses of induction/mobilization therapy with cyclophosphamide (250 mg/m²) and paclitaxel (250 mg/m²) were used to collect peripheral blood stem cells. HDCT consisted of two courses of carboplatin (area under curve (AUC) 18–22) and paclitaxel followed by one course of carboplatin and melphalan (140 mg/m²) with or without etoposide (1600 mg/m²). Main toxicity was gastrointestinal. Limiting carboplatin to AUC 20 and eliminating etoposide resulted in manageable toxicity (69% without grade 3/4 toxicity). One patient died from treatment-related pneumonitis. At 8 years median follow-up, median progression-free-survival (PFS) and overall survival (OS) is 13.3 and 37.0 months. Five-years PFS and OS is 18 and 33%. Multicycle HDCT is feasible in a multicenter setting. A European phase III trial based on this regimen is evaluating the efficacy of HDCT.

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Introduction

About one in 70 women develops ovarian cancer. Lethality is high, since 75% of patients present with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV disease and no more than 25% of them survive long-term. Progression-free (PFS) and overall survival (OS) have significantly improved with the systematic use of platinum and taxanes, median PFS now ranging from 16 to 21 months and OS from 32 to 57 months.^{1,2} Nevertheless, long-term outcome has not changed significantly. Survival curves demonstrate that patients live longer, but there is no evidence that the proportion of cured patients has increased.

Ovarian cancer is one of the most chemosensitive solid tumors. There is evidence for a dose–response relationship within the conventional dose range of systemic chemotherapy.^{3,4} Moreover, increasing the dose at the site of peritoneal metastases by intraperitoneal chemotherapy resulted in increased efficacy in three randomized trials.^{5–7} It is thus reasonable to exploit the full potential of chemotherapy by using high-dose chemotherapy (HDCT) with peripheral blood stem cell support (PBSC).

Experience with HDCT primarily comes from registry data and phase II trials of relapsed patients.^{8,9} This data shows that response rates are high, even in refractory and early relapsing disease, but patients relapse after only 3–9 months without evidence for any improvement in overall outcome. This suggests that HDCT is unable to overcome

Correspondence: Professor Dr N Frickhofen, Department of Medicine III (Hematology/Oncology), HSK, Dr Horst Schmidt Klinik, D-65199 Wiesbaden, Germany.

E-mail: norbert.frickhofen@hsk-wiesbaden.de

All institutions are in Germany and all authors are listed with their association at the time of the study.

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resistance after previous treatment. It should thus be tested in patients with chemosensitive or untreated disease.

Several phase II trials addressed the impact of HDCT in first-line treatment either as consolidation treatment^{10–14} or as multicycle HDCT up-front.^{15,16} They confirmed high response rates and showed encouraging PFS and OS figures of 24–35% and 45–60% at 5 years, respectively.

The German study groups Arbeitsgemeinschaft Internistische Onkologie (AIO) and Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) organized a multicenter phase I/II trial along the principles of multicycle up-front treatment with high dose intensity and high dose density.^{15,17}

Patients and methods

Objectives

The goal of this multicenter phase I/II trial was to develop an experimental arm of a planned phase III trial. It included a phase I part with dose escalation of carboplatin. Primary objective was evaluation of toxicity. Secondary objective was evaluation of efficacy, determined by PFS. The protocol was approved by the Institutional Review Boards of all participating institutions. All patients gave written informed consent.

Patients

Eligibility criteria included an age limit of 60 years and untreated ovarian cancer, FIGO stage III or IV. Optimal debulking surgery was encouraged, but patients were eligible irrespective of the size of residual tumor. Standard criteria for normal organ function included a glomerular filtration rate (GFR) of at least 60 ml/min.

Treatment

The protocol was based on phase II-studies performed by Fennelly *et al.*^{15,18} Two induction cycles of intermediate doses of paclitaxel and cyclophosphamide were used for peripheral blood stem harvest and were followed by three cycles of high-dose carboplatin, combined with paclitaxel (two courses) or high-dose melphalan and etoposide (one final course).^{12,16} Each of the three high-dose courses was supported by infusion of peripheral blood stem cells (PBSC) and treatment with filgrastim. Treatment was recommended to start within 4 weeks after surgery. To ensure high dose density, intervals of 14 days between induction treatment courses and 21 days between high-dose treatment courses were recommended. Supportive care was delivered according to standard procedures of each center. It included oral antimicrobial prophylaxis in all participating centers.

Induction/mobilization treatment consisted of paclitaxel, 250 mg/m², administered as a 24 h-infusion on day 1 followed by cyclophosphamide, 3 g/m², administered as a 2 h infusion on day 2. Mesna was given as an intravenous (i.v.) bolus at a dose of 1 g immediately before cyclophosphamide and continued at a dose of 3 g/m² for 24 h thereafter. Filgrastim was started on day 3 at a dose of 10 µg/kg and continued daily until the day of the

last leukapheresis. PBSC were harvested by standard leukapheresis as soon as circulating peripheral blood CD34-positive cells exceeded 20 × 10⁶/l. The protocol recommended collection of PBSC after the second cycle of paclitaxel and cyclophosphamide. At least four bags with PBSC, each containing at least 2 × 10⁶ CD34-positive cells, were harvested.

The first two courses of high-dose treatment consisted of paclitaxel, 250 mg/m² administered as a 24 h infusion on day 1, followed by carboplatin at escalating doses, also administered as a 24 h infusion on day 2, followed by an infusion of at least 2 × 10⁶/kg PBSC on day 5. The dose of carboplatin was calculated using the formula developed by Calvert *et al.*,¹⁹ based upon GFR, measured by ⁵¹Cr ethylenediamine-*N,N,N',N'*-tetraacetic acid- or DTPA clearance. The third high-dose course consisted of etoposide, 200 mg/m² as a 1 h infusion every 12 h for a total of eight doses on days 1–4. Carboplatin was added on day 3 and melphalan was delivered as a 10 min infusion at a dose of 140 mg/m² on day 5, followed by an infusion of PBSC on day 6. Filgrastim was commenced at 5 µg/kg subcutaneously 24 h after completion of each high-dose course.

Dose escalation of carboplatin

The initial target area under curve (AUC) of carboplatin was 18. It was to be escalated in steps of AUC 2 after treatment of three consecutive patients. If one of three patients experienced unacceptable toxicity – this included, but was not limited to, any grade 4 toxicity except hematotoxicity and alopecia – the patient cohort had to be increased to six at this dose level. As soon as two patients developed unacceptable toxicity, dose escalation was terminated and the dose below the last dose level was declared the maximal tolerated dose.²⁰

Statistical methods

Data accumulated up to 28 February 2006 were entered into the database. Toxicity data were compared by the χ^2 test for trend. PFS and OS were analyzed by the product limit method.²¹ Survival data were calculated from the first day of the first chemotherapy cycle. Exploratory subgroup analyses were performed in patients with optimally debulked cancer and in patients treated at the recommended dose of AUC 20 and without etoposide during the final high-dose course. All evaluations were performed on an intent-to-treat basis.

Results

Patient characteristics

Within 24 months, 49 patients were entered into the trial by 19 centers. One patient was excluded from the analysis, since she accidentally received carboplatin AUC 40 during the first high-dose course. She survived after prolonged supportive treatment, relapsed and died 14 months after entering the study. All remaining 48 patients are evaluable for clinical characteristics, toxicity and treatment outcome.

Patient characteristics are summarized in Table 1. The median age of 46 years was more than 10 years younger

Table 1 Patient characteristics (n = 48)

| Characteristics | No. of patients |
|----------------------------|-----------------|
| <i>Age (years)</i> | |
| Median | 46 |
| Range | 19–59 |
| <i>Histology</i> | |
| Serous | 4 |
| Papillary | 13 |
| Papillary serous | 16 |
| Mucinous | 1 |
| Endometrioid | 4 |
| Undifferentiated | 2 |
| Adenocarcinoma, NOS | 8 |
| <i>Histology grade</i> | |
| 1 | 3 |
| 2 | 17 |
| 3 | 28 |
| <i>Debulking</i> | |
| No residual cancer | 16 |
| Residual cancer 0.1–1 cm | 17 |
| Residual cancer 1.1–2.0 cm | 7 |
| Residual cancer >2 cm | 4 |
| Incomplete documentation | 4 |
| <i>Stage</i> | |
| IIIA | 1 |
| IIIB | 9 |
| IIIC | 28 |
| IV | 10 |

than in most chemotherapy trials in ovarian cancer. Histology and grade were representative for this tumor entity.

Thirty-four percent of evaluable patients had no macroscopic residual cancer after extensive surgery and 69% had optimal debulking surgery (residual cancer 1 cm or less). Bowel resections were carried out in 21 patients. Eastern Cooperative Oncology Group performance status at the time of chemotherapy was 0 in 31% of the patients, 1 in 63% and 2 in 6%.

Chemotherapy

The median interval from surgery to the first course of chemotherapy was 46 (range 10–57) days. Protracted recovery after bowel resection was the most common reason for delaying treatment.

Thirty-nine (81%) of the patients received all five chemotherapy courses. Reasons for stopping treatment prematurely were progressive disease after one, three and four courses (n = 3), acute pancreatitis after the second course (n = 1), DLT after the third course (n = 2) and patient request after 3 or 4 courses (n = 3).

Adherence to dose and dose density of the protocol was very good: median actual doses of chemotherapy drugs delivered compared to recommended per protocol were 101% for cyclophosphamide, 98% for carboplatin, 99% for paclitaxel, 99% for melphalan and 99% for etoposide. There were dose reductions >15% in only three patients, including one patient who did not receive carboplatin

Table 2 Treatment cohorts

| Carboplatin | Etoposide | No. of patients | % |
|-------------|-----------|-----------------|----|
| AUC 18 | Yes | 10 | 21 |
| AUC 20 | Yes | 8 | 17 |
| AUC 20 | No | 22 | 46 |
| AUC 22 | No | 8 | 17 |

The carboplatin dose was identical in all three high dose courses. Etoposide (1600 mg/m²) was only included in the third high dose course. AUC denotes area under the curve.

during the last high-dose treatment because of concerns of toxicity. Median intervals between chemotherapy courses 1–5 were 16 (9–16), 21 (9–15), 25 (21–42) and 27 (17–51) days. Intervals <28 days could be achieved in 75% of the high-dose courses.

Mobilization of PBSC

Mobilization of PBSC was excellent. Patients received filgrastim for a median of 10 days. Centers opted on harvesting PBSC after both courses in 26 patients. The median number of leukaphereses was 1 (range 1–3). The median number of CD34-positive cells harvested after the first and second chemotherapy course was similar (28 × 10⁶/kg and 16 × 10⁶/kg; P = 0.3).

Dose escalation of carboplatin

Dose escalation of carboplatin resulted in four patient cohorts (Table 2). There was no DLT at the first dose level of carboplatin AUC 18. This patient cohort included more than three patients, due to very rapid accrual of the first patients. When the dose of AUC was increased to AUC 20, there was grade IV stomatitis in one of three patients. After inclusion of three more patients at this dose level, grade III mucositis developed in two more patients, which would have allowed further dose escalation of carboplatin. However, there was additional, not dose limiting ototoxicity, peripheral neurotoxicity, cardiac arrhythmia, transient cerebral ischemia and impaired consciousness, intestinal hemorrhage due to enteritis and pneumonitis. Altogether, toxicity of this high-dose chemotherapy was felt to be unacceptable.

A review of the toxicity pattern after a total of eight patients treated at dose level 2 suggested etoposide as the major culprit of the toxicity. The protocol committee thus decided to delete etoposide from the protocol and to expand the patient cohort at the carboplatin dose level of AUC 20 to allow for careful analysis of the toxicity pattern with this new drug combination. Treatment of 22 patients at this carboplatin dose level without etoposide demonstrated excellent feasibility (for details see 'Toxicity'). Carboplatin was thus increased to AUC 22. At this dose level, we found DLT in one of three patients. This patient experienced enterocolitis, sepsis, metabolic abnormalities and confusion; she finally died from treatment-related aspiration pneumonitis. After treating a total of eight patients at this dose level, there were three additional patients with severe, although not dose limiting mucositis. As high-dose therapy is experimental in ovarian cancer,

Table 3 Nonhematologic toxicity CTC grade 3 and 4 (% grade 3/% grade 4) of all evaluable patients throughout all dose levels

| | Cycle 1 (induction course 1) | Cycle 2 (induction course 2) | Cycle 3 (high dose course 1) | Cycle 4 (high dose course 2) | Cycle 5 (high dose course 3) with and without etoposide | |
|-----------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|--|-----------|
| | Grade 3/4 | Grade 3/4 | Grade 3/4 | Grade 3/4 | Grade 3/4 | Grade 3/4 |
| Stomatitis | 0 | 0 | 2/2 | 0/5 | 6/25 | 17/4 |
| Esophagitis | 0 | 0 | 0/4 | 2/2 | 0/31 | 9/4 |
| Diarrhea | 0 | 0 | 15/4 | 5/2 | 39/13 | 30/0 |
| Ileus | 0 | 0 | 0 | 0 | 2/0 | 0 |
| Nausea | 0 | 2/0 | 22/0 | 17/0 | 50/44 | 35/35 |
| Vomiting | 0 | 0 | 7/0 | 2/2 | 44/19 | 30/13 |
| Infection | 13/6 | 7/0 | 24/0 | 24/0 | 81/6 | 26/4 |
| Hemorrhage | 0 | 0 | 2/0 | 0 | 6/13 | 0 |
| Sensory neurotoxicity | 0 | 0 | 2/0 | 0 | 0 | 0 |
| Motor neurotoxicity | 0 | 0 | 2/0 | 0 | 0 | 0 |
| Ototoxicity | 0 | 0 | 2/0 | 0 | 0 | 0 |
| Stupor/Coma | 0 | 0 | 2/0 | 0 | 0/2 | 0 |
| Hepatotoxicity | 0 | 0 | 9/0 | 2/0 | 6/0 | 5/4 |
| Nephrotoxicity | 0 | 0 | 2/0 | 0 | 0/0 | 4/4 |
| Arrhythmia | 0 | 0 | 0 | 0 | 0/6 | 5/0 |
| TRM | 0 | 0 | 0 | 0 | 2/0 | 0 |
| Others | 2/0 | 4/0 | 4/0 | 8/3 | 17/8 | 0/4 |

TRM denotes treatment-related mortality.

such severe mucositis was considered unacceptable for the planned phase III multicenter trial and dose escalation was stopped.

Toxicity

There were no significant toxicities due to PBSC infusions. Patients received a median of 5.4×10^6 /kg CD34-positive cells after each HDCT. Granulocyte nadirs below 0.5×10^9 /l lasted a median time of 3, 3, 4, 5 and 5 days after chemotherapy courses 1–5. Platelet nadirs below 20×10^9 /l lasted 4, 4, 6, 6 and 9 days, respectively. Red cell transfusions were required for 23, 47, 87, 83 and 85%, and platelet support was required for 6, 12, 67, 66 and 92% of the patients after treatment courses 1–5, respectively.

The major toxicity of the protocol was mucosal toxicity during high-dose therapy (Table 3). This toxicity was the reason why three patients requested discontinuation of the treatment. One patient died from complications triggered by extensive enterocolitis, as described in the previous paragraph. Among the first 18 patients, four with grade 3 or 4 mucositis experienced GI-tract hemorrhages. Mucositis was most probably a major contributing factor for systemic infections, even though the hematologic toxicity was numerically modest. During the three HDCT courses 37, 34 and 56% of the patients needed support with antibiotics and 9, 10 and 28% with antifungal drugs.

After deleting etoposide from the high-dose course, the incidence and severity of mucositis decreased to such an extent that 69% of the patients never experienced mucositis higher than grade 2 throughout the treatment. The better tolerability of the treatment was particularly striking after the last high-dose course: compared to previous treatments including etoposide, the decrease of toxicity was significant for diarrhea ($P=0.013$), stomatitis ($P=0.0017$), esophagitis ($P=0.048$), hemorrhage ($P=0.0046$) and infection ($P=0.0015$).

All patients developed grade 2 alopecia. A 38-year-old patient with stage IIIc disease experienced severe pancreatitis following the second mobilization course with cyclophosphamide and paclitaxel. She recovered completely and was treated off study thereafter. Ototoxicity developed in 13% (grade 1), 18% (grade 2) and 2% (grade 3) of the patients. Sensory neurotoxicity was documented in 45% (grade 1), 22% (grade 2) and 2% (grade 3) of the patients. Motor neuropathy developed in 13% (grade 1), 13% (grade 2) and 2% (grade 3) of the patients. At follow-up after 3 years, ototoxicity and neurotoxicity were reversible, but persisted as grade 1 or 2 toxicity in two (10%) and seven (33%) of surviving patients.

Other significant toxicities were bone pain caused by filgrastim during PBSC mobilization (23% grade 1 and 11% grade 2), constipation (14% grade 1 or 2 and 4% grade 4), cardiac arrhythmia (6% grade 3) and deep venous thrombosis (2% grade 3). Patients were hospitalized for a median time of 13 and 9 days (range 0–37) during cycles 1 and 2, and for 19, 18 and 23 days (range 0–47) during high-dose cycles 3–5.

All patients complained of significant deterioration of their physical and mental performance status. However, recovery was fast after the last course of treatment.

Secondary malignancies developed in two patients, 6 and 8 years after HDCT: leiomyosarcoma originating from pelvic wall structures at age 63 years and invasive ductal breast cancer pT1c, pN0, M0 at age 60 years. There was no myelodysplastic syndrome or leukemia. Nevertheless, one should keep in mind the median OS of 37 months; only 12 patients are surviving 5.8–9.5 years.

Outcome

Treatment-related mortality was 2% (1/48 patients). At a median observation time of the surviving patients of 8.0 years, median PFS is 13.3 months (95% confidence interval

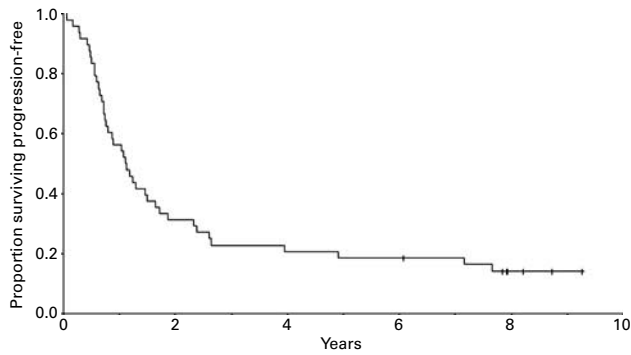


Figure 1 Progression-free survival.

(CI): 8.5–18.0). Two- and 5-year-PFS is 30 and 18%. Median overall survival is 37.0 months (95% CI: 22.8–51.1). Two- and 5-year-OS is 63 and 33% (Figure 1).

Residual cancer after surgery is the most important prognostic factor in advanced ovarian cancer. In an exploratory analysis, PFS and OS of the patients with optimal debulking surgery (residual cancer 1 cm or less) was compared to the survival of patients with residual cancer > 1 cm. Median PFS of 33 patients with optimal debulking surgery is 14.9 months (95% CI: 9.1–20.7) compared to 8.6 months (95% CI: 3.7–13.5) in the other patients. Two- and 5-year-PFS is 34 and 22% in the optimally debulked patients compared to 19 and 7% in the other patients. Median OS of optimally debulked patients is 44.3 months (95% CI: 29.6–59.1) compared to 21.9 months (95% CI: 18.1–25.8). Two- and 5-year-OS is 71 and 41% in optimally debulked patients compared to 39 and 12% in the other patients. PFS is not different between both groups on log rank testing ($P=0.17$); however, overall survival reached statistical significance ($P=0.014$).

Twenty-two patients were treated with carboplatin AUC 20 without etoposide in the last high-dose course. PFS and OS of these patients were best among all patients treated in this trial (36 and 50% at 5 years). Clinical characteristics of these patients such as age, residual cancer after surgery and stage were not significantly different compared to the patients treated with different chemotherapy regimens within this trial.

Discussion

This trial was set up in order to develop a dose-intense and dose-dense protocol in preparation of a phase III trial evaluating the concept of multicycle HDCT in advanced ovarian cancer. The trial succeeded in establishing a regimen with manageable toxicity in a multicenter setting based on prospectively collected toxicity data.

Etoposide turned out to be a drug more problematic than previously reported. Etoposide had been built into the protocol following the concept of late dose intensification.^{13,16,18,22,23} Unacceptable mucositis was observed in our trial; a well-known adverse effect both of etoposide and melphalan. Elimination of etoposide, which is not considered an essential drug in ovarian cancer, resulted in a significant reduction of the incidence and severity of

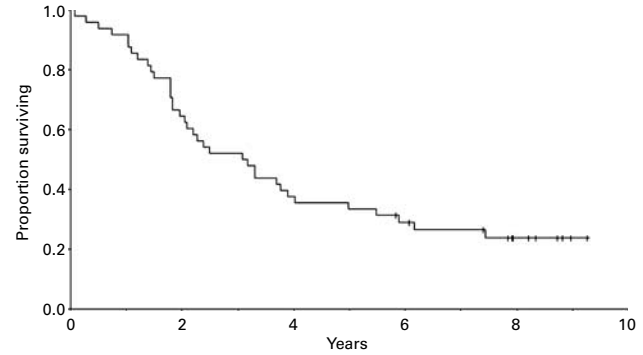


Figure 2 Overall survival.

mucositis and mucositis-associated adverse effects like mucosal hemorrhages and infections.

After dose escalation of carboplatin to AUC 22, there was only one DLT in eight patients, formally permitting additional dose escalation of carboplatin. Owing to significant adverse effects at this dose level and considering the unproven efficacy of HDCT in ovarian cancer, we felt that it was not justified to increase the dose of carboplatin further. After all, carboplatin AUC 20 represents a 3.3-fold increase of dose intensity compared to a standard dose of AUC 6.^{1,2,24}

Introducing carboplatin only with the third course of chemotherapy is a potential weakness of the protocol, since platinum is the most important drug in ovarian cancer. Cyclophosphamide was used upfront for its excellent stem cell mobilizing property and the combination of cyclophosphamide with paclitaxel has specifically been evaluated in ovarian cancer patients.¹⁸ Meanwhile, there is evidence that enough stem cells for three high-dose courses can be harvested after standard carboplatin/paclitaxel chemotherapy (N Frickhofen, unpublished observations). Starting with carboplatin/paclitaxel would also increase the total dose of platinum, which was less than twofold in our protocol compared to a standard schedule of six cycles of carboplatin AUC 6 and paclitaxel.

Long-term results of the trial are mature. PFS and OS (Figures 1 and 2) do not appear to be different from conventional dose carboplatin/paclitaxel protocols.^{1,2,24} However, this requires evaluation in a phase III trial.

Only two phase III trials have been completed and they have currently only been presented in abstract form. Both trials closed prematurely due to slow recruitment. A European Intergroup Trial, a follow-up trial of the phase I/II trial reported here, used the upfront multicycle HDCT approach,²⁵ whereas a French trial used HDCT as consolidation treatment for chemosensitive patients.²⁶ Preliminary data from both trials do not suggest an improvement of OS or PFS with HDCT compared to standard dose chemotherapy. HDCT should thus be considered experimental in ovarian cancer.

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Study groups AIO and AGO who entered patients into this trial are listed in Appendix A with their current addresses. Funding: Bristol-Myers Squibb and AMGEN supported trial meetings of the study group during conduct of the trial.

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Appendix A

Members of the German Study groups AIO and AGO, who entered patients into this trial are listed here in alphabetical order with their current addresses: HG Bender, Düsseldorf; WE Berdel, Münster;

H Heimpel, Ulm; K Diedrich, Lübeck; H Egger, Neumarkt; H Eimermacher, Hagen; H Elser, Landshut-Achdorf; N Fischer, München; M Freund, Rostock; N Frickhofen, Wiesbaden; R Haas, Düsseldorf; HJ Holländer, Duisburg; DK Hossfeld, Hamburg; C Jackisch, Offenbach; M Königsmann, Magdeburg; R Kreienberg, Ulm; W Kuhn, Bonn; Ch Kurbacher, Köln; KO Metz, Bremerhaven; B Metzner, Oldenburg; J Mezger, Karlsruhe; V Möbus, Frankfurt; D Mühlentstedt, Oldenburg; F Opri, Berlin; K-H Pflüger, Bremen; K Rothe, Halle; M Sandherr, Weilheim; G Schmitz, Herdecke; HJ Schmoll, Halle; A Schneeweiß, Heidelberg; W Schneider, Düsseldorf; R Schwarz, Rostock; C Thomssen, Halle; L Trümper, Göttingen; C Villena-Heinsen, Baden-Baden; T Wagner, Lübeck; H Wandt, Nürnberg; M Westerhausen, Duisburg.