CHAPTER 2

Advanced Stage Epithelial Ovarian Cancer

Adjuvant Chemotherapy

The standard of care adjuvant chemotherapy regimen for advanced ovarian cancer evolved from cyclophosphamide + doxorubicin/Adriamycin + cisplatin (CAP) (GOG 47) to cyclophosphamide + cisplatin (CP) (GOG 52) to paclitaxel + cisplatin (TP) (GOG 111, OV-10) to paclitaxel + carboplatin (TC) (Danish Netherlands Trial, GOG 158, AGO/OVAR-3). However, outcomes may be similar with single-agent platinum therapies (GOG 132, ICON2) or with the exclusion of paclitaxel (ICON3). Outcomes are improved but toxicities are increased with intraperitoneal cisplatin administration (GOG 104, GOG 114, GOG 172). Outcomes appear to be improved with dose density (JGOG 3016) but are not improved with dose intensity (GOG 97) or weekly administration (MITO-7). Addition of a third drug to the paclitaxel and carboplatin backbone does not improve overall survival (GOG 182/ICON5, AGO-OVAR9, OV16, ICON7, GOG218), but the substitution of a different drug for paclitaxel does not compromise outcomes (SCOTROC, MITO-2).

GOG 47 (Omura, Cancer 1986)

REFERENCE

- Omura GA, et al. A randomized trial of cyclophosphamide and doxorubicin with or without cisplatin in advanced ovarian carcinoma. *Cancer*. 1986;57(9):1725-1730. PMID: 3513943. (Omura et al. 1986)

TRIAL SPONSOR

- Gynecologic Oncology Group (GOG)

RATIONALE FOR TRIAL

- The combination of doxorubicin and cyclophosphamide resulted in a better response rate than melphalan in patients with bulky disease (32% vs 20%). However, overall survival was not improved (Omura et al. 1983).
- Cisplatin was found to be a highly active agent in ovarian cancer.
- This trial was performed to determine whether the addition of cisplatin to doxorubicin and cyclophosphamide would improve results.

PATIENT POPULATION

- N = 516, of which 440 were evaluable.
- Enrolled between June 1979 and March 1982.
- Stage IV or suboptimal stage III (defined as residual lesions greater than 3 cm) primary ovarian cancer or recurrent ovarian cancer equivalent to suboptimal stage III or stage IV.

TREATMENT DETAILS

Arm 1: CA (Cyclophosphamide + doxorubicin).

- Cyclophosphamide 500 mg/m^2.
- Adriamycin (doxorubicin) 50 mg/m^2.
- Administered every 3 weeks × 8 courses over 6 months.

Arm 2: CAP (Cyclophosphamide + doxorubicin + Cisplatin).

- Cyclophosphamide 500 mg/m^2.
- Adriamycin (doxorubicin) 50 mg/m^2.
- Cisplatin 50 mg/m^2.
- Administered every 3 weeks × 8 courses over 6 months.

Additional Treatment Details

- Complete responders underwent second-look laparotomy.
- If no evidence of disease or all disease resected, patients received cyclophosphamide alone every 3 weeks, escalating from 500 mg/m^2 to 1100 mg/m^2 until relapse or a total of 12 months after second-look surgery.
- If residual cancer after second-look surgery, patients went off treatment and were followed for survival.

Dose Reductions

- Grade 3 granulocyte or platelet toxicity with recovery by next cycle: dose reduced to 75% for doxorubicin and cyclophosphamide (not reduced for cisplatin).

- Grade 4 granulocyte or platelet toxicity with recovery to next cycle: dose reduced to 50% for doxorubicin and cyclophosphamide and cisplatin reduced to 25%.
- Dose could be escalated by 25% increments for each subsequent course until the full dose was reached if there was no further toxicity.

Doxorubicin

- Stopped if congestive heart failure or any other life-threatening cardiac toxicities.
- Total cumulative dose not to exceed 400 mg/m^2.

Cisplatin

- Held if blood urea nitrogen (BUN) >30 mg/dL or creatinine >2 mg/dL.
- Restarted only after BUN <25 mg/dLand creatinine <1.5 mg/dL.

ASSESSMENTS

Evaluation of Response

- Complete response (CR): disappearance of all gross disease for at least 1 month.
- Partial response (PR): 50% or greater reduction in product of each lesion size in 2 perpendicular diameters for at least 1 month.

ENDPOINTS

- Response rate (primary endpoint).

STATISTICAL CONSIDERATIONS

- Sample size projections were based on complete response rate of 35% for CA and an increase of 15% for CAP.

CONCLUSION OF TRIAL

- The addition of cisplatin to cyclophosphamide and doxorubicin (CAP) improves response rate, response duration, survival in patients with measurable disease, and progression-free interval in all patients (measurable and nonmeasurable) compared to CA alone. The addition of cisplatin is a significant step forward in the management of ovarian cancer.
- The value of maintenance therapy with cyclophosphamide is unclear. The benefit on continued treatment needs to be balanced against the risk of leukemogenesis from prolonged treatment with an alkylating agent.

Table 2.1 Results of GOG 47

Treatment arm	Cyclophosphamide + doxorubicin (CA) N = 215 evaluable	CA + cisplatin (CAP) N = 225 evaluable	Statistics
Patient characteristics			
Median age (range)	56 (25-70)	57 (23-70)	
Grade 3	38%	40%	
Stage III	65%	66%	
Stage IV	32%	30%	
Recurrent	3%	4%	
Serous	52%	54%	
Endometrioid	14%	11%	
Unspecified	19%	15%	
Mucinous	3%	5%	
Clear cell	4%	3%	
Other	7%	11%	
Treatment delivery	No details	No details	
Efficacy			
CR	25%	51%	$P < .0001$
PR	22%	24%	
Stable disease	43%	19%	
Progressive disease	9%	5%	
Response duration	8.8 months	14.6 months	$P = .02$
Progression-free interval	7.7 months	13.1 months	$P < .0001$
Survival (measurable disease)	15.7 months	19.7 months	$P < .03$
Survival (nonmeasurable disease)	18.7 months	18.9 months	NS
Toxicity			
G3/4 WBC	80/189 (42%)	116/195 (59%)	
G3/4 platelet	2/189 (1%)	17/195 (9%)	
G3/4 GI	14/194 (7%)	31/198 (16%)	

CR, complete response; GI, gastrointestinal; NS, not significant; PR, partial response; WBC, white blood cells.

- No survival advantage was seen for CAP in nonmeasurable cases. These cases ranged from minimally bulky to massive but clinically nonmeasurable disease. Most women treated with CA ended up receiving cisplatin as secondary therapy, and this may have influenced the measurement of postprotocol survival. However, this would be relevant to both measurable and nonmeasurable cases and does not

necessarily account for the lack of survival difference with nonmeasurable cases.

COMMENTS

- Cisplatin was commercially available when this trial was conducted, so crossover to cisplatin use after completion of the trial may have blunted survival differences.

GOG 52 (Omura, JCO 1989)

REFERENCE

- Omura GA, et al. Randomized trial of cyclophosphamide plus cisplatin with or without doxorubicin in ovarian carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol*. 1989;7(4):457-465. PMID: 2926470. (Omura et al. 1989)

TRIAL SPONSOR

- Gynecologic Oncology Group (GOG)

RATIONALE FOR TRIAL

- GOG 47 demonstrated cyclophosphamide, doxorubicin, and cisplatin (CAP) to be superior to cyclophosphamide and doxorubicin (CA). CAP improved complete response rate, response duration, and progression-free interval. CAP improved survival only in patients with measurable disease (Omura et al. 1986).
- Prior studies suggest that doxorubicin does not confer a treatment advantage.
- This study was designed to compare CP (omitting doxorubicin) with CAP in patients with optimal cytoreduction.

PATIENT POPULATION

- N = 349 evaluable patients.
- Enrolled from April 1981 to July 1985.
- Small-volume stage III ovarian cancer (<1 cm, therefore no clinically measurable lesions to follow).
- Ineligible: prior cancer, prior irradiation or chemotherapy, major organ dysfunction, history of congestive heart failure, complete disability, borderline cancers.

TREATMENT DETAILS

Arm 1: CP (cyclophosphamide + Cisplatin).

- Cyclophosphamide 1000 mg/m^2.
- Cisplatin 50 mg/m^2.
- Administered every 3 weeks for 8 cycles.

Arm 2: CAP (Cyclophosphamide + Adriamycin + Cisplatin)

- Cyclophosphamide 500 mg/m^2.
- Adriamycin (doxorubicin) 50 mg/m^2.
- Cisplatin 50 mg/m^2.
- Administered every 3 weeks for 8 cycles.
- Dosing schedules were chosen to anticipation of comparable hematologic toxicities.

Second-Look Laparotomy

- Patients without progression underwent second-look laparotomy at 6 months.
  - Negative second look—followed without additional treatment.
  - Positive second look—went off treatment part of study.

Dose Reductions

- Grade 3 granulocyte or platelet toxicity with recovery by next cycle: cyclophosphamide and doxorubicin doses were reduced to 75%; cisplatin was not decreased.
- Grade 4 granulocyte or platelet toxicity with recovery by next cycle: cyclophosphamide and doxorubicin doses were reduced to 50%; cisplatin was reduced to 75%.
- Doses could be escalated by 25% for each subsequent course until 100% if no further severe myelosuppression was noted.

Doxorubicin

- Stopped if congestive heart failure or any other life-threatening cardiac condition.
- Total cumulative dose was not to exceed 400 mg/m^2.

Cisplatin

- Held if BUN >30 mg/dL or creatinine >2 mg/dL.
- Restarted only after BUN and creatinine returned to acceptable levels.

ASSESSMENTS

- Radiographs and scans every 3 months.

Table 2.2 Results of GOG 52

Treatment arm	Cyclophosphamide + cisplatin (CP) N = 176	CP + doxorubicin (CAP) N = 173	Statistics
Patient characteristics			
Median age	56 (19-80)	53 (23-80)	
Residual disease	72%	71%	
Grade 3	33%	36%	
Stage III, optimal	100%	100%	
Serous	53%	58%	
Endometrioid	15%	12%	
Mucinous	2%	1%	
Clear cell	6%	11%	
Other	23%	18%	
Treatment delivery			
Cyclophosphamide	24% decrease in dose	21% decrease in dose	
Cisplatin	7% decrease in dose	10% decrease in dose	
Doxorubicin		22% decrease in dose	
Average cycle time	25.8 days	26.1 days	
Efficacy			
Progression-free interval	22.7 months	24.6 months	NS
Overall survival	31.2 months	38.9 months	NS
Negative second look	30.2%	32.8%	NS
Toxicity			
G3/4 leukocyte	55%	57%	NS
G3/4 thrombocytopenia	1%	2%	
G3 nausea/vomiting	3.6%	9.3%	

NS, not significant.

ENDPOINTS

- Progression-free interval (PFI) (primary endpoint).
- Frequency of negative second-look laparotomy.
- Survival.

STATISTICAL CONSIDERATIONS

Sample Size

- Study designed assuming a median PFI of 2 years for CP with a 1-tail test at the .05 level. Statistical power is 97% and 76% for a 15% and 10% increase in the 2-year PFI rate.

Statistical Tests

- Mantel-Haenszel χ^2 test to compare frequency of negative second-look laparotomy.
- Cox proportional hazards model, likelihood ratio test to compare survival.

CONCLUSION OF TRIAL

- Doxorubicin does not improve outcomes in optimal stage III ovarian cancer.

COMMENTS

- Second-look surgery does not influence survival outcomes as better options for "salvage" therapy are needed.
- Residual disease status had a large impact on progression-free interval. However, once a negative second look was documented, residual disease status no longer had an impact.
- Low grade and younger age were also favorable factors for outcome.
- Timing of chemotherapy initiation did not have an impact on survival.
- Clear cell carcinoma had the worst progression-free interval and survival.
- Cyclophosphamide dose was lower in CAP (500) vs CP (1000).

GOG 97 (McGuire, JCO 1995)

REFERENCE

- McGuire WP, et al. Assessment of dose-intensive therapy in suboptimally debulked ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 1995;13(7):1589-1599. PMID: 7602348. (McGuire et al. 1995)

TRIAL SPONSOR

- Gynecologic Oncology Group (GOG)

RATIONALE FOR TRIAL

- The current standard therapy at the time of this trial was the 2-drug regimen of cyclophosphamide and cisplatin.
- The 2-drug regimen had been shown to be as efficacious as and less toxic than a 4-drug regimen (Neijt et al. 1991).
- This trial was designed to evaluate chemotherapy dose intensity on ovarian cancer survival and response in patients with bulky residual disease.

PATIENT POPULATION

- N = 458 eligible.
- Enrolled between January 1987 and April 1990.

Inclusion Criteria

- Stage III epithelial ovarian cancer with >1 cm residual disease after surgical cytoreduction or stage IV disease.
- Patients were allowed to have clinically measurable or nonmeasurable (assessable) disease.
- GOG performance status of 0, 1, or 2.
- Adequate bone marrow (white blood cells [WBC] $>3 \times 10^9$/L, platelets $>100 \times 10^9$/L), renal (serum creatinine <2 mg/dL) and hepatic function (serum bilirubin and aspartate aminotransferase [AST] <2 times the upper limit of institutional norm)
- Study entry within 6 weeks of the surgical procedure.

Exclusion Criteria

- Borderline tumors, prior therapy, any other malignant disease other than nonmelanoma skin cancer.

TREATMENT DETAILS

Arm 1: Standard Therapy

- Cyclophosphamide 500 mg/m^2 (166 mg/m^2/wk).
- Cisplatin 50 mg/m^2 (16.6 mg/m^2/wk).
- Treatment every 3 weeks for 8 courses.

Arm 2: Intensive Therapy

- Cyclophosphamide 1000 mg/m^2 (333 mg/m^2/wk).
- Cisplatin 100 mg/m^2 (33.3 mg/m^2/wk).
- Treatment every 3 weeks for 4 courses.
- Patients in the intensive therapy group received the same total dose of chemotherapy but at 1.97 times greater dose intensity than the standard therapy group.

Management of Toxicities

- To maintain dose intensity, patients were not allowed to undergo dose reductions.
- Hematologic toxicity was managed with treatment delays. If delay was greater than 3 weeks, the patient was taken off study and monitored for survival.

- No delay was allowed for any grade gastrointestinal toxicity, G1 or G2 peripheral neurotoxicity, mild renal toxicity (creatinine ≤2 mg/dL or creatinine clearance ≥50 mL/min), or mild ototoxicity (<–10 dB reduction in high-frequency discrimination).
- Persistent and more severe neurologic, otic, or renal toxicity required removal of the patient from the study.
- If a patient developed hemorrhagic cystitis, an equitoxic dose of chlorambucil was substituted for cyclophosphamide.

ASSESSMENTS

- Baseline history and physical examination, laboratory procedures, imaging studies to assess disease measurements.
- Functional Living Index–Cancer (FLIC) given before chemotherapy, after each course of treatment, and 6 weeks after last course of treatment.
- Tumor measurements after each 2 courses of therapy.
- Second-look laparotomy performed after completing therapy on patients without measurable disease or patients who achieved a complete clinical response to determine the pathologic response rate. Failure to undergo surgery was considered a major protocol violation.
- Cancer antigen 125 (CA125) was monitored but never used as an indicator of disease status.

ENDPOINTS

- Overall survival (OS).
- Progression-free survival (PFS).
- Response.

STATISTICAL CONSIDERATIONS

- Kaplan-Meier used to estimate survival (Kaplan and Meier 1958).
- Log-rank test used to assess the independence of PFS, OS, and randomized treatment (Mantel 1966).
- Linear proportional hazards model was used to estimate the treatment effects while adjusted for other pretreatment factors (Cox 1972).
- A proportional hazards model with an interaction term was used to determine the homogeneity of the treatment effect for those with and without measurable disease.

Table 2.3 Results of GOG 97

Treatment arm	Standard-intensity CP N=235	Dose-intense CP N=223	Statistics
Patient characteristics			
Median age (range)	60 (22-80)	60 (20-83)	
Measurable disease	38%	36%	
Stage III, <2 cm	5%	9%	
Stage III, ≥2 cm	63%	57%	
Stage IV, <2 cm	8%	16%	
Stage IV, ≥2 cm	24%	19%	
Serous	70%	66%	
Endometrioid	11%	18%	
Mucinous	3%	3%	
Clear cell	4%	2%	
Other	13%	12%	
Treatment delivery			
Days between courses	21-25	22-28	
Median total dose			
Cisplatin	391 mg/m^2	394 mg/m^2	NS
Cyclophosphamide	3906 mg/m^2	3943 mg/m^2	NS
Efficacy			
Complete response	36%	30%	NS
Partial response	24%	25%	
Stable disease	32%	28%	
Progression	1%	11%	
Death before evaluation	5%	6%	
Negative SL, measurable	10%	10%	NS
Negative SL, nonmeasurable	16%	19%	
Median PFS	12.1 months	14.3 months	NS
Median OS	19.5 months	21.3 months	NS
Toxicity			
G3/4 WBC	39%	82%	<.005
G3/4 platelet	<1%	22%	<.005
G3/4 anemia	<3%	9%	<.005
G3/4 GI/vomiting	3%	16%	<.005
G3/4 renal	<1%	5%	<.005
G3/4 febrile neutropenia	0%	2%	<.005
G3/4 sepsis/infection	<2%	5%	<.05
Removed due to toxicity	7%	17%	
Death attributed to treatment	N=1	N=2	
Progression or death before completing therapy	23.8%	7.6%	

CP, cyclophosphamide+cisplatin; GI, gastrointestinal; NS, not significant; OS, overall survival; PFS, progression-free survival; SL, second look; WBC, white blood cells.

- The Kruskal-Wallis rank test adjusted for tied ranks was used to test the independence of dose intensity, total dose delivered, and severity of toxicity relative to the assigned treatment (Kruskal and Wallis 1952).
- The Mantel-Haenszel χ^2 test was used to determine the independence of treatment and response and was stratified by disease measurability (Mantel and Haenszel 1959).

CONCLUSIONS OF TRIAL

- Clinical and pathologic response rates, response duration, and survival were similar between treatment arms, but adverse events (hematologic, gastrointestinal, febrile episodes, sepsis, and renal toxicities) were more common and severe in the dose-intensive therapy group.
- This study provides no evidence to support the hypothesis that modest increases in dose intensity (without increasing total dose) have an impact on outcome.

COMMENTS

- Dose modification was rigorously controlled in this trial to maintain dose intensity.
- Neither high-dose chemotherapy (with or without autologous bone marrow rescue) nor modest dose intensification (as studied in this trial) overcame the development of chemoresistance.

GOG 111 (McGuire, NEJM 1996)

REFERENCE

- McGuire WP, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med*. 1996;334(1):1-6. PMID: 7494563. (McGuire et al. 1996)

TRIAL SPONSOR

- Gynecologic Oncology Group (GOG)

RATIONALE FOR TRIAL

- At the time of trial design, the standard of care for advanced epithelial ovarian cancer in the United States was a combination of an alkylating agent and cisplatin, specifically cyclophosphamide and cisplatin. However, long-term disease control with this regimen was less than 10% in

women with incompletely resected stage III and less than 5% in women with stage IV disease.
- In 1989, a phase II trial reported that paclitaxel produced a 24% response rate in patients with platinum-resistant ovarian cancer (McGuire et al. 1989). Another phase II trial reported a 37% response rate in 1994 (Thigpen et al. 1994). This made paclitaxel the most active single-agent drug ever evaluated by the GOG in a phase II study in ovarian cancer.
- A phase I trial of paclitaxel and cisplatin demonstrated the safety of the combination when paclitaxel was given first as a 24-hour infusion (Rowinsky et al. 1991a).
- Based on the activity of paclitaxel in the salvage setting, the safety of the combination of paclitaxel and cisplatin, and the need for better treatment alternatives than the current standard of care, the GOG conducted this phase III study to evaluate the efficacy of the paclitaxel + cisplatin combination as standard first-line therapy in patients with incompletely resected stage III or any stage IV ovarian cancer.

PATIENT POPULATION

- N = 386.
- Accrual began in April 1990 and completed its goal within 2 years.

Inclusion Criteria

- Stage IV or suboptimal stage III (defined as residual disease >1 cm) epithelial ovarian cancer.
- Having undergone surgical debulking; having received no prior chemotherapy or radiation; having a GOG performance status of 0 to 2 and having adequate hematologic (WBC $\geq$3000/mm^3, platelet count >100,000/mm^3), renal (serum creatinine <2.0 mg/dL), and liver (serum bilirubin and serum AST <2 times the upper limit of normal for the institution) function.
- Entry within 6 weeks of the debulking procedure.

Exclusion Criteria

- Borderline tumors, taking antiarrhythmic medication, any prior cancer other than nonmelanoma skin cancer.

TREATMENT DETAILS

Arm 1: Standard Therapy Group—Cyclophosphamide + Cisplatin

- Cyclophosphamide 750 mg/m^2 intravenous (IV)
- Cisplatin 75 mg/m^2 IV at rate of 1 mg/min.
- Treatment every 3 weeks for 6 courses.

Arm 2: Experimental Therapy Group—Paclitaxel and Cisplatin

- Paclitaxel 135 mg/m^2 IV as a 24-hour continuous infusion.
- Cisplatin 75 mg/m^2 IV at a rate of 1 mg/min.
- Treatment every 3 weeks for 6 courses.
- Pretreatments.
  - Dexamethasone 20 mg orally or IV 14 and 7 hours before infusion.
  - Diphenhydramine 50 mg IV 30 minutes before infusion.
  - Any histamine H_2 antagonist IV 30 minutes before infusion.

Treatment Delays

- Delayed week by week until WBC >3000/mm^3 and platelet count >100,000/mm^3.
- No delay allowed for any gastrointestinal toxicity, grade 1 or 2 peripheral neurotoxicity, mild renal toxicity (creatinine ≤2 mg/dL or creatinine clearance of ≥50 mL/min), or mild ototoxicity (reduction of ≤10 dB in high-frequency discrimination).

Treatment Withdrawal

- For treatment delays exceeding 3 weeks due to hematologic toxicity.
- For more severe neurologic, renal, or otic toxicity that had not resolved by the time of the next scheduled dose.
- For cardiac toxic effects (other than asymptomatic sinus bradycardia).
- For severe allergic reaction (bronchospasm, hypotension, diffuse urticaria) during the paclitaxel infusion.

Dose Modifications—Cyclophosphamide

- Reduction to 500 mg/m^2 for grade 4 hematologic toxicity (WBC ≤1000/mm^3, absolute neutrophil count (ANC) ≤500/mm^3, platelet count <25,000/mm^3).
- Reescalation in subsequent dose if nadir counts not grade 4.

Dose Modifications—Paclitaxel

- Reduction to 110 mg/m^2 for grade 4 hematologic toxicity (WBC ≤1000/mm^3, ANC ≤500/mm^3, platelet count <25,000/mm^3).
- Reescalation in subsequent dose if nadir counts not grade 4.

Dose Modifications—Cisplatin

- Not allowed.

ASSESSMENTS

- Imaging studies before and after every other course of therapy.
- Adverse events graded by toxicity criteria of the GOG.

- Reassessment laparotomy to determine pathologic response required for those without measurable disease and those with measureable disease and complete clinical response.

ENDPOINTS

- Progression-free survival (primary endpoint).
- Overall survival.

STATISTICAL CONSIDERATIONS

- Kaplan-Meier to estimate the cumulative proportion surviving.
- Two-tailed log-rank test to assess the independence of PFS, OS, and randomized treatment assessment.
- Linear proportional hazards analysis to estimate relative risk adjusted for pretreatment factors.
- Proportional hazards with an interaction term to assess the homogeneity of the treatment effect across prognostic groups.
- Kruskal-Wallis rank test adjusted for tiered ranks to test the independence of the severity of toxicity with the assigned treatment.
- Pearson's χ^2 test to test the independence of response and treatment.

CONCLUSION OF TRIAL

- Incorporation of paclitaxel into first-line chemotherapy for patients with incompletely resected stage III and IV epithelial ovarian cancer improves both progression-free and overall survival. Paclitaxel and cisplatin are associated with an estimated 40% reduction in the risk of death compared to cyclophosphamide and cisplatin.

COMMENTS

- At the start of the study, all women receiving paclitaxel underwent cardiac monitoring as patients receiving paclitaxel therapy had previously been reported to experience bradyarrhythmias with atrioventricular block and ventricular irritability (Rowinsky et al. 1991b). Only 7 women had grade 2 or higher cardiac episodes (first-degree heart block, ischemic events without infarction), so the requirement for cardiac monitoring was removed toward the end of the study.
- The benefit of paclitaxel did not appear to be due to a poorer than anticipated outcome among the patients receiving standard therapy.
- The benefit of paclitaxel did not appear to be limited to the subpopulations with measurable disease or stage III disease.

Table 2.4 Results of GOG 111

Treatment arm	Cisplatin + cyclophosphamide N = 202	Cisplatin + paclitaxel N = 184	Statistics
Patient characteristics			
Median age (range)	60 (27-80)	59 (20-84)	
Measurable disease	57%	54%	
Stage III	64%	67%	
Stage IV	36%	33%	
Serous	64%	76%	
Endometrioid	13%	8%	
Mucinous	5%	2%	
Clear cell	2%	2%	
Other	15%	12%	
Grade 1	7%	4%	
Grade 2	41%	45%	
Grade 3	52%	51%	
Treatment delivery			
Interval between cycles	21-28 days	21 days	
Completed 6 cycles	78%	87%	
Discontinuation due to			
Progression or death	11%	5%	
Toxicity or declined	10%	8%	
Efficacy			
Overall response rate	60%	73%	
Complete response (CR)	31%	51%	$P = .01$
Partial response (PR)	29%	22%	
Pathologic CR	20%	26%	NS
PFS	13 months	18 months	RR 0.7, $P < .001$
OS	24 months	38 months	RR 0.6, $P < .001$
Toxicity			
G3/4 neutropenia	83%	92%	<.05
G3/4 thrombocytopenia	3%	3%	
G3/4 anemia	8%	9%	
G3/4 gastrointestinal	11%	15%	
Fever	11%	20%	<.05
Alopecia	37%	63%	<.05
G3/4 renal	<2%	<1%	
Any neurologic	21%	28%	
Allergic reaction	0%	4%	<.05
Death due to treatment	N = 6	N = 4	

NS, not significant; OS, overall survival; PFS, progression-free survival; RR, relative risk.

- Paclitaxel was in limited use when this trial was conducted. Therefore, crossover occurred to a lesser degree after the conclusion of the trial and there was likely to be less blunting of the survival outcomes.

GOG 104 (Alberts, NEJM 1996)

REFERENCE

- Alberts DS, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med*. 1996;335(26):1950-1955. PMID: 8960474. (Alberts et al. 1996)

TRIAL SPONSOR

- Gynecologic Oncology Group (GOG)

RATIONALE FOR TRIAL

- In an attempt to maximize the activity of cisplatin against ovarian cancer, trials have investigated its delivery directly into the peritoneal cavity. This results in intraperitoneal cisplatin concentrations that are 12 to 15 times greater than the concentration in plasma (Howell et al. 1982; Goel et al. 1989).
- Survival may be improved with salvage intraperitoneal chemotherapy in patients with small (<1 cm) residual masses after upfront chemotherapy and second-look surgery (Howell et al. 1987; Kirmani et al. 1991).
- This trial was conducted to compare intraperitoneal and intravenous cisplatin administration in the upfront adjuvant treatment of patients with stage III ovarian cancer and residual masses less than 2 cm in size.

PATIENT POPULATION

- N = 654 enrolled, 546 eligible.
- Enrollment between June 1986 and July 1992.
- Stage III epithelial ovarian cancer with less than 2 cm residual disease.
- Surgery that included exploratory laparotomy with at least total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and debulking to optimal (<2 cm size) status.
- Enrollment within 4 weeks of surgery.
- Performance status of 0 to 2; adequate blood counts, renal function (serum creatinine ≤1.5 mg/dL or creatinine clearance ≥40 mL/min).

TREATMENT DETAILS

Arm 1: Intravenous Cyclophosphamide + Intravenous Cisplatin

- Cyclophosphamide 600 mg/m^2 in 150 mL of diluent over 60 to 90 minutes IV.
- Cisplatin 100 mg/m^2 in 500 to 1000 mL of normal saline at a rate of 1 mg/min.
- IV hydration with at least 1 L of normal saline with 3 g of magnesium sulfate and 40 g of mannitol over a period of 1 to 2 hours.
- Treatment every 3 weeks for 6 cycles.

Arm 2: Intravenous Cyclophosphamide + Intraperitoneal Cisplatin

- Cyclophosphamide 600 mg/m^2 in 150 mL of diluent over 60 to 90 minutes IV.
- Cisplatin 100 mg/m^2 in 2 L of normal saline warmed to body temperature and instilled into the peritoneal cavity as fast as possible.
- IV hydration with at least 1 L of normal saline with 3 g of magnesium sulfate and 40 g of mannitol over a period of 1 to 2 hours.
- Treatment every 3 weeks for 6 cycles.

Treatment Delays

- Delay for a maximum of 2 weeks to allow for resolution of toxic effects.

Treatment Discontinuation

- Cisplatin discontinued and cyclophosphamide increased to 1000 mg/m^2.
  - For grade 2 or higher peripheral neuropathy.
  - For serum creatinine >1.9 mg/dL.
- Treatment discontinued permanently.
  - For serum creatinine >1.9 mg/dL for 8 weeks.

ASSESSMENTS

- Serum CA125 before each cycle.
- Second-look laparotomy at completion of therapy if no clinical evidence of disease.

ENDPOINTS

- Survival.
- Pathologic complete response rate.

STATISTICAL CONSIDERATIONS

Sample Size

- Initial trial design had a power of 93% to detect a difference in the hazard ratio for death of 0.67 with a 2-sided *P* value of .05 and 215 patients per treatment arm.
- With a Pearson χ^2 approximation and 2-sided *P* value of .05, there was 85% power to detect a difference of pathologic response rate of 55% vs 40%.
- Accrual was extended for another year in January 1991 to achieve a large enough sample size to do a separate analysis of data from patients with residual tumors <0.5 cm. With the plan to accrue 560 patients (390 with tumors <0.5 cm), the power to detect a hazard ratio of 0.67 was 88%.

Statistical Tests

- Cox regression analyses.
- Two-sided Fisher's exact tests to compare toxicities.

CONCLUSION OF TRIAL

- Intraperitoneal cisplatin was associated with a 20% improvement in survival and a 24% reduction in the risk of death compared to intravenous cisplatin.
- Pathologic complete response rates are greater in the subset of patients with ≤0.5-cm residual tumor masses, supporting the observation that the penetration of intraperitoneal cisplatin is limited to a depth of 0.1 to 1 mm from the surface of the tumor (Los et al. 1989).

COMMENTS

- There was a higher rate of pathologic complete response (pCR) among patients receiving intraperitoneal compared to intravenous cisplatin. However, among the 400 patients eligible for second-look surgery (no clinical evidence of disease at completion of therapy), 103 did not undergo surgery or they had inadequate surgery, creating bias. Because of this bias, the pCR data are reported without statistical comparisons.
- Covariates associated with improved survival included (and thus included in the final Cox model).
  - No gross residual disease ($P < .001$).
  - Younger age ($P < .001$).
  - Non–clear cell and nonmucinous histology ($P < .001$).
  - Enrollment after surgery ($P < .001$).

Table 2.5 Results of GOG 104

Treatment arm	Intravenous group N=279	Intraperitoneal group N=267	Statistics
Patient characteristics			
Median age (range)	56 (21-85)	59 (24-84)	
Minimal residual <0.5 cm	72%	73%	
No gross residual	26%	25%	
Stage III	100%	100%	
Serous	66%	67%	
Endometrioid	9%	10%	
Mucinous	3%	1%	
Clear cell	2%	2%	
Other	20%	20%	
Grade 1	13%	11%	
Grade 2	30%	31%	
Grade 3	57%	58%	
Treatment delivery			
Completed 6 cycles	58%	58%	
Cisplatin discontinued for toxicity (+increase cyclophosphamide)	40%	22%	
Efficacy			
Complete PR (second look)	36%	47%	
OS	41 months	49 months	HR 0.76, *P*=.02
OS, <0.5 cm residual	46 months	51 months	HR 0.8, *P*=.10
Toxicity			
Treatment-related death	N=0	N=2	
>G3 anemia	25%	26%	NS
>G3 granulocytopenia	69%	56%	.0002
>G3 leukopenia	50%	40%	.04
>G3 thrombocytopenia	9%	8%	NS
≥G2 abdominal pain	2%	18%	<.001
≥G2 tinnitus	14%	7%	.01
≥G2 hearing loss	15%	5%	<.001
≥G2 neuromuscular	25%	15%	.02
≥G2 pulmonary effects	0.4%	3%	.002

HR, hazard ratio; OS, overall survival; PR, pathologic response.

- Neutropenia, tinnitus, and hearing loss were experienced more frequently in the intravenous arm. Abdominal pain was experienced more frequently in the intraperitoneal arm, but pain usually resolved within 24 hours and was generally manageable with weak opioid or nonopioid drugs. Dyspnea occurred more frequently with intraperitoneal administration, likely due to compression of the base of the lungs.
- This trial was published shortly after GOG 111 (McGuire et al. 1996), which demonstrated the superiority of paclitaxel + cisplatin over cyclophosphamide + cisplatin. Ongoing studies will plan to evaluate the efficacy of intraperitoneal cisplatin with paclitaxel.

ICON2 (Lancet 1998)

REFERENCE

- ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. ICON Collaborators. International Collaborative Ovarian Neoplasm Study. *Lancet*. 1998;352(9140):1571-1576. PMID: 9843101. (International Collaborative Ovarian Neoplasm Group 1998)

TRIAL SPONSORS

- International Collaborative Ovarian Neoplasm Study
  - Instituto Mario Negri in Milan, Italy
  - Swiss Institute for Cancer Research (SIAK) in Bern, Switzerland
  - Medical Research Council's Cancer Trials Office in Cambridge, United Kingdom

RATIONALE FOR TRIAL

- Five meta-analyses representing data from 45 randomized controlled trials suggest that immediate platinum-based treatment is better than non-platinum-based treatment, combination therapy is better than single-agent platinum, and there is no difference between carboplatin and cisplatin either as single agents or within combination regimens (Chemotherapy in advanced ovarian cancer . . . 1991).
- Two meta-analyses focusing on the role of doxorubicin suggest that the combination of cyclophosphamide, doxorubicin, and cisplatin (CAP)

is better than cyclophosphamide and cisplatin (CP) (Cyclophosphamide plus cisplatin . . . 1991; A'Hern and Gore 1995). The 3-drug regimen is associated with a marginal improvement in 5-year survival from 20% to 26%.
- While many believed CAP to be the most effective drug regimen for advanced ovarian cancer at this time, there was an open question as to whether single-agent platinum (the most active agent in the combination) administered at full dose would provide equivalent or better survival outcomes compared to CAP.
- Carboplatin was chosen as the single-agent platinum in this study because it is less toxic than cisplatin at optimally tolerated doses and has similar efficacy. Single-agent carboplatin was the most widely used regimen in the United Kingdom, and CAP was the most widely used regimen in Italy at this time.

PATIENT POPULATION

- N = 1526.
- Patients entered between January 1991 and July 1996.
- ICON2 was run as 3 parallel trials through (1) the Instituto Mario Negri in Milan, Italy; (2) the Swiss Institute for Cancer Research (SIAK) in Bern, Switzerland; (3) and the Medical Research Council's Cancer Trials Office in Cambridge, United Kingdom.
- Patients were recruited from 132 centers in 9 countries.
- Histologically confirmed invasive epithelial ovarian cancer; fit to receive chemotherapy; no prior chemotherapy or radiation therapy; no previous malignancy (excluding nonmelanoma skin cancer); adequate renal function.
- No restrictions on extent of surgery, but total abdominal hysterectomy, bilateral salpingo-oophorectomy, and thorough staging were recommended as the minimum procedures.
- Eligibility criteria were intentionally left wide to promote recruitment.

TREATMENT DETAILS

Arm 1: CAP (Cyclophosphamide, Adriamycin, Cisplatin)

- Cyclophosphamide 500 mg/m^2.
- Adriamycin (doxorubicin) 50 mg/m^2.
- Cisplatin 50 mg/m^2.
- One cycle every 3 weeks for 6 cycles.

Arm 2: Carboplatin

- Carboplatin area under the curve (AUC) 5.
- Dose determined by AUC method of Calvert (Calvert et al. 1989). Glomerular filtration rate (GFR) was determined by radioisotope method or the Cockcroft formula. If GFR was determined by creatinine clearance, carboplatin dose was recommended to be reduced by 10%.
- One cycle every 3 weeks for 6 cycles.

ASSESSMENTS

- Pretreatment data were collected at the time of randomization.
- Treatment and initial follow-up data were collected 6 months later.
- Further follow-data were collected 12 months after randomization and every year thereafter.

ENDPOINTS

- Five-year survival.
- OS.
- PFS.

STATISTICAL CONSIDERATIONS

Sample Size

- Five-year survival estimated to be 20% in the carboplatin group. To detect an improvement in survival with CAP to 26% with 90% power and to 25% with 85% power at a significance level of 5%, the maximum accrual target was set to 2000 patients.

Statistical Tests

- Kaplan-Meier curves, Mantel-Cox version of log-rank test.
- Stratified log-rank test to allow for differences across 3 centers.
- Cox proportional hazards model to account for imbalances in pretreatment characteristics.

CONCLUSION OF TRIAL

- There was no difference in PFS or OS between CAP and single-agent carboplatin.
- Neither treatment was more effective in any subgroup analyses, suggesting that the results of ICON2 are applicable to a broad range of patients.

Table 2.6 Results of ICON2

Treatment arm	CAP N=766	Carboplatin N=760	Statistics
Patient characteristics			
Italy	64%	64%	
United Kingdom	20%	20%	
Switzerland	7%	7%	
Other	7%	10%	
Age <55	38%	35%	
Age 55-65	31%	33%	
Age >65	31%	33%	
No residual	31%	31%	
≤2 cm residual	25%	24%	
>2 cm residual	45%	45%	
Stage I	11%	13%	
Stage II	12%	11%	
Stage III	63%	62%	
Stage IV	14%	15%	
Serous	52%	52%	
Endometrioid	13%	13%	
Mucinous	10%	9%	
Clear cell	5%	5%	
Other	21%	20%	
Grade 1	13%	11%	
Grade 2	32%	31%	
Grade 3	46%	50%	
Unknown grade	9%	10%	
Treatment delivery			
Received 6 cycles	80%	81%	
Received 0 cycles	N=34	N=14	
Efficacy			
1-year PFS	63%	60%	HR 0.92, *P*=.20
Median PFS	17 months	15.5 months	favoring CAP
2-year OS	60%	60%	HR 1, *P*=.98
Median OS	33 months	33 months	
Toxicity (collected in Italy only)			
Alopecia	70%	4%	
G 3/4 leucopenia	36%	10%	
G 3/4 Nausea, vomiting	20%	9%	
G 3/4 thrombocytopenia	6%	16%	

CAP, cyclophosphamide+Adriamycin/doxorubicin+cisplatin; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

- CAP was more toxic than carboplatin, causing more alopecia, leucopenia, nausea, and vomiting. Carboplatin caused more thrombocytopenia.
- Single-agent carboplatin is a safe and effective standard treatment option for patients with advanced ovarian cancer.

COMMENTS

- Recruitment to ICON2 was stopped in July 1996 before the planned 2000 patients had been enrolled due to an interest in testing paclitaxel-containing regimens in the context of data from GOG 111 (McGuire et al. 1996). ICON3 began recruitment in February 1995 comparing the combination of paclitaxel + carboplatin with single-agent carboplatin or CAP (International Collaborative Ovarian Neoplasm Group 2002).

GOG 132 (Muggia, JCO 2000)

REFERENCE

- Muggia FM, et al. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2000;18(1):106-115. PMID: 10623700. (Muggia et al. 2000)

TRIAL SPONSOR

- Gynecologic Oncology Group (GOG)

RATIONALE FOR TRIAL

- Despite the activity of cisplatin in advanced ovarian cancer, the long-term survival of suboptimally cytoreduced patients remains poor.
- Paclitaxel has been established as a salvage treatment of patients with platinum-sensitive and platinum-resistant ovarian cancer (McGuire et al. 1989; Thigpen et al. 1994).
- Because the possibility existed that paclitaxel may be more active than cisplatin, this trial was designed to compare the activity of single-agent cisplatin vs single-agent paclitaxel vs combination cisplatin and paclitaxel.

PATIENT POPULATION

- N = 648 registered, 614 eligible.
- Accrual between March 1992 and May 1994.

- Histologically confirmed epithelial ovarian cancer; stage III disease with at least 1 mass >1 cm residual or any stage IV disease; no prior anticancer medications or radiation; normal marrow (granulocytes >1500/μL; platelets >100,000/μL); normal renal function (serum creatinine <1.5 mg/dL); normal liver function (alanine aminotransferase [ALT], AST <2 times normal; bilirubin <1.5 mg/dL); GOG performance score of 0, 1, or 2.
- Ineligible: borderline tumors; any other prior malignancy other than basal cell carcinoma or in situ of the cervix; primary peritoneal tumor or lack of tumor in the ovaries.
- Registration within 6 weeks of staging surgery.

TREATMENT DETAILS

- Higher single-agent doses were selected because studying lower doses might have led to less definitive conclusions.

Arm 1: Single-Agent Cisplatin

- Cisplatin 100 mg/m^2 IV.
- Repeated every 3 weeks for 6 courses.
- Dose adjustment of cisplatin by 50% for grade 2 or higher thrombocytopenia or any other grade 2 nonhematologic toxicity (with the exception of nausea and vomiting); any grade tinnitus.
- Dose held for cisplatin for any grade 3 or 4 nephropathy or neuropathy until toxicity completely resolved.

Arm 2: Single-Agent Paclitaxel

- Paclitaxel 200 mg/m^2 IV over 24 hours.
- Repeated every 3 weeks for 6 courses.
- Dose adjustment of paclitaxel to 150 mg/m^2 for any grade 4 neutropenia or grade 3 neutropenia requiring hospitalization.

Arm 3: Combination Cisplatin+Paclitaxel (Same Regimen as GOG 111) (McGuire et al. 1996)

- Paclitaxel 135 mg/m^2 IV over 24 hours.
- Cisplatin 75 mg/m^2 IV.
- Repeated every 3 weeks for 6 courses.
- Dose adjustment of paclitaxel to 110 mg/m^2 for any grade 4 neutropenia or grade 3 neutropenia requiring hospitalization.
- Dose adjustment of cisplatin by 50% for grade 2 or higher thrombocytopenia or any other grade 2 nonhematologic toxicity (with the exception of nausea and vomiting); any grade tinnitus.

- Dose held for cisplatin for any grade 3 or 4 nephropathy or neuropathy until toxicity completely resolved.

Treatment Delays

- Delay until platelet count >100,000/μL and ANC >1500/μL.
- Granulocyte colony-stimulating factors (G-CSFs) were permitted if ANC failed to recover to >1500/μL within 21 days of the last treatment despite 1 dose-level reduction or if neutropenia-related complications occurred at the reduced dose level.

ASSESSMENTS

- Baseline computed tomography (CT) scan (within 3 weeks), CA125, blood work, and exam.

ENDPOINTS

- PFS.
- OS.
- Response rate.

STATISTICAL CONSIDERATIONS

Sample Size

- Sample size provides 80% chance of detecting a true 29% decrease in the hazard ratio (40% increase in PFS) with a type I error limited to .05.

CONCLUSION OF TRIAL

- Response rates were significantly lower and progression-free survival was shorter with paclitaxel monotherapy compared to the cisplatin-containing regimens.
- There was no difference in overall survival between the 3 treatment arms.
- Combination therapy had a better toxicity profile than the high-dose monotherapy regimens.

COMMENTS

- Cisplatin and paclitaxel monotherapies were discontinued more frequently than the combination regimen due to toxicity or patient refusal (cisplatin only) or due to early progression (paclitaxel only).
- Toxicities.
  - Paclitaxel associated with more severe neutropenia, fever, and alopecia.

Table 2.7 Results of GOG 132

Treatment arm	Cisplatin N=200	Paclitaxel N=213	Cisplatin+paclitaxel N=201
Patient characteristics			
Age <50	23%	23%	22%
Age 50-69	59%	59%	61%
Age≥70	18%	18%	16%
Measurable disease	61%	61%	62%
Stage III	65%	72%	73%
Stage IV	35%	28%	27%
Serous	71%	74%	65%
Endometrioid	7%	7%	10%
Mucinous	2%	3%	2%
Clear cell	1%	1%	4%
Other	19%	15%	16%
Grade 1	8%	9%	6%
Grade 2	41%	39%	37%
Grade 3	51%	52%	57%
Treatment delivery			
Completed 6 courses	69%	71%	81%
Discontinuation due to			
Toxicity or refusal	17%	4%	7%
Early progression	7%	20%	6%
Efficacy			
CR	42%	21%	43%
PR	25%	21%	23%
No response	33%	57%	33%
Pathologic CR	Not assessed	6%	24% ($P<.03$)
Median PFS	16.4 months	10.8 months	14.1 months
Median OS	30.2 months	25.9 months	26.3 months
Toxicity			
G3/4 granulocytopenia	48%	96%	94%
G3/4 thrombocytopenia	4%	3%	3%
G3/4 anemia	11%	6%	8%
G3/4 GI toxicity	33%	10%	18%
G3/4 renal toxicity	4%	0%	<1%
G3/4 neurologic toxicity	11%	1%	5%

CR, complete response; GI, gastrointestinal; OS, overall survival; PFS, progression-free survival; PR, partial response.

  - Cisplatin associated with more severe anemia, thrombocytopenia, neurotoxicity, nephrotoxicity, and gastrointestinal toxicity.
- Salvage therapy was initiated before clinical progression in all 3 treatment arms.
  - Among patients receiving cisplatin only, 52% received paclitaxel as next nonprotocol regimen.
  - Among patients receiving paclitaxel only, 69% received a regimen containing cisplatin or carboplatin as next nonprotocol regimen.
  - Among patients receiving combination cisplatin and paclitaxel, 39% received further cisplatin or carboplatin and 40% received a regimen containing neither platinum nor paclitaxel as next nonprotocol regimen.
- GOG initiated this trial before the results of GOG 111 were available (McGuire et al. 1996).
- This trial needs to be considered in the context of GOG 111 (McGuire et al. 1996) and OV-10 (Piccart et al. 2000), 2 trials that both demonstrated the superiority of cisplatin+paclitaxel over cisplatin+cyclophosphamide. In contrast, GOG 132 demonstrates no difference between cisplatin+paclitaxel vs cisplatin alone (Muggia et al. 2000).
  - Both paclitaxel and cisplatin were commercially available at the time of GOG 132, and many patients crossed over early (before disease progression) after participating in the trial. While this may be responsible for blunting of a survival difference, if one exists, this trial was not designed to evaluate differences between concurrent and sequential treatment strategies, and one cannot conclude that these are equivalent strategies from these data. However, these data are provocative and suggest that sequential therapy may be an acceptable treatment strategy for future studies.
  - During GOG 111, paclitaxel was not commercially available. During the European-Canadian OV-10 trial, paclitaxel was available, but it was not generally used until demonstrated progression. Based on the OV-10 study, the withholding of paclitaxel until clinical progression is not an acceptable treatment strategy.
  - The divergent results between GOG 132 and GOG 111/OV-10 might be explained by the higher dose of cisplatin (100 mg/m^2) in the GOG 132 regimen. This might also be explained by a possible antagonistic effect of cyclophosphamide when combined with cisplatin. However, when considered in the context of the available literature, there is no direct evidence to suggest this to be the case.

Danish Netherlands Trial (Neijt, JCO 2000)

REFERENCE

- Neijt JP, et al. Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. *J Clin Oncol*. 2000;18(17):3084-3092. PMID: 10963636. (Neijt et al. 2000)

TRIAL SPONSOR

- Supported by grants from Bristol-Meyers Squibb.

RATIONALE FOR TRIAL

- Cisplatin + paclitaxel was recommended as the current standard of care. However, paclitaxel was infused over 24 hours and administration required hospitalization for at least 48 hours. Administration of paclitaxel over 3 hours at a higher dose resulted in a different toxicity profile (Eisenhauer et al. 1994; Connelly et al. 1996).
- The substitution of carboplatin for cisplatin results in an improved toxicity profile with less nephrotoxicity, ototoxicity, and neurotoxicity but more myelotoxicity when used as a single agent. However, carboplatin was found to be less effective than cisplatin in a number of solid tumors, and its use was not recommended in the initial treatment of ovarian cancer where the goal of treatment was long-term survival and cure (Vermorken et al. 1993; Lokich and Anderson 1998).
- This exploratory trial was conducted to evaluate the combination of paclitaxel (3-hour infusion) with cisplatin or carboplatin to address the following questions:
  - How many cycles are safe and feasible when administered to outpatients?
  - Is neurotoxicity less with carboplatin compared to cisplatin?
  - Are the regimens equal in efficacy?
  - Is there enough activity to justify the costs of a larger randomized study?

PATIENT POPULATION

- N = 213; 208 eligible.
- Accrual between March 1994 and March 1997.
- Epithelial ovarian cancer, International Federation of Gynecology and Obstetrics (FIGO) stages IIB to IV.
- Adequate bone marrow function (WBC $>3 \times 10^9$/L; platelet count $>100 \times 10^9$/L); adequate renal function (serum creatinine >120 μmol/L;

creatinine clearance >60 mL/min/1.73 m^2); adequate liver function (bilirubin level >25 μmol/L).
- Exclusion criteria: World Health Organization (WHO) performance status of 4; age >75 years or <18 years; complete bowel obstruction; symptomatic brain metastases; prior chemotherapy or radiation therapy; history of ventricular arrhythmia; history of congestive heart failure; myocardial infarction within 6 months of randomization; borderline tumors; second malignant disease; active infection; other serious medical conditions; prior allergic reactions to Cremophor EL.

TREATMENT DETAILS

Arm 1: Paclitaxel + Cisplatin (Administered as Inpatient)
- Paclitaxel 175 mg/m^2 IV over 3 hours.
- Cisplatin 75 mg/m^2 IV.
- Treatment every 3 weeks for 6 cycles.

Arm 2: Paclitaxel + Carboplatin (Administered as Outpatient)
- Paclitaxel 175 mg/m^2 IV over 3 hours.
- Carboplatin AUC 5 IV. GFR based on creatinine clearance, EDTA (ethylenediaminetetraacetic acid) clearance, or the Cockcroft-Gault formula (Cockroft and Gault 1976). Dose (mg) = 5 × (GFR + 25) (Calvert et al. 1989).
- Treatment every 3 weeks for 6 cycles

Standard Premedications
- Dexamethasone 20 mg orally 12 and 6 hours prior to chemotherapy.
- Diphenhydramine 50 mg IV.
- Cimetidine 300 mg IV (or ranitidine 50 mg IV).
- Antiemetics at investigators discretion.

Dose Reductions
- According to nadirs and nadir duration (Neijt et al. 1997).

Treatment Continuations
- Six cycles of treatment unless progressive disease or unacceptable toxicity.
- If assessable disease and no change in disease status after 6 cycles, then 2 additional courses and additional treatment at the discretion of the investigator.
- If partial response, treatment continuation until progression or toxicity.

- If complete response, then 3 additional courses after date of documented response.
- If nonassessable disease, then treatment with 6 cycles until progression or toxicity with subsequent treatment at the discretion of the investigator.

Surgery

- Initial cytoreductive surgery.
- If unresectable disease at time of initial surgery, then maximum cytoreductive surgery recommended as soon at tumor masses were deemed resectable.
- Second-look laparotomy was not recommended.

ASSESSMENTS

- Baseline CA125, CT scan, labs.
- Blood counts weekly.
- CA125 with each cycle of treatment, 1 month after completing therapy and every 3 months thereafter.
- Pelvic examination after 3 and 6 cycles.
- Scans performed at the time CA125 started to increase or when progressive disease suspected on exam. Scans repeated after 3 courses if normal CA125 level at study entry or if CA125 values had not decreased to normal values after 3 courses.

ENDPOINTS

- PFS.

STATISTICAL CONSIDERATIONS

Sample Size

- With a PFS estimate of 20 months for cisplatin+paclitaxel, the study was designed with α of .05 and power of 80% to detect a hazard ratio of 1.67 (PFS as low as 12 months for carboplatin+paclitaxel). Assuming an accrual over 3 years, a total number of 196 patients were needed with 140 events.
- PFS and OS analyzed with Kaplan-Meier survival curves with *P* values calculated by the log-rank and Breslow tests for significance.

Statistical Tests

- Neurotoxicity-free period assessed by Kaplan-Meier.
- Cox proportional hazards model used for effects of treatment, age, WHO performance status, residual tumor size, FIGO stage, grade,

Table 2.8 Results of the Danish Netherlands Trial

Treatment arm	Paclitaxel + cisplatin N = 108	Paclitaxel + carboplatin N = 100	Statistics
Patient characteristics			
Median age	56 years	56 years	
Residual disease ≤1 cm	44%	41%	
Residual disease >1 cm	56%	59%	
Stage II	10%	11%	
Stage III	69%	70%	
Stage IV	20%	19%	
Serous	60%	55%	
Endometrioid	14%	5%	
Mucinous	5%	6%	
Clear cell	1%	6%	
Other	20%	28%	
Grade 1	5%	11%	
Grade 2	33%	20%	
Grade 3	39%	47%	
Unknown grade	23%	22%	
Treatment delivery			
6 cycles (at least)	79%	89%	
12 cycles	3%	4%	
Discontinued for toxicity	17%	5%	
Efficacy			
Overall response	62%	66%	
Clinical complete	35%	40%	
Partial	26%	25%	
No change	19%	16%	
Progression	11%	13%	
Median PFS			HR 1.07 (95% CI, 0.78-1.48)
Median OS	30 months	32 months	HR 0.85 (95% CI, 0.59-1.24)
Toxicity (6 cycles)			
G3/4 hemoglobin	1%	6%	NS
G3/4 granulocytes	50%	70%	<.01
G3/4 platelets	1%	6%	<.01
G2/3 fever	8%	11%	NS
G3 nausea	17%	14%	<.01
G3 neurotoxicity	6%	2%	NS

CI, confidence interval; HR, hazard ratio; NS, not significant; PFS, progression-free survival; OS, overall survival.

histology, body weight, body surface, and baseline laboratory values on PFS.

CONCLUSION OF TRIAL

- The paclitaxel + carboplatin combination is safe and easy to administer to outpatients and is less toxic than paclitaxel + cisplatin. Due to the small number of patients and the wide confidence intervals around survival outcomes, conclusions about efficacy cannot be made with this study.

COMMENTS

- Toxicities.
  - No difference in hair loss, fever, mucositis, diarrhea, allergic reactions, pulmonary toxicity, cutaneous complications, cardiac events, arthralgia, myalgia, constipation, or renal toxicities.
  - Neurotoxicity (greater than grade 1) occurred earlier with paclitaxel + cisplatin.
  - Neurotoxicity occurred in the paclitaxel + carboplatin arm, but it was less frequent, was less severe, and occurred later compared to the neurotoxicity occurring in the cisplatin-containing arm.
- CA125 assessments were performed and elevations were the first sign of progressive disease in 70% of patients who had an elevated level at study entry.
- Because this study determined treatment duration differently from other studies, many patients received more than 6 cycles of treatment. Likely due to the better tolerability of the carboplatin-containing regimen, more women on this arm received prolonged treatment. It is not clear whether this resulted in an impact on PFS.
- Univariate analysis found the following factors to predict worse PFS: residual disease, stage, low hemoglobin levels, high platelet counts, and high number of granulocytes. These findings may implicate interleukin 6 (IL-6) and C-reactive protein in poor outcome. The prognostic impact of hemoglobin, platelets, and granulocytes disappears in a multivariate analysis that included tumor mass, suggesting that IL-6 cytokine release may be related to tumor size.

OV-10 (Piccart, JNCI 2000)

REFERENCE

- Piccart MJ, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst*. 2000;92(9): 699-708. PMID: 10793106. (Piccart et al. 2000)

TRIAL SPONSORS

- EORTC (European Organization for Research and Treatment of Cancer)
- NOCOVA (Nordic Gynecological Cancer Study Group)
- NCI-C-CTG (National Cancer Institute of Canada Clinical Trials Group)
- Scottish Group

RATIONALE FOR TRIAL

- GOG 111 was conducted in the United States and reported better outcome with paclitaxel-cisplatin than cyclophosphamide-cisplatin in suboptimally debulked stage III/IV ovarian cancer patients (abstract at ASCO in 1993, published in 1996) (McGuire et al. 1996).
- This was a confirmatory trial conducted in Europe and Canada.
- In contrast to the administration of Taxol over 24 hours in GOG 111, Taxol was given as a 3-hour infusion in this trial. A prior European-Canadian collaborative trial found a PFS advantage for Taxol 175 mg/m^2 administration over 3 hours in a 2×2 factorial design evaluating paclitaxel dose (135 or 175 mg/m^2) and infusion time (3 hours or 24 hours) in patients with recurrent ovarian cancer (Eisenhauer et al. 1994).

PATIENT POPULATION

- N = 680 recruited.
- Trial organized in April 1994, accrual completed in August 1995.

Inclusion Criteria

- Histologically confirmed epithelial ovarian cancer, stage IIB, IIC, III, or IV.
- Initial surgery within 8 weeks.
- Optimal (≤1 cm residual) or suboptimal (>1 cm residual) cytoreduction.

Exclusion Criteria

- WHO performance status of 4.
- Inadequate bone marrow function (neutrophil count $<1.5 \times 10^9$/L; platelet count $<100 \times 10^9$/L).
- Inadequate liver function (bilirubin >25 μmol/L).
- Inadequate renal function.
- Prior chemotherapy or radiotherapy.
- Complete bowel obstruction.
- Brain metastases.
- Borderline histology.
- Carcinoma of unknown origin.
- Atrial or ventricular arrhythmias.
- Congestive heart failure.
- Myocardial infarction within 6 months.
- Second malignant disease excluding basal cell carcinoma of the skin or in situ carcinoma of the cervix.
- Inability to follow up.
- Active infection.
- Other serious underlying medical conditions.

TREATMENT DETAILS

Arm 1: Cyclophosphamide + Cisplatin (CP)

- Cyclophosphamide 750 mg/m^2 IV rapid injection.
- Cisplatin 75 mg/m^2 IV over 1 hour.
- Administered every 3 weeks.
- Premedications with antiemetics.
- Hydration: 1-L prehydration over 3 hours + posthydration of 1 L over 3 hours (outpatient) or 2 to 3 L over 15 hours (inpatient).

Arm 2: Taxol + Cisplatin (TP)

- Paclitaxel 175 mg/m^2 IV over 3 hours. Dose was escalated to 200 mg/m^2 IV in the second cycle if no febrile neutropenia.
- Cisplatin 75 mg/m^2 IV over 1 hour.
- Premedications.
  - Dexamethasone 20 mg orally 12 hours and 6 hours before paclitaxel.
  - Diphenhydramine 50 mg IV 30 minutes before paclitaxel.
  - Ranitidine 50 mg IV 30 minutes before paclitaxel.
  - Antiemetics.

- Hydration: 1-L prehydration over 3 hours + posthydration of 1 L over 3 hours (outpatient) or 2 to 3 L over 15 hours (inpatients).

Dose Modifications and Drug Substitutions

- For febrile neutropenia or prolonged myelosuppression (G4 neutropenia and/or thrombocytopenia for 2 successive weekly counts):
  - Paclitaxel reduced 20%.
  - Cyclophosphamide reduced 20%.
  - Cisplatin dose not reduced.
  - G-CSF used only if toxic effects occurred despite dose reduction.
- Substitution of carboplatin for cisplatin.
  - Severe renal toxicity (creatinine clearance <45 mL/min per 1.73 m^2).
  - Substantial hearing loss.
  - WHO grade 3 or 4 neurotoxicity.
- Discontinuation of paclitaxel.
  - WHO grade 3 or 4 neurotoxicity.
  - Severe hypersensitivity reactions.
  - Severe cardiac arrhythmias.

Other Treatment Details

- Interval cytoreduction and second-look surgeries allowed.
- Patients who had progressed were allowed to receive any secondary treatment at the investigator's discretion, including taxanes.
- Patients without disease progression after 6 cycles could receive another 3 cycles of optional protocol treatment.
- Cyclophosphamide + cisplatin—options for 3 additional cycles.
  - Cyclophosphamide + cisplatin.
  - Cyclophosphamide + carboplatin.
  - Cyclophosphamide.
  - Cisplatin.
  - Carboplatin.
- Paclitaxel + cisplatin—options for 3 additional cycles.
  - Paclitaxel + cisplatin.
  - Paclitaxel + carboplatin.
  - Paclitaxel.
  - Cisplatin.
  - Carboplatin.
  - Cyclophosphamide + carboplatin.

ASSESSMENTS

- Clinical and radiologic assessment after 3 cycles of therapy.
- Final response status was assigned after 6 cycles of therapy by clinical and radiologic assessment or by second-look surgery.
- CA125 measurements were not used to assess response, except for normalization required for complete response status.
- CT scans were performed at baseline and after 3 cycles, 6 cycles, and 9 cycles.
- Once off protocol therapy, patients were monitored with exam and CA125 assessment every 3 months for 2 years and every 6 months thereafter. CT scans were not performed routinely but were ordered in the setting of symptoms or CA125 elevation.

ENDPOINTS

- PFS (defined as date of randomization to date of progression, death, or start of new therapy).
- Clinical response rate.
- Overall survival (defined as date of randomization to date of death).
- Quality of life.
- Cost-effectiveness.
- Potential use of CA125 as a surrogate for patient outcome.

STATISTICAL CONSIDERATIONS

Sample Size

- Target accrual of 600 patients to have an 80% probability of detecting an increase in the median PFS by 33% with a 2-sided significance level of 5%. Calculations were based on an accrual time of 18 months.

Statistical Tests

- Kaplan-Meier curves with 2-sided unstratified log-rank test.
- Cox proportional hazards regression model.
- Two-sided χ^2 test or 2-sided Fisher's exact test.
- Two-sided Kruskal-Wallis test.

CONCLUSION OF TRIAL

- This trial confirms the conclusions of GOG 111, which demonstrated the superiority of paclitaxel + cisplatin over cyclophosphamide + cisplatin.

Table 2.9 Results of OV-10

Treatment arm	Cyclophosphamide + cisplatin (CP) N = 338	Paclitaxel + cisplatin (TP) N = 342	Statistics
Patient characteristics			
Median age (range)	58 (22-85)	58 (23-79)	
No residual	15.7%	17.5%	
Residual disease ≤1 cm	18.6%	21.1%	
Residual disease >1 cm	65.4%	61.1%	
Stage II	6.8%	6.4%	
Stage III	72.5%	74.9%	
Stage IV	20.7%	18.7%	
Serous	62.7%	68.7%	
Endometrioid	13.6%	9.1%	
Mucinous	5.3%	3.5%	
Clear cell	5.3%	4.4%	
Other	13.0%	14.3%	
Grade 1	8.6%	8.2%	
Grade 2	25.4%	26.9%	
Grade 3	56.8%	57.6%	
Unknown grade	9.2%	7.3%	
Treatment delivery			
Median cycles (range)	6 (0-10)	6 (0-10)	
>6 cycles	26.2%	33.3%	
Switch to carboplatin	8.9%	11.8%	
Cisplatin dose reduction	21.4%	30.1%	$P < .001$
Cisplatin dose delay	59.8%	36.3%	
Paclitaxel dose increase		71.1%	
D/C for toxicity	4.5%	6.5%	
Crossover to paclitaxel	48%		
Efficacy			
Pathologic CR	25%	42.5%	
Microscopic residual	20.5%	23%	
Overall response	44.7%	58.6%	$P = .01$
Complete response	27.3%	40.7%	$P = .01$
Partial response	17.4%	17.9%	
Stable disease	15.5%	11.7%	
Progressive disease	13.0%	4.9%	
Median PFS	11.5 months	15.5 months	HR 0.74, $P = .0005$
Median OS	25.8 months	35.6 months	HR 0.73, $P = .0016$
Toxicity (first 6 cycles)			
G3/4 neutropenia	71%	64%	
Febrile neutropenia	3%	2%	

Table 2.9 Results of OV-10 *(continued)*

Treatment arm	Cyclophosphamide + cisplatin (CP) N = 338	Paclitaxel + cisplatin (TP) N = 342	Statistics
G3/4 thrombocytopenia	5%	2%	
G3/4 nausea	19%	13.3%	
G3/4 vomiting	17%	10%	
G3 stomatitis	0%	0.6%	
G3 alopecia	20%	50%	
G3 arthralgia	0.6%	3%	
G3 myalgia	0%	6%	
G3/4 neurosensory	0.6%	14.3%	
G3 neuromotor	0.3%	3%	
G3 ototoxicity	4%	2%	
Severe hypersensitivity	1%	4%	

CR, complete response; D/C, discontinued; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

COMMENTS

- Accrual completed in 1995, 4 months before GOG 111 was published (McGuire et al. 1996).
- A total of 680 patients were accrued in only 15 months and marked a turning point in the ability to conduct intergroup trials.
- PFS was selected as the primary endpoint as more crossover to paclitaxel was anticipated. Despite the 48% crossover rate, this study found PFS and OS differences in favor of the paclitaxel-containing regimen (vs 8% crossover rate in GOG 111).
- Differences between OV-10 and GOG 111.
  - OV-10 had broader inclusion criteria with inclusion of stage II patients, inclusion of patients with suboptimal cytoreduction, ability of patients to undergo secondary cytoreduction, and interval debulking surgery.
  - OV-10 allowed up to 9 cycles of chemotherapy, administered paclitaxel over 3 hours rather than 24 hours, mandated dose escalation of paclitaxel, and allowed substitution of carboplatin for cisplatin in the setting of toxicity.
- The rate of neurotoxicity of 14% in OV-10 was higher than the 4% rate reported in GOG 111.
  - This may be attributed to the paclitaxel dose escalation (built into the protocol due to the uncertainties of optimal dosing schedule) and the option to give 9 cycles of treatment (built into the protocol to

account for the possibility that prior evidence supporting 6 cycles did not apply to this new regimen).
- This trial provides strong level I evidence to support paclitaxel + cisplatin as the new standard of care, and it refutes the claim that paclitaxel administration should be delayed until relapse.

GOG 114 (Markman, JCO 2001)

REFERENCE

- Markman M, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol*. 2001;19(4):1001-1007. PMID: 11181662. (Markman et al. 2001)

TRIAL SPONSORS

- Gynecologic Oncology Group (GOG)
- Southwest Oncology Group (SWOG)
- Eastern Cooperative Oncology Group (ECOG)

RATIONALE FOR TRIAL

- Current standard of care is platinum + paclitaxel, but the majority of patients still die of ovarian cancer.
- Studies suggest the utility of giving cisplatin by the intraperitoneal (IP) route (Alberts et al. 1996; Markman 1998).
- This trial also employed the concept of administering systemic chemotherapy to chemically debulk residual tumors by giving 2 cycles of moderately high-intensity carboplatin (AUC 9) before administering IP chemotherapy (Shapiro et al. 1997).

PATIENT POPULATION

- N = 523 patients entered, 462 eligible.
- Enrollment from August 1992 to April 1995.

Inclusion Criteria

- Stage III epithelial ovarian cancer.
- Tumor debulking to optimal residual (<1 cm).

- Entry within 6 weeks of surgery.
- Adequate bone marrow (WBC ≥3000 cells/mm^3; platelets ≥100,000/mm^3); adequate renal function (creatinine clearance ≥50 mL/min); adequate hepatic function (bilirubin ≤1.5 times normal; serum ALT ≤3 times normal function); GOG performance status of 0, 1, or 2.

Exclusion Criteria

- Borderline tumors.
- Suboptimal residual disease.
- Stage IV disease.
- Prior chemotherapy or radiotherapy.
- Septicemia, severe infection acute hepatitis, or severe bleeding.
- GOG performance status of 3 or 4.
- Other malignancy excluding nonmelanoma skin cancer.
- Congestive heart failure, unstable angina, or myocardial infarction within 6 months.
- Not expected to tolerate the hemodynamic effects of sinus bradycardia.
- Abnormal cardiac conduction.
- Taking medications known to affect cardiac conduction.

TREATMENT DETAILS

- Originally designed as a 3-arm trial with 1 arm receiving cisplatin + cyclophosphamide. When the results of GOG 111 showed inferiority of this regimen to paclitaxel + cisplatin (McGuire et al. 1996), this arm was discontinued and the 66 patients enrolled to this arm were not analyzed.

Arm 1: Paclitaxel IV + Cisplatin IV

- Paclitaxel 135 mg/m^2 IV over 24 hours.
- Cisplatin 75 mg/m^2 IV on day 2.
- Administered every 21 days for 6 cycles.

Arm 2: High-Dose Carboplatin Followed by Paclitaxel IV + Cisplatin IP

- Carboplatin AUC 9 IV for 2 courses every 28 days. Dose calculated by Calvert formula (Calvert et al. 1989) with glomerular filtration rate being considered equivalent to the creatinine clearance, which was calculated by the Jelliffe method (Jelliffe 1973).
- Paclitaxel 135 mg/m^2 IV over 24 hours on day 1.

- Cisplatin 100 mg/m^2 IP on day 2. Administered in 2 L of normal saline through an implantable peritoneal dialysis catheter (ie, Tenckhoff catheter).
- Paclitaxel and cisplatin administered every 21 days for 6 cycles.

Premedications

- Standard prophylaxis to prevent paclitaxel hypersensitivity (dexamethasone, diphenhydramine, either cimetidine or ranitidine).
- Antiemetics and hydration programs were left to the discretion of the investigator.

Treatment Modifications

- To maintain dose intensity, dose reductions were not allowed.
- Treatments were delayed until WBC ≥3000 cells/mm^3 and platelets ≥100,000/mm^3.
- Grade 3 or 4 peripheral neuropathy resulted in treatment interruption until resolution to a maximum of grade 1.

ASSESSMENTS

- Second-look surgery performed within 8 weeks for all patients without evidence of progressive disease.
- Frequency of CT scans not stated in manuscript.

ENDPOINTS

- PFS (defined as date from entry onto the protocol to the date of appearance of disease as determined clinically or radiographically—not surgically).
- OS (defined as date from entry onto the protocol to the date of death).

STATISTICAL CONSIDERATIONS

Sample Size

- Accrual goal of 440 patients and follow-up until 150 deaths had occurred to provide 80% power to detect a 33% decrease in the hazard ratio at the .05 level (1-sided).

Statistical Tests

- Kaplan-Meier survival analyses, log-rank test.
- Cox model.
- Pearson's χ^2 test significance level of .20.
- Mann-Whitney *U* test.

Table 2.10 Results of GOG 114

Treatment arm	IV paclitaxel + IV cisplatin N = 227	Carboplatin + IV paclitaxel + IP cisplatin N = 235	Statistics
Patient characteristics			
Age <51	37%	33%	
Age 51-70	51%	58%	
Age >70	12%	9%	
No residual	36%	35%	
Residual disease ≤1 cm	64%	65%	
Stage III	100%	100%	
Serous	70%	63%	
Endometrioid	10%	14%	
Mixed	9%	9%	
Other	11%	14%	
Grade 1	14%	11%	
Grade 2	40%	39%	
Grade 3	46%	50%	
Treatment delivery			
Received 6 courses	86%	71%	
Refusal of second look	15.0%	22.6%	
Efficacy			
Median PFS	22.2 months	27.9 months	HR 0.78, $P = .01$
Median OS	52.2 months	63.2 months	HR 0.81, $P = .05$
Toxicity			
G3/4 WBC	62%	77%	Significant
G3/4 platelets	3%	49%	Significant
G3/4 hematologic	88%	92%	
G3/4 gastrointestinal	17%	37%	Significant
G3/4 cardiovascular	3%	4%	
G3/4 neurologic	9%	12%	
G3/4 infection	2%	5%	
G3/4 metabolic	1%	10%	Significant
Deaths	N = 2	N = 2	

HR, hazard ratio; IP, intraperitoneal; IV, intravenous; OS, overall survival; PFS, progression-free survival; WBC, white blood cells.

CONCLUSIONS OF TRIAL

- Because the improvement in survival was of borderline significance and at the expense of greater toxicity, the experimental arm in this trial is not recommended for use.
- This study confirms the relative safety as well as the survival advantage of administering IP cisplatin compared to IV cisplatin (as seen in GOG 104) (Alberts et al. 1996).
- Given the superior outcomes with paclitaxel plus cisplatin over cyclophosphamide and cisplatin (as seen in GOG 111 and OV-10) (McGuire et al. 1996; Piccart et al. 2000), it is important to study the impact of IP cisplatin when combined with paclitaxel (design of GOG 172) (Armstrong et al. 2006).

COMMENTS

- This study was designed recognizing that the results would not give a clear answer regarding the separate effects of high-dose IV carboplatin or IP cisplatin. Because the increases in survival with the experimental arm were marginal and at the expense of greater toxicity, the question of future directions from this study are raised.
- Due to the imbalance and higher than expected refusals of second-look procedures, the endpoint of pathologic response was thought to be likely biased and was not reported.

ICON3 (Lancet 2002)

REFERENCE

- International Collaborative Ovarian Neoplasm Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet*. 2002;360 (9332):505-515. PMID: 12241653. (International Collaborative Ovarian Neoplasm Group 2002)

TRIAL SPONSORS

- Istituto Mario Negri in Milan, Italy
- Swiss Group for Cancer Research (SAKK) in Bern, Switzerland
- Nordic Society for Gynecologic Oncology (NSGO) in Odense, Denmark

- Medical Research Council (MRC) Cancer Trials Office in Cambridge, United Kingdom

RATIONALE FOR TRIAL

- The ICON2 trial compared single-agent carboplatin with the 3-drug regimen of cyclophosphamide, Adriamycin, and cisplatin (CAP) and found no difference in progression-free or overall survival between the treatment arms (International Collaborative Ovarian Neoplasm Group 1998).
- Based on GOG 111, OV-10, and GOG 132, many have suggested that paclitaxel and cisplatin should be the standard of care for advanced ovarian cancer (McGuire et al. 1996; Muggia et al. 2000; Piccart et al. 2000).
- Because of the equivalence of cisplatin and carboplatin and the concern over neurotoxicity when cisplatin and paclitaxel are administered together, others have suggested that carboplatin and paclitaxel should be given as routine treatment (GOG 158, AGO/OVAR-3, Neijt trials) (Neijt et al. 2000; du Bois et al. 2003; Ozols et al. 2003).
- ICON3 aims to compare paclitaxel + carboplatin against a non-taxane-containing platinum-based regimen. At the time of trial initiation, the results from ICON2 were not yet mature and a firm recommendation for the regimens in the control arm (carboplatin vs CAP) could not be made.

PATIENT POPULATION

- N = 2074 enrolled.
- Enrollment from February 1995 to October 1998 from 130 centers in 8 countries.
- Invasive epithelial ovarian cancer; fit to receive chemotherapy; no other malignant disease; no prior chemotherapy or radiotherapy.
- Minimum recommended surgical procedure was total abdominal hysterectomy, bilateral salpingo-oophorectomy, and thorough staging.

TREATMENT DETAILS

- The treating physician could choose the control regimen (carboplatin or CAP), but this had to be specified before randomization.

Control Group—Carboplatin

- Dose determined by the AUC method of Calvert (Calvert et al. 1989) of 5 (GFR + 25) mg.

Control Group—CAP

- Cyclophosphamide 500 mg/m^2 IV.
- Doxorubicin 50 mg/m^2 IV.
- Cisplatin 50 mg/m^2 IV.

Experimental Group—Paclitaxel + Carboplatin

- Paclitaxel 175 mg/m^2 IV over 3 hours.
- Carboplatin (same dosing as control arm).

ASSESSMENTS

- Data were collected pretreatment and after each cycle of treatment. During follow-up, data were collected every 3 months for the first 2 years, every 6 months for the next 3 years, and every year thereafter.

ENDPOINTS

- OS (time from randomization to death from any cause).
- PFS (time from randomization to first appearance of progressive disease or death from any cause) and toxicity.

STATISTICAL CONSIDERATIONS

Sample Size

- Power analysis based on expectation of 2-year survival of 50% in the control groups. An accrual target of 1000 patients in the control groups was selected to detect a 10% difference in 2-year survival from 50% to 60% with 85% power and 5% significance level, translating into a hazard ratio of 0.74.
- One year into the trial, the trial sample size was increased to a new target of 2000 patients to detect more a subtle difference of 7% difference from 50% to 57% 2-year survival with 85% power and 5% significance level, corresponding to a hazard ratio of 0.81.

Statistical Tests

- Kaplan-Meier survival curves for OS and PFS were compared using the Mantel-Cox version of the log-rank test. The stratified log-rank test was used to account for the 2 control groups, the differences across the 4 participating centers, and the difference in randomization ratios (1:1 at 2 centers and 2:1 at 2 centers).
- χ^2 test for interaction or χ^2 test for trend used to test of differences in the relative size of effect in different subgroup.

Table 2.11 Results of ICON3

Treatment arm	Carboplatin N=943	Paclitaxel, carboplatin N=478	CAP N=421	Paclitaxel, carboplatin N=232
Patient characteristics				
Median age	59.4	60.7	56.9	56.6
No residual	27%	28%	38%	34%
Residual disease <2 cm	26%	26%	19%	19%
Residual disease≥2 cm	47%	46%	44%	47%
Stage I	8%	9%	10%	9%
Stage II	11%	10%	12%	13%
Stage III	65%	64%	63%	63%
Stage IV	16%	17%	15%	15%
Serous	54%	57%	51%	54%
Endometrioid	16%	14%	16%	16%
Mucinous	7%	7%	9%	7%
Clear cell	5%	6%	7%	6%
Other	18%	16%	16%	17%
Grade 1	9%	13%	12%	11%
Grade 2	35%	28%	39%	34%
Grade 3	56%	60%	49%	55%

(continued)

Table 2.11 Results of ICON3 *(continued)*

Treatment arm	Carboplatin N=943	Paclitaxel, carboplatin N=478	CAP N=421	Paclitaxel, carboplatin N=232
Treatment delivery				
Total dose	73% Carboplatin	74% Paclitaxel 70% Carboplatin	72% Cyclophosphamide 71% Doxorubicin 75% Cisplatin	79% Paclitaxel 80% Carboplatin
Efficacy				
OS	35.4 months	36.1 months		
PFS	16.1 months	17.3 months		
Toxicity (G3/4)				
Alopecia	4%	73%	76%	80%
Nausea and vomiting	9%	9%	23%	10%
Hematologic	32%	25%	33%	29%
Fever, antibiotics	3%	10%	23%	13%
Sensory neuropathy	1%	19%	3%	18%
Motor neuropathy	<1%	3%	1%	1%

CAP, cyclophosphamide+Adriamycin/doxorubicin+Cisplatin; OS, overall survival; PFS, progression-free survival.

CONCLUSIONS OF TRIAL

- The combination of paclitaxel + carboplatin is not superior to single-agent carboplatin or CAP.
- Paclitaxel + carboplatin is more toxic and causes more fever, alopecia, and sensory neuropathy than carboplatin alone.
- ICON3 suggests that single-agent carboplatin, CAP, and paclitaxel + carboplatin are all safe and have similar efficacy as first-line treatments for ovarian cancer.

COMMENTS

- In the context of other phase III trials, ICON3 seems to contradict the findings of GOG 111 (McGuire et al. 1996) and OV-10 (Piccart et al. 2000) but are in line with GOG 132 (Muggia et al. 2000). One explanation is that the control arm of cisplatin + cyclophosphamide (as given in GOG 111 and OV-10) is inferior to the control arm of single-agent platinum (as given in GOG 132 and ICON3).
- About one-third of patients in the ICON3 control arms went on to receive a taxane later. This raises the question of the optimum time to use paclitaxel in the treatment of advanced ovarian cancer and whether this would be at the time of progression after single-agent platinum.

GOG 158 (Ozols, JCO 2003)

REFERENCE

- Ozols RF, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2003;21(17):3194-200. PMID: 12860964. (Ozols et al. 2003)

TRIAL SPONSOR

- Gynecologic Oncology Group (GOG)

RATIONALE FOR TRIAL

- The GOG 111 and OV-10 studies both demonstrated superiority of cisplatin + paclitaxel over the control treatment of cisplatin + cyclophosphamide (McGuire et al. 1996; Piccart et al. 2000).
- Carboplatin is an analogue of cisplatin with less hematologic toxicity and comparable efficacy.

- A 1993 International Ovarian Cancer Consensus Conference recommended that carboplatin should not be routinely used in the upfront treatment of patients with small-volume stage III ovarian cancer (Vermorken et al. 1993).
- A GOG pilot study found the combination of carboplatin and paclitaxel to be active with an overall response rate of 75% and a complete response rate of 67% (Bookman et al. 1996).
- GOG 158 was designed as a noninferiority study to compare the efficacy and toxicity of carboplatin + paclitaxel vs the standard regimen of cisplatin + paclitaxel.

PATIENT POPULATION

- N = 840, 792 eligible.
- Stage III epithelial ovarian cancer with <1 cm residual disease.
- No prior chemotherapy; GOG performance status of 0 to 2; WBC ≥3000/μL; platelets ≥100,000/μL; serum creatinine ≤2.0 mg/dL; serum bilirubin and AST levels of no more than 2 times the institutional upper limit of normal.

TREATMENT DETAILS

Control Arm: Paclitaxel + Cisplatin

- Paclitaxel 135 mg/m^2 IV over 24 hours.
- Cisplatin 75 mg/m^2 IV at a rate of 1 mg/min.
- Treatment every 3 weeks for 6 cycles.

Experimental Arm: Paclitaxel + Carboplatin

- Paclitaxel 175 mg/m^2 IV over 3 hours.
- Carboplatin AUC 7.5 mg/mL/min. Dose based on the Calvert formula of AUC × (GFR + 25). Creatinine clearance was calculated using the Jelliffe formula (Jelliffe 1973).

Premedications Before Paclitaxel

- Dexamethasone 20 mg orally 12 and 6 hours before treatment.
- Diphenhydramine 50 mg IV 30 minutes before treatment.
- Cimetidine 300 mg IV 30 minutes before treatment.

Treatment Modifications

- If ANC ≤1000/μL and/or platelets <100,000/μL, then cycle delay, dose reduction, and addition of G-CSF in this sequence.
- No dose modification for uncomplicated nadirs.

- If delay of 2 weeks or less, no dose modification and no G-CSF.
- If delay of 2 to 3 weeks, dose modification.
- If recurrent delays of more than 2 weeks or febrile neutropenia, G-CSF added at dose of 5 μg/kg/d for 14 days starting 24 hours after the completion of chemotherapy.
- No cycle delay for gastrointestinal toxicity, grade 1 to 2 peripheral neuropathy, or mild renal toxicity (serum creatinine ≤2 mg/dL or creatinine clearance ≥50 mL/min).
- Discontinuation of protocol therapy for more severe renal or neurologic toxicity that had not resolved before the next scheduled dose of therapy.

ASSESSMENTS

- Because eligibility included tumors <1 cm only, imaging procedures were not required until after the completion of 6 cycles of chemotherapy.
- The decision of whether to undergo second-look laparotomy was made at the time of random assignment.

ENDPOINTS

- OS and PFS (measured from the date of random assignment to treatment).

STATISTICAL CONSIDERATIONS

Sample Size

- A sample size of 720 patients was set with an estimated 3 years of follow-up to observe 382 recurrences before testing the noninferiority hypothesis. This was a 1-sided test with the probability of a type I and type II error both set at 0.1 for a hazard ratio of 1.3 (favoring cisplatin plus paclitaxel). These characteristics were chosen to detect a moderate-size loss of efficacy with the use of carboplatin plus paclitaxel.

Statistical Tests

- Cumulative proportions of survival were based on Kaplan-Meier procedures.
- Relative risk estimates of treatment effects were calculated with the Cox model adjusting for prognostic factors.
- The Kruskal-Wallis rank test adjusted for ties was used to test the independence of severity of toxicity (grade 0 to 4) to the assigned treatment.

Table 2.12 Results of GOG 158

Treatment arm	Paclitaxel and cisplatin N=400	Paclitaxel and carboplatin N=392	Statistics
Patient characteristics			
Age 21-50	33%	29%	
Age 51-70	56%	58%	
Age 71-90	11%	13%	
No residual	36%	35%	
Residual disease≤1 cm	64%	65%	
Stage III	100%	100%	
Serous	70%	74%	
Endometrioid	11%	9%	
Mucinous	3%	2%	
Clear cell	3%	5%	
Other	14%	9%	
Grade 1	11%	9%	
Grade 2	35%	36%	
Grade 3	54%	55%	
Optional second look	50%	49%	
Treatment delivery			
Received 6 cycles	85%	87%	
Efficacy			
Median PFS	19.4 months	20.7 months	RR 0.88 (0.75-1.03)
Median OS	48.7 months	57.4 months	RR 0.84 (0.70-1.02)
pCR	46%	53%	
Toxicity			
G3/4 leukopenia	63%	59%	$P<.05$
G3/4 thrombocytopenia	5%	39%	$P<.05$
G3/4 granulocytopenia	93%	89%	
G3/4 gastrointestinal	23%	10%	$P<.05$
G/34 neurologic	8%	7%	
G3/4 metabolic	8%	3%	$P<.05$
G3/4 genitourinary	3%	1%	$P<.05$
G1/2 pain	15%	26%	$P<.05$

pCR, pathologic complete response; OS, overall survival; PFS, progression-free survival; RR, relative risk.

CONCLUSION OF TRIAL

- The combination of paclitaxel plus carboplatin is not inferior to the combination of paclitaxel plus cisplatin in patients with small-volume stage III epithelial ovarian cancer.

COMMENTS

- This trial was designed as a noninferiority trial, not to determine the superiority of carboplatin over cisplatin.
  - The 16% reduced risk of death with carboplatin is suggestive of a possible increase in efficacy over cisplatin.
  - The carboplatin dose (AUC 7.5) may have resulted in more platinum exposure than the cisplatin dose (75 mg/m^2).
  - In trials combining carboplatin with cyclophosphamide, there was no benefit to increasing doses of carboplatin (Jakobsen et al. 1997; Gore et al. 1998). The pharmacodynamic interaction between carboplatin and paclitaxel may favor higher doses of carboplatin.
- Other prospective randomized trials comparing paclitaxel + carboplatin vs paclitaxel + cisplatin:
  - Danish Netherlands Trial (Neijt et al. 2000) had an insufficient number of patients to determine statistical equivalency.
  - Arbeitsgemeinschaft Gynakologische trial from Germany (du Bois et al. 2003) showed no difference in PFS or OS between treatments. Paclitaxel was administered as 185 mg/m^2 over 3 hours (vs 135 mg/m^2 over 24 hours in GOG 158) and carboplatin was dosed at AUC 6 (vs AUC 7.5 in GOG 158).
  - Both the Netherlands and German trials included patients with stage II to IV disease.
- GOG 158 fails to support the concern that a 3-hour infusion of paclitaxel is less efficacious than a 24-hour infusion.
- Different toxicity profiles.
  - Cisplatin was responsible for more gastrointestinal and metabolic toxicity.
  - There was no difference in neurotoxicity between arms. This is in contrast to the results of the 2 European trials that both showed less neurotoxicity with carboplatin. This may be because cisplatin was combined with a 3-hour infusion of paclitaxel in the control arms.
- Median survival after recurrence was 23 months without difference between treatment groups.

- While this trial demonstrates carboplatin + paclitaxel to be the treatment of choice for patients with small-volume stage III ovarian cancer, it also highlights the need for more effective therapies. More than 70% of patients experienced recurrence with the majority occurring in the first 2 years following therapy.
- GOG 182 was designed subsequently to test the addition of a third drug to the carboplatin and paclitaxel base.

AGO/OVAR-3 (du Bois, JNCI 2003)

REFERENCE

- du Bois A, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst*. 2003;95(17):1320-9. PMID: 12953086. (du Bois et al. 2003)

TRIAL SPONSOR

- Arbeitsgemeinschaft Gynakologische Onkologie (AGO) Ovarian Cancer Study Group

RATIONALE FOR TRIAL

- In the 1980s, 2 trials demonstrated improved survival when cisplatin was added to doxorubicin and cyclophosphamide (Neijt et al. 1984; Omura et al. 1986). Subsequent studies showed no difference between 2-drug and 3-drug regimens (Bertelsen et al. 1987; Omura et al. 1989), resulting in the combination of cisplatin and cyclophosphamide being considered the standard of care for about a decade.
- In the 1990s, paclitaxel replaced cyclophosphamide in the first-line treatment of advanced ovarian cancer (McGuire et al. 1996; Piccart et al. 2000). Paclitaxel plus cisplatin was considered the new standard of care, but this was challenged by the results of the ICON3 trial (International Collaborative Ovarian Neoplasm Group 2002).
- Despite these advances, more than 50% of patients with advanced ovarian cancer die within 5 years of original diagnosis. This makes tolerability of treatment and quality-of-life important considerations in ongoing research. Carboplatin is better tolerated than cisplatin when combined with cyclophosphamide with no loss in efficacy (Alberts et al. 1992; Swenerton et al. 1992).
- Several phase I/II studies tested the feasibility of combining carboplatin with paclitaxel (du Bois et al. 1997). The maximum tolerated dose

of paclitaxel ranged from 175 to 275 mg/m^2 and the maximum tolerated dose of carboplatin ranged from 300 to 550 mg/m^2 or AUC 5 to AUC 7.5.
- This trial and GOG 158 were both designed as noninferiority studies to test the efficacy and toxicity of carboplatin vs cisplatin when combined with paclitaxel.

PATIENT POPULATION

- N = 883 screened, 798 eligible.
- Enrollment between November 1995 and November 1997.

Inclusion Criteria

- Histologically confirmed FIGO stage IIB to IV epithelial ovarian cancer.
- Radical debulking surgery within 6 weeks or random assignment.
- Adequate hematologic, renal, and hepatic function: ANC >1.5 × 10^9 cells/L, platelet count >100 × 10^9 cells/L, serum creatinine and bilirubin <1.25 times upper normal limit.

Exclusion Criteria

- Low malignant potential tumors.
- ECOG performance status >2 or Karnofsky index <60%.
- Estimated GFR <60 mL/min.
- Other malignancies.
- Previous chemotherapy, immunotherapy, or radiotherapy for ovarian cancer.
- Severe neuropathy.
- Cardiac arrhythmias.
- Congestive heart failure.

TREATMENT DETAILS

Arm 1: Paclitaxel Plus Cisplatin (PT)

- Paclitaxel 185 mg/m^2 IV over 3 hours (dose capped at 400 mg).
- Cisplatin 75 mg/m^2 IV over 30 minutes (dose capped at 165 mg).

Arm 2: Paclitaxel Plus Carboplatin (TC)

- Paclitaxel 185 mg/m^2 IV over 3 hours (dose capped at 400 mg).
- Carboplatin AUC 6 IV over 30 to 60 minutes (dose capped at 880 mg). Calculated by the method of Calvert (Calvert et al. 1989) of AUC × (GRF +25). GFR estimated by the Jelliffe formula (Jelliffe 1973).

- This dose was the maximum tolerated dose (MTD) in a preceding phase I/II trial (du Bois et al. 1997).

Dose Reductions Allowed for Toxicity

- Level 1.
  - Carboplatin AUC 5.
  - Cisplatin 60 mg/m^2.
  - Paclitaxel 160 mg/m^2.
- Level 2.
  - Carboplatin AUC 4.
  - Cisplatin 50 mg/m^2.
  - Paclitaxel 135 mg/m^2.
- Treatment delayed for ANC $<1.5 \times 10^9$ cells/L or platelet count $<100 \times 10^9$ cells/L.
- Prophylaxis with G-CSF was not allowed, but supportive use could be initiated if ANC recovery took more than 36 days.

Premedications

- Dexamethasone 20 mg single dose before paclitaxel.
- Clemastine 2 mg IV 30 minutes before paclitaxel.
- Cimetidine 300 mg IV 30 minutes before paclitaxel.
- Antiemetics: serotonin type 3 receptor antagonists and corticosteroids.
- Hydration with cisplatin: pre- and postchemotherapy hydration to avoid nephrotoxicity.

Treatment Discontinuation

- For disease progression during therapy.

Treatment Continuation

- Patients with partial remission and residual tumor after 6 cycles could receive additional treatment cycles.

ASSESSMENTS

- Chemistries before each treatment cycle.
- Hematologic parameters measured weekly.
- Quality of life measured by the EORTC quality-of-life questionnaire (QLQ)–C30, version 2.0 (Aaronson et al. 1993) after each treatment cycle and 3 and 6 months after completion of treatment.
- Tumor measurement was recorded before each treatment cycle by physical examination and before each third treatment cycle by imaging in patients with measurable or evaluable disease. Imaging consisted

of ultrasound, x-ray, computed tomography, or magnetic resonance imaging (MRI), and a consistent modality was used at baseline and follow-up.
- Second-look surgery was not recommended.
- Follow-up visits were schedule every 3 months for the first 2 years and every 6 months thereafter until 5 years after treatment cessation.

ENDPOINTS

- Proportion of patients without progression at 2 years (primary endpoint).
- Toxicity.
- Response to treatment.
- Quality of life.
- Overall survival (measured from time of randomization).
- Progression-free survival time (measured from time of randomization).

STATISTICAL CONSIDERATIONS

Stratification

- Patients were stratified based on residual tumor size and FIGO stage.
  - Stratum 1: patients with residual tumor ≤1 cm and FIGO stage IIB, IIC, or III.
  - Stratum 2: residual tumor >1 cm or FIGO stage IV.

Sample Size

- This was a noninferiority trial with a sample size of 692 patients to exclude a difference between the proportion of patients without progression at 2 years of more than 8% between arms with 80% power and α of 5%. This calculation was based on the assumption of an equal number of patients per stratum and a dropout rate of 10%. During the trial, the sample size was increased to 798 patients to account for more patients in stratum 1.

CONCLUSION OF TRIAL

- Because carboplatin is more tolerable than cisplatin with equal treatment efficacy, the combination of carboplatin with paclitaxel may be in the best interest of patients with advanced ovarian cancer.

COMMENTS

- There was greater toxicity and worse quality of life with cisplatin compared to carboplatin.

Table 2.13 Results of AGO/OVAR-3

Treatment arm	Paclitaxel+ cisplatin N=386	Paclitaxel+ carboplatin N=397	Statistics
Patient characteristics			
Median age (range)	57.7 years	56.7 years	
Stratum 1 (≤1 cm, II, III)	59.3%	52.9%	
Stratum 2 (>1 cm, IV)	40.7%	47.1%	
Residual≤1 cm	65.9%	59.5%	
Residual >1 cm	34.1%	40.5%	
Stage II	7.5%	9.3%	
Stage III	76.4%	72.5%	
Stage IV	16.1%	18.1%	
Serous	69.9%	70.8%	
Other	30.1%	29.2%	
Grade 1	6.7%	9.5%	
Grade 2	37.3%	38.5%	
Grade 3	56.0%	52.0%	
Treatment delivery			
Received 6 cycles	84.0%	87.7%	
Treatment delay >7 days	10.3%	14.0%	
Dose reductions	10.5%	11.2%	
Efficacy			
Complete response	43.3%	36.5%	
Partial response	33.3%	41.9%	
Stable disease	10.0%	10.8%	
Progressive disease	13.3%	10.8%	
No progression at 2 years	40.0%	37.5%	NS
Median PFS	19.1 months	17.2 months	HR 1.095 (95% CI, 0.89-1.23)
Strata 1	24.2 months	26.0 months	HR 0.91 (95% CI, 0.72-1.15)
Strata 2	14.3 months	13.4 months	HR 1.14 (95% CI, 0.91-1.43)
Median OS	44.1 months	43.3 months	HR 1.05 (95% CI, 0.87-1.26)
Strata 1	55.4 months	59.4 months	HR 0.92 (95% CI, 0.70-1.22)
Strata 2	30.7 months	31.4 months	HR 1.08 (95% CI, 0.85-1.38)
Toxicity			
G3/4 platelets	1%	12.9%	
G3/4 anemia	3.9%	5.9%	
G3/4 leukopenia	10.8%	31.9%	
G3/4 neutropenia	22.0%	37.0%	
Febrile neutropenia	3.6%	8.0%	
G3/4 infections	22.6%	35.6%	
G3 nausea	13.8%	5.4%	
G3 vomiting	9.1%	2.3%	
Any ototoxicity	16.9%	8.8%	
Any renal toxicity	19.9%	5.4%	
G3/4 sensory neuropathy	13.5%	7.2%	

CI, confidence interval; HR, hazard ratio; NS, not significant; PFS, progression-free survival; OS, overall survival.

- Response rates were higher with cisplatin than carboplatin, but this did not translate into improved survival.
- Patients receiving carboplatin had greater myelosuppression, but this rarely led to symptoms such as febrile neutropenia or nonneutropenic infections.
- This trial supports the findings from other trials of platinum plus paclitaxel chemotherapy (McGuire et al. 1996; Neijt et al. 2000; Piccart et al. 2000).
  - Direct comparisons of toxicities are difficult due to the different grading systems used.
  - Gastrointestinal and neurologic toxicities are less with carboplatin.
  - The median OS time with paclitaxel + cisplatin is higher in this trial than others (44.1 months vs 38 months [McGuire et al. 1996], 35.6 months [Piccart et al. 2000], and 30 months [Neijt et al. 2000]), which likely reflects a patient population with more favorable tumor characteristics.

SCOTROC—Scottish Randomised Trial in Ovarian Cancer (Vasey, JNCI 2004)

REFERENCE

- Vasey PA, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst*. 2004;96(22):1682-1691. PMID: 15547181. (Vasey et al. 2004)

TRIAL SPONSOR

- Scottish Gynaecological Cancer Trials Group
- Supported by grants from Aventis Pharmaceuticals

RATIONALE FOR TRIAL

- Docetaxel is a semisynthetic taxane with superior activity to anthracyclines and paclitaxel in metastatic breast cancer.
- Phase II trials of docetaxel in ovarian cancer demonstrate activity comparable to paclitaxel.
- The combination of docetaxel and carboplatin was found to be feasible.

PATIENT POPULATION

- N = 1077.
- Recruited from 83 international centers between October 1988 and May 2000.
- Women 18 years and older.
- Histologically confirmed epithelial ovarian cancer, stages IC to IV.
- ECOG performance status of 0 to 2.
- No prior chemotherapy or radiotherapy.
- Adequate bone marrow, hepatic, and renal function.
- Excluded if peripheral neuropathy more than grade 2.
- Randomization within 6 weeks of surgery.
- First treatment cycle within 2 weeks of randomization.

TREATMENT DETAILS

Arm 1: Paclitaxel + Carboplatin

- Paclitaxel 175 mg/m^2 IV over 3 hours.
- Carboplatin AUC 5 IV over 1 hour.

Arm 2: Docetaxel + Carboplatin

- Docetaxel 75 mg/m^2 IV over 1 hour.
- Carboplatin AUC 5 over 1 hour.

Paclitaxel Treatment Details

- Dexamethasone 20 mg 12 and 6 hours prior to chemotherapy.
- Chlorpheniramine 10 mg or diphenhydramine 50 mg 1 hour prior to chemotherapy.
- Ranitidine 50 mg or cimetidine 300 mg 1 hour prior to chemotherapy.
- Starting dose 175 mg/m^2 over 3 hours.
- Dose reduction to 135 mg/m^2 over 3 hours for complicated grade 4 neutropenia.
- Discontinued for deterioration of liver function or neurotoxicity grade 3 or more.
- Hypersensitivity reactions—infusion stopped, symptoms treated, paclitaxel reinfused within 3 hours if appropriate.

Docetaxel Treatment Details

- Dexamethasone 8 mg twice a day for 3 days starting on day prior to chemotherapy.
- Starting dose 75 mg/m^2 over 1 hour.
- Dose reduction to 60 mg/m^2 over 1 hour for complicated grade 4 neutropenia.

- Discontinued for deterioration of liver function or neurotoxicity grade 3 or more.
- Hypersensitivity reactions—infusion stopped, symptoms treated, docetaxel reinfused within 3 hours if appropriate.

Carboplatin Treatment Details

- Carboplatin dose calculated by Calvert formula with edetic acid to measure GFR.
- Starting dose AUC 5 in both treatment arms.
- Dose reduction to AUC 4 for complicated grade 4 thrombocytopenia.

Antiemetics

- Granisetron 3 mg.
- Ondansetron 8 mg.

Treatment Delays

- Allowed for up to 2 weeks for:
  - ANC <1500/μL.
  - Platelets <100,000 /μL.
  - Mucositis grade 3 or more.
  - Skin toxicity grade 2 or more.

Dose Reductions

- Complicated grade 4 neutropenia.
  - G-CSF 300 mg/d added for persistent neutropenia despite dose reduction of paclitaxel or docetaxel.
  - Prophylactic antibiotics added for all subsequent cycles.

Interval Cytoreduction

- Allowed between cycles 3 and 4.

Treatment Continuation

- If partial response or complete response with elevated CA125, 3 cycles of carboplatin AUC 7 allowed for up to 3 additional cycles.

ASSESSMENTS

- CT scan at baseline and after cycles 3 and 6—classified according to Response Evaluation Criteria in Solid Tumors (RECIST).
- CA125 at baseline and before each cycle—classified according to method of Rustin.
- Toxicity assessed by NCI-CTC, version 2.0.
- Quality of life assessed before each cycle and at 6 months and then every 4 months for up to 2 years using EORTC QLQ-C30 (version 3.0) and EORTC QLQ-OV28 (version 1).

Table 2.14 Results of SCOTROC

Treatment arm	Paclitaxel-carboplatin N=538	Docetaxel-carboplatin N=539	Statistics
Patient characteristics			
Median age (range)	59 years (19-84)	59 years (21-85)	
Stage IC-II	20%	19%	
Stage III-IV	80%	81%	
No residual	33%	33%	
≤2 cm residual	30%	30%	
>2 cm residual	37%	37%	
Serous	44%	44%	
Endometrioid	10%	12%	
Clear cell	4%	5%	
Mucinous	2%	4%	
Other	38%	34%	
Grade 3	54%	54%	
Treatment delivery			
Withdrawal from protocol	21%	15%	
Additional carboplatin AUC 7	13%	11%	
Efficacy			
Median PFS (95% CI)	14.8 months (13.5-16.1)	15 months (13.3-16.6)	HR 0.97, *P*=NS
2-year survival	68.9%	64.2%	HR 1.13, *P*=NS
Complete response	28%	28%	*P*=NS
Toxicity			
G3-4 neutropenia	84%	94%	*P*<.001
G4 neutropenia+fever	2%	11%	*P*<.001
G4 neutropenia >7 days	3%	14%	*P*<.001
G3-4 thromobocytopenia	10%	9%	*P*=NS
G3-4 anemia	8%	11%	*P*=NS
Deaths	N=1	N=2	
G2-4 neurosensory	30%	11%	*P*<.001
G2-4 neuromotor	7%	3%	*P*<.001
Other toxicities	More arthralgia, myalgia, alopecia, abdominal pain	More gastrointestinal toxicity, peripheral edema, allergic reactions, nail changes	

AUC, area under the curve; CI, confidence interval; HR, hazard ratio; NS, not significant; PFS, progression-free survival.

- Neurotoxicity assessment at some centers with 12 questions and 5 neurologic tests to report NScore at baseline, after cycles 3 and 6, at 6 months and every 4 months for up to 2 years.
- Follow-up every 2 months with exam and CA125. CT scans for rising CA125.

ENDPOINTS

- Progression-free survival (primary endpoint).
- Overall survival.
- Quality of life.

STATISTICAL CONSIDERATIONS

Sample Size

- Study designed with 80% power to detect a difference of 25% increase in median PFS from 17 to 21.25 months. Required 1050 patients with minimum follow-up of 1 year.

CONCLUSIONS OF TRIAL

- Similar efficacy between arms and acceptable toxicities in both arms.
- Compared to paclitaxel-carboplatin, docetaxel-carboplatin resulted in greater myelosuppression but less neurotoxicity during therapy and follow-up.
- Docetaxel-carboplatin is an alternative to treatment with paclitaxel-carboplatin in the upfront treatment of patients with stage IC to IV ovarian cancer.

COMMENTS

- This trial has shorter survival times compared to other trials. Authors state this may be due to different patient populations (more residual disease) or the broad definition of progressive disease used in this trial.
- According to the authors, the higher rate of neurotoxicity of 30% reported in the paclitaxel-carboplatin arm may be due to the more comprehensive approach to neurotoxicity monitoring in this trial.

GOG 172 (Armstrong, NEJM 2006)

REFERENCE

- Armstrong DK, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med*. 2006;354(1):34-43. PMID: 16394300. (Armstrong et al. 2006)

TRIAL SPONSOR

- Gynecologic Oncology Group (GOG)

RATIONALE FOR TRIAL

- Most patients with advanced ovarian cancer attain clinical remission, but the majority eventually relapse and die of disease.
- The intensity of intravenous therapy is limited by myelotoxicity. However, several drugs can be administered directly into the peritoneal cavity. Intraperitoneal administration of chemotherapy allows for tumor to receive sustained exposure to high concentrations of drug while bone marrow and other normal tissues are relatively spared.
- Two prior GOG trials (GOG 104 and GOG 114) evaluated intraperitoneal administration of cisplatin in patients with low-volume ovarian cancer. GOG 104 demonstrated a survival advantage with intraperitoneal cisplatin, but paclitaxel was not administered in the regimen (Alberts et al. 1996). GOG 114 demonstrated a PFS advantage and only borderline OS advantage with intraperitoneal cisplatin, but the interpretation of the trial was complicated by the use of 2 cycles of moderately intensive carboplatin, which added to the toxicity of the treatment (Markman et al. 2001).
- Intraperitoneal chemotherapy had not been widely accepted and used based on high cost, high toxicity, and lack of familiarity with intraperitoneal administration and catheter-placement techniques.

PATIENT POPULATION

- N = 429 enrolled, 415 eligible.
- Enrollment between March 1998 and January 2001.
- Stage III epithelial ovarian cancer with <1 cm residual mass after surgery.
- GOG performance status of 0 to 2.
- Normal blood counts, adequate renal and hepatic function.
- Ineligibility criteria: prior chemotherapy or radiation; second primary cancer; low malignant potential tumors.

TREATMENT DETAILS

Arm 1: Intravenous Therapy

- Paclitaxel 135 mg/m^2 IV over 24 hours on day 1.
- Cisplatin 75 mg/m^2 IV on day 2.
- Treatment given every 3 weeks for 6 cycles.

Arm 2: Intravenous/Intraperitoneal Therapy

- Paclitaxel 135 mg/m^2 IV over 24 hours on day 1.
- Cisplatin 100 mg/m^2 IP on day 2.
- Paclitaxel 60 mg/m^2 IP on day 8.
- Intraperitoneal chemotherapy was reconstituted in 2 L of warmed normal saline and infused as rapidly as possible.
- Treatment given every 3 weeks for 6 cycles.

Premedications

- Standard premedications to prevent paclitaxel hypersensitivity.
- Hydration and antiemetics given before cisplatin.

Treatment Delays

- If ANC <1500 cells/mm^3, platelets <100,000/mm^3, or serum creatinine >2 mg/dL, then treatment delay, dose reduction, then addition of G-CSF (in this sequence)
- If grade 3 or 4 peripheral neuropathy, creatinine >2 mg/mL or creatinine clearance <50 mL/min, then treatment was postponed.
- If treatment was delayed for more than 3 weeks, patients were removed from study.
- In the intraperitoneal therapy group:
  - For grade 2 abdominal pain, the dose of intraperitoneal drug was reduced.
  - For grade 3 abdominal pain, recurrent grade 2 abdominal pain after dose reduction, or intraperitoneal catheter complications, dosing was changed to intravenous.
- For grade 2 peripheral neuropathy, the dose of cisplatin was reduced.
- For cisplatin-related toxic effects requiring discontinuation of protocol therapy, carboplatin was substituted for cisplatin.

ASSESSMENTS

- At registration, patients decided whether they would undergo second-look laparotomy.
- Physical exam, history, complete blood count (CBC), chemistries, and CA125 were measured at baseline, at the completion of therapy, every 3 months for 24 months, then after 6 months thereafter.
- Quality-of-life assessment with the Functional Assessment of Cancer Therapy—Ovarian (FACT-O) instrument (Basen-Engquist et al. 2001) at registration, before cycle 4, 3 to 6 weeks after cycle 6 and 12 months after the completion of therapy.

ENDPOINTS

- PFS (measured from date of randomization).
- OS (measured from date of randomization).
- Quality of life.

STATISTICAL CONSIDERATIONS

Stratification Factors

- Patients were randomized with stratification according to residual disease and decision of whether to undergo second-look surgery.

Sample Size

- A sample size of 384 patients with follow-up to observe 208 recurrences and 208 deaths allowed testing for a hazard ratio of 1.5 (favoring intraperitoneal administration) for recurrence and survival using a 1-sided log-rank test with 90% power and an α level of .05.

Statistical Tests

- Kaplan-Meier to estimate the cumulative proportions of survival (Kaplan and Meier 1958).
- Cox model to estimate the relative risk and confidence intervals for treatment effects on progression and death (Cox 1972).
- Adjusted estimates were based on covariates of age and histology.
- Wilcoxon rank-sum test to test the independence of the risk of severe and life-threatening toxic effects from treatment.
- Quality-of-life assessments were analyzed with linear models with an unstructured covariance matrix. Covariance parameters were estimated with the restricted maximum likelihood.

CONCLUSION OF TRIAL

- Intravenous/intraperitoneal chemotherapy improves survival at the expense of greater toxicity in patients with optimally debulked stage III ovarian cancer.

COMMENTS

- Intraperitoneal therapy was associated with significantly worse fatigue, pain, and hematologic, gastrointestinal, neurologic, and metabolic toxicities.
  - The increased toxicity with intraperitoneal therapy might be attributed to the higher dose of cisplatin. The rationale for the higher dose

Table 2.15 Results of GOG 172

Treatment arm	Intravenous N=210	Intraperitoneal N=205	Statistics
Patient characteristics			
Age 21-50	27%	31%	
Age 51-70	62%	56%	
Age 71-80+	10%	13%	
No residual	36%	38%	
Residual disease≤1 cm	64%	62%	
Stage III	100%	100%	
Serous	81%	77%	
Endometrioid	6%	8%	
Clear cell	4%	5%	
Other	9%	9%	
Grade 1	9%	12%	
Grade 2	40%	35%	
Grade 3	50%	52%	
Elected second look	49%	49%	
Treatment delivery			
Completed 6 cycles	83%	42%	
Efficacy			
Pathologic CR	41%	57%	
Median PFS	18.3 months	23.8 months	RR 0.80, $P=.05$
With gross residual	15.4 months	18.3 months	RR 0.81, NS
With no visible residual	35.2 months	37.6 months	RR 0.80, NS
Median OS	49.7 months	65.6 months	RR 0.75, $P=.03$
With gross residual	39.1 months	52.6 months	RR 0.44, NS
With no visible residual	78.2 months	Not yet reached	RR 0.69, NS
Toxicity			
Treatment-related death	N=4	N=5	
G3/4 leukopenia	64%	76%	$P<.001$
G3/4 thrombocytopenia	4%	12%	$P=.002$
G3/4 gastrointestinal	24%	46%	$P<.001$
G3/4 renal	2%	7%	$P=.03$
G3/4 cardiovascular	5%	9%	$P=.06$
G3/4 neurologic	9%	19%	$P=.001$
G3/4 fever	4%	9%	$P=.02$
G3/4 infection	6%	16%	$P=.001$
G3/4 fatigue	4%	18%	$P<.001$
G3/4 metabolic	7%	27%	$P<.001$
G3/4 pain	1%	11%	$P<.001$
G3/4 hepatic	<1%	3%	$P=.05$

CR, complete response; NS, not significant; PFS, progression-free survival; OS, overall survival; RR, relative risk.

is that capillary uptake of cisplatin from the intraperitoneal surfaces is slow and incomplete. This results in prolonged but lower systemic exposure compared to intravenous administration (Schneider 1994).
    - The increased toxicity with intraperitoneal therapy might be attributed to the use of intraperitoneal paclitaxel. Paclitaxel has very slow intraperitoneal clearance and remains in the peritoneal cavity for 1 week after administration (Francis et al. 1995). The peritoneal clearance could be altered by administration after intraperitoneal cisplatin.
    - It is not known whether altering the treatment regimen to reduce toxicity will compromise its efficacy.
- Quality of life was worse with intraperitoneal therapy at cycle 4 and 3 to 6 weeks after treatment. However, there was no difference in quality of life between groups at 1 year after treatment.
- Patients who had a left colonic or rectosigmoid resection were less likely to receive all 6 cycles of intraperitoneal therapy.
- The single-lumen venous-access catheter attached to an implantable subcutaneous port is associated with minimal fibrous sheath formation and less risk of bowel obstruction or perforation compared to the fenestrated intraperitoneal catheter (Alberts et al. 2002).
- The median OS time of 65.6 months in the patients receiving intraperitoneal therapy is the longest survival reported in a GOG phase 3 trial.

GOG 182/ICON5 (Bookman, JCO 2009)

REFERENCE

- Bookman MA, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. *J Clin Oncol*. 2009;27(9):1419-1425. PMID: 19224846. (Bookman et al. 2009)

TRIAL SPONSORS

- Gynecologic Oncology Group (GOG)
- Medical Research Council in the United Kingdom (MRC-UK) representing the International Collaborative Ovarian Neoplasm (ICON) group
- Australia and New Zealand Gynecologic Oncology Group (ANZGOG; Camperdown, Australia)

- Istituto Mario Negri (Milan, Italy)
- Southwest Oncology Group
- Five other groups managed by the National Cancer Institute (NCI)

RATIONALE FOR TRIAL

- Despite response rates of greater than 80%, long-term survival of ovarian cancer remains poor as a result of recurrence and drug resistance.
- While platinum and taxanes are the core of primary treatment, other drugs have demonstrated activity in the recurrent setting, including topotecan, gemcitabine, and pegylated liposomal doxorubicin (Gordon et al. 2004; ten Bokkel Huinink et al. 2004; Pfisterer et al. 2006a).
- A multiarm, multistage study was designed to compare 4 different treatment arms against a single reference arm of carboplatin and paclitaxel.
- This collaborative trial with a target accrual of 4000 patients would report clinical outcomes but also provide an international database, including outcomes in patients with uncommon histologies and genetic mutations associated with cancer risk.

PATIENT POPULATION

- N = 4312 enrolled.
- Patients enrolled between February 2001 and September 2004.
- Stage III or IV epithelial ovarian cancer, either optimal (≤1 cm) or suboptimal residual disease.
- GOG performance status of 0, 1, or 2.
- Labs: ANC ≥1500/μL, platelets ≥100,000/μL, creatinine ≤1.5 times upper limit of normal, bilirubin ≤1.5 times upper limit of normal, AST and alkaline phosphatase ≤2.5 times upper limit of normal.
- Baseline sensory or motor neuropathy of grade 1 or lower by the NCI Common Toxicity Criteria version 2.
- Breast cancer: eligible if disease free for at least 3 years.
- Early-stage synchronous endometrial cancer: eligible if minimal invasion and no high-grade features.
- Ineligible: low malignant potential tumors, carcinosarcoma, nonepithelial histology.

TREATMENT DETAILS

- Dose and schedule were designed to maximize delivery of newer agents, preserve exposure to paclitaxel and carboplatin, and equilibrate the risk of hematologic toxicity.

Arm 1: CP (Carboplatin Paclitaxel)

- Cycles 1 to 8.
  - Carboplatin AUC 6 IV on day 1.
  - Paclitaxel 175 mg/m^2 IV over 3 hours on day 1.

Arm 2: CPG (Carboplatin Paclitaxel + Gemcitabine)

- Cycles 1 to 4.
  - Carboplatin AUC 5 IV on day 1.
  - Paclitaxel 175 mg/m^2 IV over 3 hours on day 1.
  - Gemcitabine 800 mg/m^2 IV over 30 minutes on day 1 and day 8.
- Cycles 5 to 8.
  - Carboplatin AUC 5 IV on day 1.
  - Paclitaxel 175 mg/m^2 IV over 3 hours on day 1.

Arm 3: CPD (Carboplatin Paclitaxel + Pegylated Liposomal Doxorubicin)

- Cycles 1 to 8.
  - Carboplatin AUC 5 IV on day 1.
  - Paclitaxel 175 mg/m^2 IV over 3 hours on day 1.
- Cycles 1, 3, 5, and 7.
  - Pegylated liposomal doxorubicin (PLD) 30 mg/m^2 IV on day 1 (dosing of PLD every 3 weeks was associated with unacceptable risk of mucosal, skin, and/or hematologic toxicity due to prolonged clearance, and tolerability is improved with use in alternating cycles).

Arm 4: CT → CP (Carboplatin Topotecan → Carboplatin Paclitaxel)

- Cycles 1 to 4.
  - Topotecan 1.25 mg/m^2/d IV on days 1, 2, and 3.
  - Carboplatin AUC 5 IV on day 3 (delay to day 3 based on evidence of sequence-specific hematologic toxicity in phase I trials).
- Cycles 5 to 8.
  - Carboplatin AUC 6 IV on day 1.
  - Paclitaxel 175 mg/m^2 IV over 3 hours on day 1.

Arm 5: CG → CP (Carboplatin Gemcitabine → Carboplatin Paclitaxel)

- Cycles 1 to 4.
  - Gemcitabine 1000 mg/m^2 IV on day 1 and day 8.
  - Carboplatin AUC 6 IV on day 8 (delay to day 8 based on evidence of sequence-dependent hematologic toxicity in patients with lung cancer).

- Cycles 5 to 8.
  - Carboplatin AUC 6 IV on day 1.
  - Paclitaxel 175 mg/m^2 IV over 3 hours on day 1.

Supportive Measures

- Prophylactic hematopoietic growth factors were not required but could be added after cycle delay and/or dose reduction for recurrent toxicity.

Surgery

- Interval cytoreduction allowed between the fourth and fifth cycles for patients with suboptimal residual disease if the intent was declared at registration.
- Reassessment second-look surgery was not allowed as this approach provides no clinical benefit and surgical assessment of small-volume disease could interfere with determination of PFS (Greer et al. 2005).

ASSESSMENTS

- Not stated in manuscript.
- International criteria were adopted to permit use of CA125 to identify progression after completion of primary therapy (Rustin et al. 2006).

ENDPOINTS

- OS.
- PFS.
- Toxicities.
- Complications.
- Dose intensity.
- Cumulative dose delivery.

STATISTICAL CONSIDERATIONS

Sample Size

- In patients receiving the control CP regimen, the estimated median PFS and OS were 15 months and 36 months, respectively.
- An event-triggered interim analysis was scheduled to occur after 240 PFS events in the control CP arm to eliminate regimens that demonstrated insufficient activity. A regimen was continued if the relative PFS event rate was at least 7% lower than the reference arm by pairwise PFS comparisons using a stratified log-rank test (Peto and Peto 1972).
- The sample size provided 90% power to declare a regimen superior if it reduced the risk of death by 25% compared to the reference arm with α limited to 0.125 (0.05/4; 2-tail test) for each pairwise comparison

Table 2.16 Results of GOG 182/ICON5

Treatment arm	CP N=864	CPG N=864	CPD N=862	CT → CP N=861	CG → CP N=861
Patient characteristics					
Median age	57.5 years	59.1 years	59.5 years	58.5 years	59.3 years
Microscopic	About 25%	About 25%	About 25%	About 25%	About 25%
≤1 cm residual	About 45%	About 45%	About 45%	About 45%	About 45%
>1 cm residual	About 30%	About 30%	About 30%	About 30%	About 30%
Stage III	83.8%	86.7%	86.2%	86.4%	83.7%
Stage IV	16.2%	13.3%	13.8%	13.7%	16.3%
Serous	About 80%	About 80%	About 80%	About 80%	About 80%
Endometrioid	About 10%	About 10%	About 10%	About 10%	About 10%
Mucinous	About 1%	About 1%	About 1%	About 1%	About 1%
Clear cell	About 1%	About 1%	About 1%	About 1%	About 1%
Other	About 5%	About 5%	About 5%	About 5%	About 5%
Treatment delivery					
Overall, 79% completed 8 cycles					
Efficacy					
Median PFS, 16 mo	HR 1.00 (ref)	HR 1.028, NS	HR 0.984, NS	HR 1.066, NS	HR 1.037, NS
Median OS, 44.1 mo	HR 1.00 (ref)	HR 1.006, NS	HR 0.952, NS	HR 1.051, NS	HR 1.114, NS
Toxicity					
≥G4 ANC	About 60%	About 75%	About 70%	About 58%	About 58%
≥G3 PLT	About 25%	About 60%	About 40%	About 29%	About 58%
≥G3 Hgb	About 15%	About 20%	About 17%	About 18%	About 21%
≥G3 fever	About 10%	About 16%	About 16%	About 10%	About 10%
≥G2 hepatic	About 5%	About 11%	About 5%	About 5%	About 9%
≥G2 neuropathy	About 25%	About 27%	About 25%	About 15%	About 16%
≥G2 pulmonary	About 11%	About 13%	About 12%	About 11%	About 16%
≥G3 GI	About 10%	About 15%	About 14%	About 13%	About 10%

ANC, absolute neutrophil count; CG, carboplatin+gemcitabine; CP, carboplatin+paclitaxel; CPD, carboplatin+paclitaxel+pegylated liposomal doxorubicin; CPG, carboplatin+paclitaxel+gemcitabine; CT, carboplatin+topotecan; GI, gastrointestinal; Hgb, hemoglobin; HR, hazard ratio; NS, not significant; PFS, progression-free survival; OS, overall survival; PLT, platelets.

(Schoenfeld 1981). This effect size was comparable to an increase in the 3-year surviving proportion from 50% to 59.3%.

CONCLUSION OF TRIAL

- The addition of a third cytotoxic agent to paclitaxel and carboplatin provided a benefit in PFS or OS after optimal or suboptimal cytoreduction for ovarian cancer.

COMMENTS

- At the time of the interim analysis, none of the experimental regimens reduced the PFS event rate by at least 7% compared to the control arm, so the study was closed in September 2004 to further accrual.
- Extent of cytoreductive surgery was an important prognostic factor for OS (second only to stage).
  - Suboptimal (>1 cm): PFS 13 months, OS 33 months.
  - Gross optimal (≤1 cm): PFS 16 months, OS 40 months.
  - Microscopic residual: PFS 29 months, OS 68 months.
- This trial accrued approximately 1200 patients per year, representing about 6.25% of all women with newly diagnosed ovarian cancer in the United States during this period.

JGOG 3016 (Katsumata, Lancet 2009; Katsumata, Lancet Oncol 2013)

REFERENCES

- Katsumata N, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet*. 2009;374(9698):1331-1338. PMID: 19767092. (Katsumata et al. 2009)
- Katsumata N, et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. *Lancet Oncol*. 2013;14(10):1020-6. PMID: 23948349. (Katsumata et al. 2013)

TRIAL SPONSOR

- Japanese Gynecologic Oncology Group (JGOG)

RATIONALE FOR TRIAL

- Standard first-line chemotherapy for advanced ovarian cancer consists of paclitaxel and carboplatin given every 3 weeks. The 3rd International Gynecologic Cancer Consensus Conference in 2004 recommended paclitaxel 175 mg/m^2 over 3 hours plus carboplatin AUC 5 to 7.5 mg/mL per minute over 30 to 60 minutes every 3 weeks for 6 cycles as first-line chemotherapy (du Bois et al. 2005b).

- The addition of another drug to paclitaxel and carboplatin given either concurrently or sequentially has not improved outcomes (du Bois et al. 2006b; Bookman et al. 2009; Hoskins et al. 2010).
- Dose-dense weekly administration of paclitaxel may be a strategy to improve survival as the duration of exposure, even at low concentrations, can result in adequate cytotoxicity (Lopes et al. 1993; Jordan et al. 1996). Phase 2 trials combining dose-dense paclitaxel with carboplatin have demonstrated feasibility and efficacy (Rose et al. 2005; Sehouli et al. 2008).
- This trial was conducted to compare standard paclitaxel and carboplatin dosing against a regimen containing dose-dense weekly paclitaxel with carboplatin.

PATIENT POPULATION

- N = 637 enrolled, 631 eligible.
- Recruited from 85 centers in Japan from April 2003 to December 2005.
- Stage II to IV epithelial ovarian cancer, fallopian tube cancer, peritoneal cancer.
- Patient with a cytological diagnosis only had to meet the following criteria:
  - Cytological diagnosis of adenocarcinoma.
  - An abdominal mass of at least 2 cm in diameter on abdominal images.
  - A CA125/carcinoembryonic antigen (CEA) ratio >25 (Yedema et al. 1992) or no evidence of gastrointestinal cancer if CA125/CEA ratio ≤25.
- ECOG performance status of 0 to 3.
- Adequate organ function: ANC >1500 cells per μL; platelet count >100,000 cells per μL; serum bilirubin <25.7 μmol/L; serum AST <100 IU/L; serum creatinine <132.6 μmol/L.
- Exclusions: prior chemotherapy; low malignant potential tumor; synchronous or metachronous malignant disease within 5 years other than carcinoma in situ.

TREATMENT DETAILS

Arm 1: Conventional Paclitaxel + Carboplatin

- Paclitaxel 180 mg/m^2 IV over 3 hours on day 1.
- Carboplatin AUC 6 mg/mL per minute IV over 1 hour on day 1; dose calculated with formula of Calvert (Calvert et al. 1989) using creati-

nine clearance calculated by method of Jelliffe (Jelliffe 1973), not glomerular filtration rate.
- Standard premedications prior to paclitaxel to prevent hypersensitivity.
- Treatment every 3 weeks for 6 cycles.
- Hematologic parameters to treat—day 1: ANC >1000 cells/μL, platelets >75,000 cells/μL.
- Treatment was delayed for a maximum of 3 weeks.

Arm 2: Dose-Dense Paclitaxel + Carboplatin
- Paclitaxel 80 mg/m^2 IV over 1 hour on days 1, 8, and 15.
- Carboplatin AUC 6 mg/mL per minute IV over 1 hour on day 1; dose calculated with formula of Calvert (Calvert et al. 1989) using creatinine clearance calculated by method of Jelliffe (Jelliffe 1973), not glomerular filtration rate.
- Standard premedications prior to paclitaxel to prevent hypersensitivity.
- Treatment every 3 weeks for 6 cycles.
- Hematologic parameters to treat—day 1: ANC >1000 cells/μL, platelets >75,000 cells/μL.
- Hematologic parameters to treat—days 8 and 15: ANC >500 cells/μL, platelets >50,000 cells/μL.
- Treatment was delayed for a maximum of 3 weeks.

Dose Modifications
- Carboplatin reduced for hematologic toxicity, including febrile neutropenia, ANC <500 cells/μL persisting for ≥7 days, platelets <10,000 cells/μL, platelets 10,000 to 50,000 cells/μL with bleeding tendencies, or treatment delayed for more than 1 week for hematologic toxicity.
  - Level 1 reduction to AUC 5 mg/mL per minute.
  - Level 2 reduction to AUC 4 mg/mL per minute.
- Paclitaxel reduced for nonhematologic toxicity, including grade 2 or higher peripheral neuropathy.
  - Conventional dose level 1 reduction to 135 mg/m^2.
  - Conventional dose level 2 reduction to 110 mg/m^2.
  - Dose-dense dose level 1 reduction to 70 mg/m^2.
  - Dose-dense dose level 2 reduction to 60 mg/m^2.

Supportive Measures
- Patients did not receive G-CSF unless they had treatment delays or neutropenic complications.

Treatment Continuation

- Patients with partial or complete responses received an additional 3 cycles of chemotherapy.

Surgery

- Interval debulking surgery after 2 to 4 cycles of chemotherapy was allowed.
- Secondary debulking surgery or second-look surgery after 6 cycles of chemotherapy was allowed.

ASSESSMENTS

- Radiological studies at baseline and after 2, 4, and 6 cycles of chemotherapy. After discontinuation of protocol therapy, patients had follow-up every 3 months for the first 2 years and every 6 months thereafter with exam and CA125. CT scans were performed for symptoms or elevated CA125 levels.
- CA125 criteria for disease progression (Oken et al. 1982).
  - Patients with raised CA125 before treatment with return to normal after treatment needed to show reelevation of CA125 to 2 times the upper limit of normal.
  - Patients with raised CA125 before treatment that did not return to normal need to show evidence of CA125 $\geq$2 times the nadir level.
  - Patients with CA125 in the normal range before treatment needed to show evidence of CA125 $\geq$2 times the upper limit of normal with at least 2 values recorded at least 1 week apart.
- In patients with measurable disease, clinical and radiographic measurements had priority over CA125 levels and progression during treatment could not be based on CA125 measurements alone.
- Assessment of response had to be confirmed on 2 occasions at least 4 weeks apart.

ENDPOINTS

- PFS (measured from date of randomization) (primary endpoint).
- OS.
- Response rates.
- Adverse events.

STATISTICAL CONSIDERATIONS

Sample Size

- Hypothesis was that the dose-dense regimen would prolong PFS by 37.5% (from 16 months with conventional therapy to 22 months with dose-dense therapy). In April 2003, a sample size of 380 patients was planned to detect this difference with 80% power, 2-sided log-rank test, and α of .05.
- In January 2005, the sample size was increased to 600 to detect a smaller prolongation of PFS of 31.3% (from 16 to 21 months) with 80% power, 2-sided log-rank test, α of 0.05, accrual of 3 years, and a follow-up of 1.5 years.

Statistical Tests

- Cumulative survival curve and median PFS time were estimated by the Kaplan-Meier method.
- Two-sided χ^2 tests or 2-sided Fisher's exact tests were used to compare proportions of adverse events between groups.
- Fisher's exact test was used to compare responses.

CONCLUSIONS OF TRIAL

- Dose-dense paclitaxel with carboplatin improves survival compared to the conventional 3-week regimen with a 29% lower risk of disease progression and a 25% lower risk of death.
- With long-term follow-up, dose-dense treatment improves survival compared to conventional treatment and may be considered a new standard of care for first-line treatment of ovarian cancer.

COMMENTS FROM 2009 PUBLICATION

- With a Cox proportional hazards model, PFS was longer in the dose-dense treatment group across all subgroups except for in patients with clear-cell or mucinous tumors.
- The concept of dose density is based on the hypothesis that shorter intervals between chemotherapy exposures would be more effective than dose escalation in reducing tumor burden (Norton 2001).
- Dose-dense administration was associated with more hematologic toxicity and more dose delays and modifications.
- Despite improving PFS and OS, the response rate did not differ. A lower dose of paclitaxel has antiangiogenic activity (Klauber et al. 1997), and

Table 2.17 Results of JGOG 3016

Treatment arm	Conventional regimen N=319	Dose-dense regimen N=312	Statistics
Patient characteristics			
Median age (range)	57 (25-84)	57 (25-87)	
Residual disease ≤1 cm	45%	46%	
Residual disease >1 cm	55%	54%	
Cytology only	11%	11%	
Primary debulking	89%	89%	
Interval debulking	9%	11%	
Second-look surgery	18%	12%	
Stage II	17%	20%	
Stage III	67%	65%	
Stage IV	16%	15%	
Serous	57%	55%	
Endometrioid	12%	12%	
Mucinous	3%	7%	
Clear cell	12%	10%	
Other	16%	15%	
Grade 1	13%	13%	
Grade 2	22%	19%	
Grade 3	23%	25%	
Unknown grade	43%	42%	
Treatment delivery			
Completed 6+ cycles	73%	62%	
Treatment delays	67%	76%	*P*=.02
Dose reductions	35%	48%	*P*=.001
Efficacy			
In 2009 publication			
Median PFS	17.2 months	28.0 months	HR 0.71, *P*=.0015
OS at 3 years	65.1%	72.1%	HR 0.75, *P*=.03
Overall response	53%	56%	*P*=NS
In 2013 publication			
Median PFS	17.5 months	28.2 months	HR 0.76, *P*=.0037
Median OS	62.2 months	100.5 months	HR 0.79, *P*=.039
OS at 5 years	51.1%	58.7%	
PFS, residual >1 cm	12.1 months	17.6 months	HR 0.71, *P*=.0029
PFS, residual ≤1 cm	60.9 months	Median not reached	HR 0.74, *P*=.08
OS, residual >1 cm	33.5 months	51.2 months	HR 0.75, *P*=.0027
OS, residual ≤1 cm	Median not reached	Median not reached	HR 0.76, *P*=.23
PFS, serous/other	17.5 months	28.7 months	HR 0.70, *P*=.0007

Table 2.17 Results of JGOG 3016 *(continued)*

Treatment arm	Conventional regimen N=319	Dose-dense regimen N=312	Statistics
PFS, clear cell/mucinous	16.7 months	18.7 months	HR 1.06, *P*=.84
OS, serous/other	61.2 months	100.5 months	HR 0.76, *P*=.0252
OS, clear cell/mucinous	62.2 months	Median not reached	HR 0.92, *P*=.776
Toxicity			
Higher with dose-dense			
G3/4 anemia	44%	69%	*P*=.0001
No difference			
G3/4 neutropenia	88%	92%	*P*=NS
G3/4 thrombocytopenia	38%	44%	*P*=NS
G3/4 motor neuropathy	4%	5%	*P*=NS
G3/4 sensory neuropathy	6%	7%	*P*=NS
G3/4 hypersensitivity	1.6%	1.9%	*P*=NS

HR, hazard ratio; NS, not significant; PFS, progression-free survival; OS, overall survival.

antiangiogenic agents might promote tumor dormancy by maintaining tumor size and prevention outgrowth (Folkman 1971).

- Frequency of neurotoxicity was similar between the groups. This may be due to the fact that patients receiving dose-dense therapy discontinued treatment more frequently.

COMMENTS FROM 2013 PUBLICATION

- The median OS in patients with optimally resected disease (<1 cm residual) who received conventional treatment (62.2 months) was better than in other trials conducted in Europe and the United States, demonstrating that Asian patients with ovarian cancer have better survival than non-Asian patients. This may be due to biological differences, environmental factors, socioeconomic differences, and/or response to treatment.
- In the subgroup analyses, the greatest benefit of the dose-dense regimen was in patients with optimally cytoreduced (<1 cm) non–clear cell and nonmucinous histologies (ie, serous or other). Other treatment strategies are needed for clear cell and mucinous tumors.
- Carboplatin was dosed with the formulas of Calvert and Jelliffe without adjustment of serum creatinine concentrations. Glomerular filtration rate was estimated using the enzymatic peroxidase-antiperoxidase method, which can result in excessive dosing and more myelosuppression. Other methods to calculate the GFR have been proposed (Ando et al. 2000; Levey et al. 2006; Matsuo et al. 2009), but no consensus

exists. Based on an analysis demonstrating no association between relative dose intensity of carboplatin and PFS or OS, possible excessive doses of carboplatin are not thought to have contributed to the survival differences seen in this trial.
- Dose-dense regimens are also being evaluated in MITO-7, ICON8, and GOG 262. The best dosing schedule has yet to be established.

MITO-2 (Pignata, Oncology 2009; Pignata, JCO 2011)

REFERENCES

- Pignata S, et al. Carboplatin and pegylated liposomal doxorubicin for advanced ovarian cancer: preliminary activity results of the MITO-2 phase III trial. *Oncology*. 2009;76(1):49-54. PMID: 19039248. (Pignata et al. 2009)
- Pignata S, et al. Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial. *J Clin Oncol*. 2011;29(27):3628-3635. PMID: 21844495. (Pignata et al. 2011)

TRIAL SPONSOR

- Multicentre Italian Trials in Ovarian Cancer (MITO)
- Integrated Therapeutics Group (ITG)—no role in trial design and data interpretation
- Schering-Plough Italy provided experimental drug—no role in trial design and data interpretation
- Nonprofit Italian Association for Cancer Research

RATIONALE FOR TRIAL

- After treatment for ovarian cancer, the risk of recurrence and death remains high.
- Standard treatment affects quality of life due to toxicities that include alopecia, neurotoxicity, and fatigue.
- Anthracyclines were used in first-line treatment of ovarian cancer before the introduction of taxanes and a meta-analysis demonstrated the addition of doxorubicin improved survival (Cyclophosphamide plus cisplatin . . . 1991; Fanning et al. 1992; A'Hern and Gore 1995; Muggia et al. 1997; West and Zweig 1997). However, safety concerns with

anthracyclines include dose-limiting acute toxicity of myelosuppression and gastrointestinal toxicities and chronic cumulative cardiotoxicity and alopecia.

- PLD is doxorubicin encapsulated in liposomes coated with methoxypolyethylene glycol, which prolongs the circulation of the drug and its concentration in the tumor. This formulation results in a different pharmacokinetic and toxicity profile (Theodoulou and Hudis 2004). Compared to anthracyclines, PLD has less myelotoxicity, alopecia, nausea, vomiting, and cardiomyopathy but has more skin and mucosal toxicity, including palmar-plantar erythrodysesthesia (PPE) and stomatitis (Muggia et al. 1997; O'Brien et al. 2004).
- In second-line treatment for platinum-sensitive ovarian cancer, a randomized trial demonstrated PLD treatment to have better survival than topotecan treatment as well as a favorable toxicity profile (Gordon et al. 2004).
- A phase II study by the Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens treated patients with platinum-sensitive relapsed ovarian cancer with carboplatin AUC 5 and PLD 30 mg/m^2 every 4 weeks and demonstrated a 63% response rate, median PFS of 9.4 months, and median OS of 32 months. Toxicities included severe neutropenia (about 50%), fever (3%), PPE (32%), and neuropathy (28%) but was well tolerated overall (Ferrero et al. 2007).
- Several phase I and II studies combine PLD and carboplatin in relapsed ovarian cancer (Goncalves et al. 2003; du Bois et al. 2006a; du Bois et al. 2007; Ferrero et al. 2007; Alberts et al. 2008a).
- This trial was designed to evaluate whether carboplatin/PLD has superior PFS to carboplatin/paclitaxel in first-line treatment of advanced ovarian cancer. To provide the same dose intensity of carboplatin in both arms, the carboplatin/PLD was dosed on an every 3-week schedule.

PATIENT POPULATION

- N = 820 enrolled.
- Enrolled between January 2003 and November 2007.
- Cytologic or histologic diagnosis of epithelial ovarian cancer, stages IC to IV.
- Age less than 75 years.
- ECOG performance status of 0, 1, or 2.
- Life expectancy ≥3 months.

- Adequate bone marrow, kidney, and liver function.
- Exclusions: prior chemotherapy; clinically relevant heart disease; other concomitant diseases representing contraindications to treatment drugs; prior or concomitant other malignancy except nonmelanoma skin cancer or carcinoma in situ of the uterine cervix.

TREATMENT DETAILS

Arm 1: Standard Arm: Paclitaxel + Carboplatin

- Paclitaxel 175 mg/m^2 IV on day 1 every 3 weeks. Paclitaxel was diluted in 250 mL of normal saline and infused over 3 hours.
- Carboplatin AUC 5 IV on day 1 every 3 weeks. Doses were calculated according to the Calvert formula with creatinine clearance estimated by the Cockcroft formula. Carboplatin was diluted in 250 mL of 5% dextrose in water (D5W) and infused over 30 minutes.
- Treatment for 3 cycles with assessment and a further 3 cycles if stable or responding disease.

Arm 2: Experimental Arm: Carboplatin + PLD

- Carboplatin AUC 5 IV on day 1 every 3 weeks.
- PLD 30 mg/m^2 IV on day 1 every 3 weeks. PLD was diluted in 250 mL of D5W and infused over 60 minutes after carboplatin infusion.
- Treatment for 3 cycles with assessment and a further 3 cycles if stable or responding disease.

Conditions for Retreatment

- Leukocytes >3000/μL, neutrophils >1500/μL, platelets ≥100,000/μL, absence of grade 2 or more organ toxicity (excluding alopecia).

Dose Modifications

- Twenty percent dose reduction for all drugs if ANC <500/μL or platelets <50,000/μL for more than 7 days.
- Twenty percent reduction of carboplatin and paclitaxel for neuropathy.
- Carboplatin reduced to AUC 4 for creatinine clearance <60 mL.
- For grade 2 or more skin toxicity, PLD was delayed for up to 2 weeks or until toxicity resolved to grade 1 or less; otherwise, PLD was interrupted; 25% subsequent dose reduction if grade 3 or 4 skin toxicity cleared within 2 weeks.

Treatment Discontinuation

- For treatment delays of ≥2 weeks.

ASSESSMENTS

- CT or MRI of the abdomen and pelvis at baseline and after 3 and 6 cycles of chemotherapy.
- Quality of life was assessed with the EORTC QLQ-C30 (Aaronson et al. 1993).
- Toxicity graded according to the National Institute Common Toxicity Criteria (version 2.0).
- RECIST version 1.0 used for evaluation of response (Therasse et al. 2000).
  - Progression defined as 20% increase in the sum of the largest diameters of known lesions; appearance of new lesions; increase in CA125 level of more than 25%; death from any cause.

ENDPOINTS

- PFS (primary endpoint).
- OS.
- Treatment activity.
- Toxicity.
- Quality of life.

STATISTICAL CONSIDERATIONS

Sample Size

- In total, 820 patients and 632 progression events were needed for 80% power of detecting a 0.80 hazard ratio of progression with a 2-tailed α of 0.05. This represented an improvement in PFS from 18 to 22.5 months. No interim analyses were planned.
- At the time of analysis, only 556 events had occurred due to a relatively good prognosis population (>50% optimal debulking, one-third with no residual disease, high proportion of early-stage patients). This number of events allowed for detection of a hazard ratio (HR) of 0.79 with 80% power.

Stratification Factors

- Stratification variables included center, residual disease (absent, ≤1 cm, >1 cm, no primary surgery), stage (IC, II, III, IV), and ECOG performance status (0, 1, 2).

Statistical Tests

- Inverted Kaplan-Meier method (Schemper and Smith 1996) to calculate median follow-up and Kaplan-Meier product-limit method to

Table 2.18 Results of MITO-2

Treatment arm	Standard (PC) N=410	Experimental (C-PLD) N=410	Statistics
Patient characteristics			
Median age (range)	57 (21-77)	57 (25-77)	
No residual	36.1%	36.6%	
Residual disease ≤1 cm	17.1%	19.3%	
Residual disease >1 cm	28.3%	27.1%	
No surgery	18.5%	17.1%	
Stage IC	9.0%	9.0%	
Stage II	9.8%	9.5%	
Stage III	59.8%	60.5%	
Stage IV	21.5%	21.0%	
Serous	63%	66%	
Endometrioid	12%	12%	
Mucinous	2.9%	3.2%	
Clear cell	3.7%	2.9%	
Other	18.1%	16.1%	
Grade	Not reported	Not reported	
Treatment delivery			
No treatment	1.0% (N=4)	1.5% (N=6)	
Received 6 cycles	86.5%	81.1%	
Cycles delayed for toxicity	11.5%	34.5%	
Discontinuation			
Progression/death	5.6%	7.2%	
Toxicity/refusal	5.1%	9.4%	
Violation/other	2.0%	1.5%	
Efficacy			
Median PFS	16.8 months	19.0 months	HR 0.95, *P*=NS
Median OS	53.2 months	61.6 months	HR 0.89, *P*=NS
ORR	59%	57%	*P*=NS
Toxicity			
Deaths	N=4	N=2	
Worse with PC			
Alopecia	63%	14%	*P*<.001
Any diarrhea	13%	6%	*P*<.001
≥G3 neuropathy	3%	<1%	*P*=.003
Worse with C-PLD			
≥G3 thrombocytopenia	2%	16%	*P*<.001
≥G3 anemia	4%	10%	*P*<.001
Skin toxicities	6%	21%	*P*<.001
Stomatitis	<10%	19%	*P*<.001

Table 2.18 Results of MITO-2 *(continued)*

Treatment arm	Standard (PC) N=410	Experimental (C-PLD) N=410	Statistics
No difference			
≥G3 leukopenia	19%	15%	NS
≥G3 neutropenia	50%	43%	NS
Febrile neutropenia	2%	<2%	NS
Infections	<4%	<3%	NS
Bleeding	<1%	<1%	NS

C-PLD, carboplatin+pegylated liposomal doxorubicin; HR, hazard ratio; NS, not significant; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; PC, paclitaxel+carboplatin.

estimate PFS and OS curves (Kaplan and Meier 1958). Curves compared with the log-rank test (Mantel 1966).
- Cox proportional hazards model used to assess treatment effect adjusted by baseline prognostic variables.
- χ^2 used to compared the difference in overall response rates.
- Exact linear rank test used to compare patters of toxicity, considering all grades.
- χ^2 and Fisher's exact tests used to compare rates of severe toxicity.
- Quality-of-life analyses were performed according to the EORTC manual (Fayers 2001).

CONCLUSION OF TRIAL

- Carboplatin and PLD does not improve survival compared to carboplatin and paclitaxel but can be considered as an alternative front-line therapy for ovarian cancer due to its different toxicity profile. This might be a particular consideration for patients at high risk of neurotoxicity or those wishing to avoid alopecia.

COMMENTS

- Residual disease and stage were independent predictors of PFS. There was no heterogeneity of treatment effect.
- There were no reported differences in quality of life except for more loss of appetite with the experimental arm and more diarrhea in the standard arm.
- Toxicity profiles were dramatically different. Carboplatin/PLD was associated with less hair loss and less neurotoxicity but with more skin toxicity and stomatitis. Carboplatin and PLD also caused

worse hematologic toxicity but within acceptable limits for clinical practice.
- These authors previously demonstrated that residual neurotoxicity occurs frequently after carboplatin and paclitaxel treatment and 14% have persistent symptoms even after 1 year (Pignata et al. 2006). Residual neurotoxicity may affect later treatment choices.
- The MITO-2 study adds to the data regarding the role of anthracyclines in ovarian cancer treatment with prior data suggesting the addition of doxorubicin to improve survival outcomes (A'Hern and Gore 1995).
- The final MITO-2 analysis was done with fewer events than planned (556 instead of 632 events) due to the favorable prognostic factors of enrolled patients. A much longer follow-up time would have been required, and this may have resulted in dilution of PFS differences.

AGO-OVAR9 (du Bois, JCO 2010)

REFERENCE

- du Bois A, et al. Phase III trial of carboplatin plus paclitaxel with or without gemcitabine in first-line treatment of epithelial ovarian cancer. *J Clin Oncol*. 2010;28(27):4162-4169. PMID: 20733132. (du Bois et al. 2010)

TRIAL SPONSORS

- Gynecologic Cancer Intergroup
- Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR)
- Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO)
- Nordic Society of Gynecologic Oncology (NSGO)

RATIONALE FOR TRIAL

- A possible method for improving survival in advanced ovarian cancer is to add a non-cross-resistant drug to platinum and paclitaxel.
- Gemcitabine was thought be a good candidate based on:
  - It has single-agent activity in relapsed ovarian cancer comparable to standard liposomal doxorubicin in randomized trials (Mutch et al. 2007; Ferrandina et al. 2008).

  - It can be combined with platinum in platinum-sensitive ovarian cancer (du Bois et al. 2001; Brewer et al. 2006).
  - The combination has been shown to have higher efficacy than carboplatin alone in this population (Pfisterer et al. 2006a).
  - It can be added as a third drug to platinum and taxane, which would allow assessment of a triplet regimen without compromising therapy by withholding a standard drug (Gupta et al. 2005; Hensley et al. 2006; Friedlander et al. 2007).
- This trial was designed to compare paclitaxel/carboplatin/gemcitabine (du Bois et al. 2005a) to paclitaxel/carboplatin in advanced ovarian cancer.

PATIENT POPULATION

- N = 1784 screened, 1742 eligible.
- Between 2002 and 2004, 1742 patients were enrolled (175 in stratum 1, 891 in stratum 2, and 676 in stratum 3).
- FIGO stages I to IV ovarian cancer with upfront debulking surgery within 6 weeks before random assignment.
- Adequate hematologic, renal, and hepatic function defined as ANC ≥1500 cells/μL, platelets ≥100,000 cells/μL, and serum creatinine and bilirubin ≤1.25 times upper normal limit.
- Exclusions: low malignant potential tumors; ECOG performance status >2; an estimated glomerular filtration rate of <50 mL/min; other malignancies; pervious chemotherapy, immunotherapy, or radiotherapy; severe neuropathy; cardiac arrhythmias; or congestive heart failure.

TREATMENT DETAILS

Arm 1: Paclitaxel, Carboplatin (TC)

- Paclitaxel 175 mg/m^2 IV over 3 hours on day 1 every 3 weeks.
- Carboplatin AUC 5 IV over 30 to 60 minutes on day 1 every 3 weeks.

Arm 2: Paclitaxel, Carboplatin, Gemcitabine (TCG)

- Paclitaxel 175 mg/m^2 IV over 3 hours on day 1 every 3 weeks.
- Carboplatin AUC 5 IV over 30 to 60 minutes on day 1 every 3 weeks.
- Gemcitabine 800 mg/m^2 IV over 30 to 60 minutes on days 1 and 8 every 3 weeks.

Dosing Details and Supportive Measures

- Paclitaxel maximum dose of 385 mg. Dose reduction to 150 mg/m^2 (level 1) or 135 mg/m^2 (level 2).

- Carboplatin—dose calculated according to formula of Calvert (Calvert et al. 1989). GFR estimated using Jelliffe formula (Jelliffe 1973). Maximum dose of 800 mg. Dose reduction to AUC 4 (level 1/level 2).
- Gemcitabine—maximum dose of 1600 mg. Dose reduction by omission of day 8 dose (level 1).
- Dose reductions allowed for hematologic and nonhematologic toxicity.
- Treatment cycles were delayed for ANC <1500 cells/μL or platelet count <100,000 cells/μL.
- Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) was not allowed.
- Supportive G-CSF/GM-CSF could be initiated at the discretion of the investigator.
- All patients received antiallergic and antiemetic premedications.
- Treatment was discontinued for disease progression.
- Patients with partial remission after 6 cycles of treatment could receive additional cycles.

ASSESSMENTS

- Tumor measurements were made before each cycle by exam, before every third cycle by imaging (in patients with measurable or evaluable disease), and after the last cycle. Tumor response was graded by RECIST (Therasse et al. 2000).
- Adverse events and toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). Toxicities were evaluated per course and per patient to capture the worst score over all courses.
- Quality of life was evaluated by using global health status/quality-of-life score of the EORTC QLQ-C30, version 3.0 (Aaronson et al. 1993) and the OV-28 module specific for ovarian cancer, version 1.0 (Greimel et al. 2003). Quality of life was assessed at baseline, after the third and last treatment cycles, and 3 months after completion of treatment, and responses were evaluated according to the EORTC guidelines.
- Follow-up visits were scheduled every 3 months in the first 2 years and every 6 months thereafter for a total of 5 years.

ENDPOINTS

- OS (defined as time from random assignment to death from any cause) (primary endpoint).

- PFS.
- Response to treatment.
- Toxicity.
- Quality of life.

STATISTICAL CONSIDERATIONS

Stratification Factors

- Patients were stratified according to residual tumor size and FIGO stage.
  - Stratum 1: FIGO I to IIA disease.
  - Stratum 2: FIGO IIB to IIIC and residual <1 cm.
  - Stratum 3: Residual tumor ≥1 cm or FIGO stage IV.

Sample Size

- To detect a clinically meaningful HR of 0.818, which corresponds to an increased median survival of 8 months, and to compensate for a 10% loss to follow-up rate, recruitment of 1716 patients was planned.

Statistical Tests

- Kaplan-Meier method used to analyze time-to-event data.
- Log-rank test used to compare survival distributions between groups.
- Cox proportional hazards model used to estimate hazard ratios.
- Method of Blyth-Still-Casella used to estimate response rates.
- Exact methods for stratified testing including the Zelens exact test were used to compare response rates.
- Wilcoxon-Mann-Whitney test was used to compare global health score and its difference from baseline (reflecting summary quality-of-life measures).

CONCLUSION OF TRIAL

- The addition of gemcitabine to the paclitaxel and carboplatin backbone increased treatment burden, increased toxicities, and reduced PFS in patients with advanced epithelial ovarian cancer.

COMMENTS

- Exploratory analysis of different prognostic subgroups demonstrated no evidence of benefit from addition of gemcitabine to treatment of any subgroup.

Table 2.19 Results of AGO-OVAR9

Treatment arm	TC N=882	TCG N=860	Statistics
Patient characteristics			
Median age (range)	60 (23-82)	59 (20-80)	
Residual disease≤1 cm	70.9%	69.2%	
Residual disease >1 cm	29.1%	30.8%	
Stage I	8.6%	8.2%	
Stage II	9.4%	10.1%	
Stage III	65.8%	65.3%	
Stage IV	16.2%	16.3%	
Serous	73.7%	75.1%	
Mucinous/clear cell	4.5%	4.7%	
Other	21.8%	20.2%	
Grade 1	10.7%	6.9%	
Grade 2	29.1%	33.7%	
Grade 3	60.2%	59.4%	
Treatment delivery			
Received at least 6 cycles	87.2%	86.2%	
Received >6 cycles	15.8%	15.8%	
Treatment delay >7 days	7.5%	11.6%	$P<.001$
At least 1 dose reduction	8.7%	15.1%	$P<.001$
Efficacy			
Objective response rate	77.5%	86.2%	$P=.0303$
Median PFS	19.3 months	17.8 months	$P<.01$
Median OS	51.5 months	49.5 months	$P=$NS
Toxicity			
Worse with TCG			
G3/4 hemoglobin	4.3%	17.8%	$P<.001$
G3/4 leukocytes	28.1%	70.2%	$P<.001$
G3/4 neutrophils	62.1%	81.5%	$P<.001$
G3/4 platelets	4.7%	35.8%	$P<.001$
Febrile neutropenia	2.3%	6.6%	$P<.001$
Transfusion blood	10.0%	32.5%	$P<.001$
Supportive care EPO	11.6%	26.7%	$P<.001$
Supportive care G-CSF	12.8%	28.0%	$P<.001$
Supportive care antibiotic	14.1%	21.6%	$P<.001$

EPO, epogen; G-CSF, granulocyte colony-stimulating factor; NS, not significant; PFS, progression-free survival; OS, overall survival; TC, taxol+carboplatin; TCG, taxol+carboplatin+gemcitabine.

- The addition of gemcitabine resulted in a disadvantage to survival in early ovarian cancer patients and a disadvantage to PFS in advanced disease, and it added to hematologic toxicity and fatigue.
- The addition of a third drug may have a detrimental effect by affecting immune suppression (Zhang et al. 2003; Alberts et al. 2008).
- More than 10,000 patients have been enrolled in intergroup trials that have evaluated the addition of anthracyclines, topotecan, and gemcitabine to standard therapy (du Bois et al. 2006b; Pfisterer et al. 2006b; Bookman et al. 2009). These trials consistently show no added benefit but increased toxicities with the addition of the third drug.
- Despite this evidence, the next generation of trials in the GCIG network is using the same design of addition of a third drug sequentially or concurrently to TC, but these new trials are using targeted therapies (bevacizumab, erlotonib, pazopanib, vargatef). This strategy is based on the assumption that the model did not fail, but the wrong drugs were selected for use (Hoskins 2009).
- Promising results from phase II studies do not always translate into success in phase III (Zia et al. 2005). Most phase II studies choose a primary endpoint of response rate, but this is a surrogate endpoint that does not necessarily correlate with survival. Response is only measured in the subgroup of patients with bulky disease, and the addition of a third drug may speed the disappearance of these masses. Survival is more dependent on the regrowth of chemoresistant tumor masses, which are not reduced by the addition of the third agent.
- The selection of drugs for phase III evaluation might be improved by the use of different endpoints that are more reflective of chemoresistant disease. This includes time to treatment failure in relation to prior recurrence-free survival (Harrison et al. 2007). Another approach may be the use of tumor kinetics seen in phase II studies to predict the survival gain achievable in phase III (Claret et al. 2009).

OV16 (Hoskins, JNCI 2010)

REFERENCE

- Hoskins P, et al. Advanced ovarian cancer: phase III randomized study of sequential cisplatin-topotecan and carboplatin-paclitaxel vs carboplatin-paclitaxel. *J Natl Cancer Inst*. 2010;102(20):1547-1556. PMID: 20937992. (Hoskins et al. 2010)

TRIAL SPONSOR

- Gynecologic Cancer Intergroup
  - NCIC Clinical Trials Group (NCIC CTG)
  - European Organization for Research and Treatment of Cancer–Gynecologic Cancer Group (EORTC-GCG)
  - Grupo de Investigacion de Cancer de Ovario (GEICO)

RATIONALE FOR TRIAL

- A potential strategy to improve the efficacy of treatment of advanced ovarian cancer is to add a third cytotoxic agent to the backbone of standard paclitaxel and carboplatin.
- Topotecan is a camptothecin analogue that has single-agent activity in recurrent ovarian cancer, including platinum-resistant disease (Creemers et al. 1996; Kudelka et al. 1996; ten Bokkel Huinink et al. 1997; Bookman et al. 1998; Hoskins et al. 1998).
- To address the issue the issue of myelosuppression with paclitaxel + carboplatin + topotecan triple therapy, the NCIC Clinical Trials Groups (NCIC-CTG) tested a regimen that consisted of sequential doublets of cisplatin + topotecan followed by carboplatin + paclitaxel and found sufficient phase II activity to warrant a phase III study (Hoskins et al. 2000).
- This trial was designed to evaluate the efficacy of topotecan when combined with standard front-line chemotherapy for advanced ovarian cancer.

PATIENT POPULATION

- N = 819 enrolled.
- Enrollment between August 2001 and June 2005.
- Newly diagnosed stage IIB to IV epithelial ovarian, fallopian tube, or primary peritoneal cancer and completed all planned primary surgery.
- Diagnosis based on:
  - Histologic findings, or
  - Cytology if the patient had a pelvic mass with an abdominal metastasis ≥2 cm in diameter, a normal mammogram within the preceding 6 weeks, and CA125 to CEA ratio ≥25. If CA125 to CEA ratio <25, patients were eligible if colonoscopy/barium enema and gastroscopy/barium meal were negative.
- No prior chemotherapy.

- ECOG performance status of 0 or 1.
- Adequate hematologic reserve and liver function.
  - Granulocytes ≥2000/μL.
  - Platelets ≥150,000/μL.
  - Creatinine less than or equal to upper normal limit.
- Exclusions: borderline ovarian tumors, prior nonsurgical therapy for ovarian cancer, other malignancy other than nonmelanoma skin cancer, in situ carcinoma of the cervix, or a solid tumor treated with curative intent and no evidence of disease for ≥5 years; myocardial infarction within 6 months; second- or third-degree heart block unless a pacemaker had been implanted; contraindication to high-volume saline diuresis; preexisting hearing loss; neuropathy greater than grade 1.

TREATMENT DETAILS

Arm 1: Standard Treatment

- Eight cycles every 3 weeks.
  - Paclitaxel 175 mg/m^2 IV over 3 hours on day 1.
  - Carboplatin AUC 5 IV over 30 minutes on day 1.

Arm 2: Experimental Treatment

- Four cycles every 3 weeks.
  - Cisplatin 50 mg/m^2 IV over 60 minutes on day 1.
  - Topotecan 0.75 mg/m^2 IV over 30 minutes on days 1 through 5.
- Four cycles every 3 weeks.
  - Paclitaxel 175 mg/m^2 IV over 3 hours on day 1.
  - Carboplatin AUC 5 over 30 minutes (or per institutional standard) IV on day 1.

Administration Details

- Carboplatin dosed using either the measured glomerular filtration rate by nuclear renogram or a calculated GFR using the Cockcroft formula.
- All drugs were administered in solution as per the product monograph.
- Hydration and premedications were administered per local institutional standards and were not specified by protocol.

Treatment Delays

- Until granulocytes ≥1500/μL and platelets >100,000/μL.

Dose Reductions and Discontinuations

- Granulocytes ≤500/μL for >7 days; platelets <25,000/μL; febrile neutropenia; grade 3 or more infection.

  - Topotecan decreased by 25% in the next cycle (no change in cisplatin dosing).
  - Paclitaxel deceased by 25 mg/m^2 and carboplatin decreased by 1 AUC.
- Arthralgia or myalgia.
  - Grade 3: paclitaxel decreased by 25 mg/m^2.
  - Grade 4: paclitaxel discontinued.
- Grade 4 anaphylaxis (life threatening).
  - Protocol therapy discontinued.
- Neurotoxicity.
  - Grade 2: paclitaxel decreased by 25 mg/m^2.
  - Grade 3: protocol therapy discontinued.
- Mucositis.
  - Grade 2 or more: paclitaxel decrease by 25 mg/m^2.
- Renal toxicity after rehydration.
  - With creatinine at 1 to 1.5 × upper limit of normal: cisplatin decreased by 25%.
  - With creatinine >1.5 × upper limit of normal: protocol therapy discontinued.

Surgery

- Interval debulking was allowed after 3 or 4 cycles of therapy for those not optimally debulked at the time of study entry.

ASSESSMENTS

- On day 1 of each cycle: physical exam, CBC, serum creatinine, AST or ALT, serum CA125.
- On day 15 of each cycle: CBC.
- Imaging with CT scan or MRI prior to cycle 1 to obtain baseline measures except when no debulking had been done or when optimal debulking had been achieved. Further imaging after cycle 4 (or cycle 3 if interval debulking had been planned) and after cycle 8 or earlier if progression was suspected.
- Quality of life assessed using the EORTC QLQs C30 (Aaronson et al. 1993) and OV28 (Cull et al. 2001) module at baseline and on day 1 of cycles 3, 5, and 7; at the end of the last cycle; and 3 and 6 months after completing protocol therapy.
  - QLQ C30 contains 9 multi-item scales. Five functional scales measure physical, role, cognitive, emotional, and social domains. Three

symptom scales measure fatigue, pain, and nausea and vomiting. The final scale is a global health and quality-of-life scale.
  - The OV28 module assess symptoms that may be specific to ovarian cancer or its treatment, including abdominal symptoms, peripheral neuropathy, hormonal symptoms, attitude to disease treatment, and sexual functioning.
- After treatment, follow-up every 3 months for the first 3 years, then every 6 months for the next 2 years, then annually thereafter. History and physical exam, CA125 assessed at each visit.
  - Progression was defined by Gynecologic Cancer Intergroup definition, including objective progression using RECIST criteria (Therasse et al. 2000) or CA125 progression (Vergote et al. 2000).
  - RECIST progression: either a 20% increase in the sum of diameters over the nadir or the appearance of new disease.
  - CA125 progression: increase to more than twice the upper limit of normal (or of the nadir value if levels had not normalized) and confirmed at least 1 week later. CA125 values measured within 4 weeks of surgery or other abdominal procedure such as paracentesis were not considered in this evaluation.

ENDPOINTS

- PFS, defined as time from randomization to time of first observation of disease progression or death from any cause (primary endpoint).
- OS.
- Adverse effects.
- Quality of life.
- Objective response (in patients with measurable disease by RECIST).
- CA125 normalization rates 3 months after randomization.

STATISTICAL CONSIDERATIONS

Stratification Factors

- Patients were stratified based on treatment center, age (≤65 or >65), extent of surgery (no debulking, no residual, residual <1 cm, residual ≥1 cm).

Sample Size

- Assuming PFS of 16 months with standard therapy, this trial was designed to have 80% power to detect a 25% improvement in PFS from a median of 16 months to 20 months (HR, 0.8) using a 2-sided α of 5%.

At the time of final analysis, 631 progression events would be needed, requiring recruitment of 800 patients over 2 years and 29 months of follow-up.

Statistical Tests

- Stratified log-rank test used to compare PFS and OS.
- Cochran-Mantel-Haenszel test used to compare CA125 normalization rates with adjustment for stratification factors.
- Cox proportional hazards model used to assess treatment effect after adjusting for potential confounding factors and to identify factors predictive of PFS. Covariates included:
  - Treatment.
  - Stratification factors.
  - Stage (II vs III/IV).
  - Grade (1/2 vs 3/undifferentiated/unknown).
  - Histology (serous vs other).
  - Performance status (0 vs 1).
- The assumption of proportionality in the Cox model was assessed by Schoenfeld residuals.
- Fisher's exact test was used to compare the incidence of adverse events between arms.
- Wilcoxon rank-sum test was used to compare changes of quality-of-life scores from baseline between treatment arms.

CONCLUSION OF TRIAL

- The addition of topotecan to paclitaxel and carboplatin does not improve outcomes and adds to the toxicity profile in the treatment of advanced ovarian cancer.

COMMENTS

- More mature OS outcomes will be reported after continued follow-up.
- The results of this study parallel those of the GOG 182-ICON5 study, which demonstrated no improvement in survival with the addition of a third cytotoxic agent to the paclitaxel and carboplatin backbone in the treatment of advanced ovarian cancer (Bookman et al. 2009).
  - In GOG 182-ICON5, topotecan was dosed at 1.25 mg/m^2 per day for 3 days; topotecan was combined with carboplatin, which was given on day 3 rather than day 1; and the topotecan doublet was given in the last 4 cycles of therapy.

Table 2.20 Results of OV16

Treatment arm	Standard treatment N=410	Experimental sequential doublets N=409	Statistics
Patient characteristics			
Median age (range)	57 (33-75)	57 (28-78)	
No residual	22%	22%	
Residual disease <1 cm	20%	25%	
Residual disease≥1 cm	36%	33%	
No debulking	20%	19%	
Measurable disease	47%	48%	
Stage II	8.0%	9.0%	
Stage III	64.6%	67.2%	
Stage IV	27.3%	23.7%	
Serous	68%	65%	
Endometrioid	5%	7%	
Mucinous	2%	2%	
Clear cell	5%	6%	
Other	19%	21%	
Grade	Not reported	Not reported	
Treatment delivery			
Completed 8 cycles	81%	78%	
At least 1 cycle delay	50%	85%	
Dose reductions	18%	43%	
Interval debulking	17.4%	13.5%	
Efficacy			
Objective response	77.2%	67.9%	*P*=.04
Complete response	37.3%	31.1%	Not reported
CA125 normalization	66.3%	57.5%	*P*=.006
Median PFS	16.2 months	14.6 months	HR 1.10 (95% CI, 0.94-1.28)
Median OS	42.1 months	42.3 months	NS
Toxicity			
Death	N=2	N=2	
Worse with experimental			
G4 granulocytopenia	58%	85%	*P*<.001
Febrile neutropenia	6%	22%	*P*<.001
G3/4 thrombocytopenia	9%	46%	*P*<.001
Thromboembolic events	2%	7%	*P*<.001
Nausea	77%	84%	*P*=.01

(continued)

Table 2.20 Results of OV16 *(continued)*

Treatment arm	Standard treatment N=410	Experimental sequential doublets N=409	Statistics
Vomiting	41%	57%	$P<.001$
Hospitalization	7.1%	11.3%	
Erythropoietin use	13.4%	25.8%	
G-CSF use	13.7%	34.7%	
Worse with standard			
Neurosensory	84%	74%	$P<.001$
Allergic reactions	35%	24%	$P<.001$

CA125, cancer antigen 125; CI, confidence interval; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; NS, not significant; PFS, progression-free survival; OS, overall survival.

  - In this current trial, topotecan was dosed at 0.75 mg/m^2 per day for 5 days, topotecan was combined with cisplatin which was given on day 1, and the topotecan doublet was given in the first 4 cycles of therapy.
- The hypothesis that the 5-day topotecan schedule with day 1 cisplatin would be synergistic was not observed to be true in this study.
- Topotecan has been tested as triplet and consolidation therapy, but no trial has demonstrated a survival benefit (De Placido et al. 2004; Pfisterer et al. 2006b; Bookman et al. 2009). The cells that are resistant to platinum and taxanes do not appear to be responsive to topotecan treatment.
- For a drug to be non-cross-resistant, it should have activity against refractory tumors (cancer that grows during treatment). In 4 single-agent studies of topotecan in the refractory setting, only 9% of patients responded to treatment (Creemers et al. 1996; ten Bokkel Huinink et al. 1997; Bookman et al. 1998; Hoskins et al. 1998). Future trials should evaluate drugs that demonstrate more efficacy against refractory cells.
- Phase III ovarian cancer trials that use the PFS endpoint (whose median is approximately 15 months for front-line trials) for early stopping often complete accrual before sufficient progression events have been seen to perform an interim analysis. This trial suggests that CA125 normalization rates at 3 months may be predictive of treatment efficacy and would provide an earlier opportunity to perform futility analyses in future phase III studies. This endpoint would require confirmatory validation as an endpoint predictive of PFS in other trials.

ICON7 (Perren, NEJM 2011; Oza, Lancet Oncol 2015)

REFERENCES

- Perren TJ, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med*. 2011;365(26):2484-96. PMID: 22204725. (Perren et al. 2011)
- Oza AM, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol*. 2015;16(8):928-936. PMID: 26115797. (Oza et al. 2015)

TRIAL SPONSORS

- Gynecologic Cancer InterGroup (GCIG) Internal Collaboration on Ovarian Neoplasms (ICON7)
- Led by UK Medical Research Council Clinical Trials Unit (MRC CTU)
- Participating GCIG Groups:
  - AGO-OVAR
  - ANZGOG
  - GINECO
  - GEICO
  - MRC/NCRI
  - NSGO
  - NCIC CTG

RATIONALE FOR TRIAL

- Although intraperitoneal chemotherapy administration improves survival, this is an option limited to patients with small-volume residual disease.
- Angiogenesis leads to tumor growth and metastasis and is an attractive target as ovarian cancers frequently express vascular endothelial growth factor (VEGF).
- Bevacizumab is a monoclonal antibody that binds to VEGF-A with demonstrated efficacy in colorectal, lung, renal, breast, and brain cancers (Hurwitz et al. 2004; Eskens and Sleijfer 2008). Phase 2 trials have shown efficacy in women with ovarian cancer (Burger et al. 2007; Cannistra et al. 2007; Garcia et al. 2008).
- This trial (like GOG 218) was designed to evaluate the addition of bevacizumab to standard chemotherapy in front-line treatment of ovarian cancer.

PATIENT POPULATION

- N = 1528 enrolled.
- From December 2006 to February 2009, patients were enrolled from 263 centers in the United Kingdom, Germany, France, Canada, Australia, New Zealand, Denmark, Finland, Norway, Sweden, and Spain.
- Newly diagnosed ovarian cancer that was either
  - High-risk, stage I or IIA clear cell, or grade 3 ovarian cancer (enrollment limited to 10% of total study population) or
  - Advanced stage IIB to IV epithelial ovarian, fallopian tube, or peritoneal cancer.
- ECOG performance status of 0, 1, or 2.
- Adequate coagulation values, bone marrow, liver, and renal function.
- No plans for further surgery before disease progression.
- Exclusions: other tumor types; previous systemic therapy; planned surgery; uncontrolled hypertension.
- A high-risk subgroup was defined as at risk for progression and had similar patient characteristics to those enrolled in GOG 218. This subgroup included the following:
  - Stage IV.
  - Inoperable stage III.
  - Suboptimally debulked stage III (>1 cm residual).

TREATMENT DETAILS

Arm 1: Standard Chemotherapy (PC)

- Paclitaxel 175 mg/m^2 IV every 3 weeks for 6 cycles.
- Carboplatin AUC 5 or 6 IV every 3 weeks for 6 cycles.

Arm 2: Standard Chemotherapy + Bevacizumab (PCB)

- Paclitaxel 175 mg/m^2 IV every 3 weeks for 6 cycles.
- Carboplatin AUC 5 or 6 IV every 3 weeks for 6 cycles.
- Bevacizumab 7.5 mg/kg IV every 3 weeks during chemotherapy until 12 additional cycles or disease progression. To prevent delayed wound healing, bevacizumab was started with cycle 1 if chemotherapy started >4 weeks after surgery and delayed until cycle 2 if chemotherapy started ≤4 weeks from surgery.

ASSESSMENTS

- Clinical assessments and CA125 were performed before each cycle of chemotherapy, every 6 weeks in year 1, every 3 months in years 2 and 3, every 6 months in years 4 and 5, and then yearly thereafter.

- After disease progression, assessments were performed every 6 months for 5 years, then yearly thereafter.
- CT or MRI was performed at baseline, after cycles 3 and 6, at 9 and 12 months after randomization, every 6 months in years 2 and 3, and then as clinically indicated until disease progression.
- Quality of life was assessed with the EORTC QLQ-C30 and QLQ-OV28 questionnaires.
- Progression was defined by RECIST criteria (Therasse et al. 2000) and did not include asymptomatic progression by CA125 levels only.
- The biologic progression-free interval as calculated from date of randomization to date of first CA-125-based progression (Rustin et al. 2004) or first RECIST-based progression.

ENDPOINTS

- PFS (calculated from date of randomization) (primary endpoint).
- OS.
- Biologic progression-free interval.
- Response to therapy.
- Toxicity.
- Quality of life.
- Laboratory results.
- Worsened ECOG performance status.
- Health economics and translational research.

STATISTICAL CONSIDERATIONS

Stratification Factors

- Patients were stratified by GCIG group, FIGO stage, and residual disease (stage I to III with ≤1 cm residual disease, stage I to III with >1 cm residual disease, stage III inoperable or stage IV), and planned interval between surgery and chemotherapy (≤4 weeks or >4 weeks).

Sample Size

- Primary analysis was carried out with an unstratified log-rank test for the difference in PFS between the 2 groups. The trial was designed to detect a 28% increase in median PFS from 18 months with standard chemotherapy to 23 months with the addition of bevacizumab (HR, 0.81) with 90% power at the 5% significance level. A sample size of 1520 women and a total of 684 events (disease progression or death) were required. After submission of the primary analysis of PFS, regulatory

authorities requested an OS analysis with at least 365 deaths (50% of the required total number of deaths).
- Study was also powered to detect a difference in OS. This analysis needed 715 deaths to detect an improvement in OS from 43 to 53 months (HR, 0.81) with 80% power at a 2-sided significance level of 5%.

Statistical Tests
- Log-rank test stratified by factors used for randomization.
- Cox regression analyses adjusted for baseline covariates when proportional hazards could be assumed.
- When nonproportional hazards, flexible parametric survival models (Royston and Parmar 2002) to smooth survival curves were used.
- Interaction analyses to evaluate differences in size of treatment effects in subgroups classified by baseline characteristics, risk of progression, and stratification factors.
- Hazard functions to analyze the magnitude and timing of treatment effect.

CONCLUSIONS OF TRIAL
- Bevacizumab improved PFS by about 2 months and increased the response rate by about 20% in patients with ovarian cancer. Survival benefits were greater among patients at high risk for progression with improved PFS of 3.6 months.
- Final overall survival results (Oza et al. 2015).
  - No difference in overall survival in the trial population as a whole.
  - OS benefit of 4 months seen in highest risk subgroup.

COMMENTS
- The benefit of bevacizumab changed over time with maximum impact at 12 months. The benefit disappeared by 24 months. The maximum treatment effect coincided with the end of bevacizumab treatment and suggest that prolonged therapy beyond 12 months may further improve outcomes.
- Because results showed evidence of nonproportional hazards, the restricted mean difference (the difference in areas under the whole length of the PFS curves) was a better estimate of treatment effect in this trial. The restricted mean difference of PFS was 20.3 months vs 21.8 months for standard therapy vs bevacizumab, for a mean difference of 1.5 months.

Table 2.21 Results of ICON7

Treatment arm	Standard chemotherapy (PC) N = 764	Bevacizumab (PCB) N = 764	Statistics
Patient characteristics			
Median age (range)	57 (18-81)	57 (24-82)	
≤1 cm residual	74%	74%	
>1 cm residual	26%	26%	
Inoperable	2%	2%	
High risk (III >1 cm/IV)	31%	30%	
Stage I/IIA	10%	9%	
Stage IIB/IIC	9%	9%	
Stage III	69%	68%	
Stage IV	12%	13%	
Serous	69%	69%	
Endometrioid	7%	8%	
Mucinous	2%	2%	
Clear cell	8%	9%	
Other	13%	12%	
Grade 1	7%	5%	
Grade 2	19%	23%	
Grade 3	74%	71%	
Treatment delivery			
Received 6 cycles	91%	94%	
Efficacy			
Reported in 2011			
Overall response rate	48%	67%	$P < .001$
Median PFS	17.4 months	19.8 months	HR 0.87, $P = .04$
High-risk group	10.5 months	16.0 months	HR 0.73, $P = .002$
Median OS	Not reached	Not reached	HR 0.85, P = NS
High-risk group	28.8 months	36.6 months	HR 0.64, $P = .002$
Reported in 2015			
Median OS	44.6 months	45.5 months	P = NS
Non-high-risk group	49.7 months	48.4 months	P = NS
High-risk group	34.5 months	39.3 months	HR 0.78, $P = .03$
Clear cell	48.0 months	47.6 months	P = NS
Low stage, high grade	56.2 months	57.5 months	P = NS
Low-grade serous	50.4 months	50.5 months	P = NS
Updated PFS analysis	17.5 months	19.9 months	P = NS
High-risk group	10.5 months	16.0 months	HR 0.73, $P = .001$

(continued)

Table 2.21 Results of ICON7 *(continued)*

Treatment arm	Standard chemotherapy (PC) N = 764	Bevacizumab (PCB) N = 764	Statistics
Toxicity			
Deaths	N = 1	N = 4	
Worse with bevacizumab			
Bleeding	12%	39%	
≥G2 hypertension	2%	18%	
≥G3 thromboembolism	3%	7%	
GI perforations	N = 3	N = 10	

GI, gastrointestinal; HR, hazard ratio; NS, not significant; PFS, progression-free survival; OS, overall survival.

- The addition of bevacizumab did not affect chemotherapy delivery but increased the range of toxic effects, including hypertension and bowel perforation.
- Differences between ICON7 and GOG 218: (1) patient population in ICON7 include patients with high-risk early-stage disease; (2) half of the dose of bevacizumab was used (7.5 mg/kg vs 15 mg/kg) for a shorter maintenance period (12 cycles vs 16 cycles).
- The bevacizumab dose used in ICON7 is one of the licensed doses for metastatic colorectal cancer but is half the dose for metastatic breast cancer.
- Final OS analysis demonstrated an association between increasing disease severity and greater benefit of bevacizumab.
- Women who might not benefit from bevacizumab in the upfront setting:
  - Early-stage I/II disease, even if high grade or clear cell histology.
  - Optimally debulked (<1 cm residual) stage III disease.
  - Low-grade serous cancer.
  - Low-stage, high-risk tumors.
- The maximum PFS benefit coincided with the duration of bevacizumab treatment. The overall survival difference outlasts the duration of exposure and suggests a durable benefit in the high-risk group. The possibility of additional benefit with extension of treatment is being evaluated in the BOOST trial (NCT01426890).
- Data from ICON7 support early use of bevacizumab based on risk and disease burden. The role of repeated administration of bevacizumab

in the recurrent setting after upfront use is being evaluated in the MITO16MANGO2b trial (NCT01802749). Benefit to this approach in colorectal and breast cancer (Bennouna et al. 2013; von Minckwitz et al. 2014).
- Trial suggests that residual tumor burden with active angiogenesis is necessary for drug activity.
- Cost-effectiveness would be improved with an effective biomarker predicting response.
  - May not work as well in immunologically active subtype.
  - May benefit mesenchymal subtype.

GOG 218 (Burger, NEJM 2011)

REFERENCE

- Burger RA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med*. 2011;365(26):2473-2483. PMID: 22204724. (Burger et al. 2011)

TRIAL SPONSOR

- Gynecologic Oncology Group (GOG)

RATIONALE FOR TRIAL

- VEGF and angiogenesis promote ovarian cancer progression and are inversely correlated with survival.
- Bevacizumab is a humanized anti-VEGF monoclonal antibody that inhibits tumor angiogenesis and has single-agent activity against epithelial ovarian cancer in phase II trials (Burger et al. 2007; Cannistra et al. 2007).
- This trial (like ICON7) was performed to evaluate the addition of bevacizumab to standard chemotherapy and as maintenance in the frontline treatment of ovarian cancer.

PATIENT POPULATION

- N = 1873 enrolled.
- Between October 2005 and June 2009, patients were enrolled from 336 institutions in the United States, Canada, South Korea, and Japan.
- Stage III or IV epithelial ovarian, primary peritoneal, or fallopian tube cancer.

- Standard abdominal surgery with maximal debulking effort within 12 weeks of study entry.
- GOG performance status of 0, 1, or 2.
- No history of clinically significant vascular events or intestinal obstruction.
- Patients with optimal resection (<1 cm residual lesions) were originally excluded but then later included after protocol modification in July 2007.

TREATMENT DETAILS

Arm 1: Standard Chemotherapy (PC)

- Treatment every 3 weeks for 22 cycles.
- Paclitaxel 175 mg/m^2 IV on day 1 during cycles 1 to 6.
- Carboplatin AUC 6 IV on day 1 during cycles 1 to 6.
- Placebo during cycles 2 to 22.

Arm 2: Standard Chemotherapy + Initiation Bevacizumab (PCB)

- Treatment every 3 weeks for 22 cycles.
- Paclitaxel 175 mg/m^2 IV on day 1 during cycles 1 to 6.
- Carboplatin AUC 6 IV on day 1 during cycles 1 to 6.
- Bevacizumab 15 mg/kg added during cycles 2 to 6.
- Placebo during cycles 7 to 22.

Arm 3: Standard Chemotherapy + Initiation Bevacizumab + 15 Months of Bevacizumab Maintenance (PCB + B)

- Treatment every 3 weeks for 22 cycles.
- Paclitaxel 175 mg/m^2 IV on day 1 during cycles 1 to 6.
- Carboplatin AUC 6 IV on day 1 during cycles 1 to 6.
- Bevacizumab 15 mg/kg added during cycles 2 to 22.

Treatment Discontinuation

- For disease progression, unacceptable toxic effects, completion of all 22 cycles or withdrawal.

Supportive Care Measures

- Myeloid growth factor allowed only to manage febrile neutropenia, grade 4 neutropenia (ANC <500/mm^3) for 7 days or longer or for subsequent prophylaxis

Dose Modifications

- For limiting peripheral neuropathy or hypersensitivity, paclitaxel was replaced with docetaxel 75 mg/m^2.

- For weight change >10%, bevacizumab dose was modified.
- Bevacizumab was delayed or discontinued based on duration and severity of:
  - Hypertension: systolic blood pressure >150 mm Hg or diastolic blood pressure >90 mm Hg.
  - Proteinuria: urine protein-to-creatinine ratio 3.5.
  - Wound or bowel wall disruption (any grade, cycle 2 or later).
  - Reversible posterior leukoencephalopathy syndrome.
  - Arterial thrombosis of grade 3 at any time or grade 2 during cycle 2 or later.
  - Venous thrombosis.
  - Coagulopathy.
  - Intestinal obstruction.
  - Hypersensitivity of grade 3 or greater.

ASSESSMENTS

- Before cycle 1: physical exam, CA125 level, and CT or MRI of at least abdomen and pelvis.
- For patients without progression, imaging after cycles 3, 6, 10, 14, 18, and 22.
- Serum CA125 and physical exams performed before each cycle during cycles 1 to 6, every other cycle during cycles 7 to 22, every 3 months for 2 years, every 6 months for years 3 to 5, and annually thereafter.
- Adverse events were recorded with every cycle using the National Cancer Institute Common Terminology Criteria for adverse events (Version 3) and until 30 days after last study treatment.
- Quality of life measured by the Functional Assessment of Cancer Therapy–Ovary Trial Outcome Index (FACT-O TOI) survey (Basen-Engquist et al. 2001) before cycles 1, 4, 7, 13, 22, and 6 months after completing study therapy.

ENDPOINTS

- Primary endpoint was initially OS, then changed to PFS in October 2008. This occurred when patients and investigators contested maintaining the blinding of treatment assignments after disease progression, which would be necessary to maintain the integrity of the data for an OS endpoint.
- PFS was calculated from date of enrollment to progression by RECIST (Therasse et al. 2000), increase in CA125 according to GCIG criteria

(Rustin et al. 2001) in patients who had completed chemotherapy, global deterioration of health, or death from any cause. If patients were free of progression, data were censored at the date of the last radiographic assessment.

STATISTICAL CONSIDERATIONS

Stratification Factors

- Patients were stratified by GOG performance status, cancer stage, and debulking status (stage III optimal, stage III suboptimal, stage IV).

Sample Size

- A sample size of 1800 was estimated to provide 90% power to detect a 23% reduction in the hazard of progression with either of the 2 bevacizumab-containing regimens compared to the control regimen while limiting the overall 1-sided type I error for both comparisons to 2.5%.

Statistical Tests

- Relative hazard ratios were estimated with the proportional hazards model (Cox 1972).
- Differences in FACT-O TOI scores were assessed with a linear mixed model adjusted for baseline score and age.
- Differences in adverse events were examined by Fisher's exact test (Mehta and Petal 1983).
- Hypotheses were tested at a 1.67% significance level to account for multiple comparisons.

Other Considerations

- Treatment assignments could be revealed to investigators and patients in the setting of documented disease progression.
- Database was locked on February 5, 2010.

CONCLUSION OF TRIAL

- The addition of bevacizumab during and up to 10 months after paclitaxel and carboplatin chemotherapy extends median PFS by 4 months but does not have an impact on OS in patients with advanced epithelial ovarian cancer.

Table 2.22 Results of GOG 218

Treatment arm	PC N=625	PCB N=625	PCB+B N=623
Patient characteristics			
Median age (range)	60 (25-86)	60 (24-88)	60 (22-89)
White	84.2%	83.0%	83.6%
Asian	6.6%	5.9%	6.3%
Black	4.0%	4.5%	4.3%
Hispanic	3.4%	4.5%	4.0%
Other	1.9%	2.1%	1.8%
Stage III, ≤1 cm	34.9%	32.8%	34.7%
Stage III, >1 cm	40.6%	41.0%	38.8%
Stage IV	24.5%	26.2%	26.5%
Serous	86.6%	83.0%	84.1%
Endometrioid	3.4%	2.2%	3.9%
Mucinous	1.0%	0.8%	1.3%
Clear cell	1.9%	3.7%	3.2%
Other	7.2%	10.2%	7.5%
Grade 1	5.8%	4.5%	2.9%
Grade 2	16.3%	13.8%	15.6%
Grade 3	71.2%	74.4%	73.8%
Unknown grade	6.7%	7.4%	7.7%
Treatment delivery			
Completed therapy	16%	17%	24%
Discontinuation			
Disease progression	48%	42%	26%
Adverse events	12%	15%	17%
Efficacy			
Median PFS[a]	10.3 months	11.2 months (P=NS)	14.1 months (P=.001)
Median OS[a]	39.3 months	38.7 months (P=NS)	39.7 months (P=NS)
Toxicity			
Deaths	1%	1.6%	2.3%
Worse with bevacizumab ≥G2 hypertension[a]	7.2%	16.5% (P<.05)	22.9% (P<.05)
No difference			
GI perforation, fistula	1.2%	2.8%	2.6%
≥G3 proteinuria	0.7%	0.7%	1.6%
≥G2 pain	41.6%	41.5%	47.0%
≥G4 neutropenia	57.5%	63.3%	63.3%
Venous thrombosis	5.8%	5.3%	6.7%

(continued)

Table 2.22 Results of GOG 218 *(continued)*

Treatment arm	PC N=625	PCB N=625	PCB+B N=623
Arterial thrombosis	0.8%	0.7%	0.7%
Wound disruption	2.8%	3.6%	3.0%
CNS bleeding	0	0	0.3%
Non-CNS bleeding	0.8%	1.3%	2.1%
PRES	0	0.2%	0.2%

CNS, central nervous system; GI, gastrointestinal; NS, not significant; PFS, progression-free survival; OS, overall survival; PC, paclitaxel+carboplatin; PCB, paclitaxel+carboplatin+bevacizumab; PCB+B, paclitaxel+carboplatin+bevacizumab followed by bevacizumab maintenance; PRES, posterior reversible encephalopathy syndrome.

[a]*P* values are compared to PC control arm.

COMMENTS

- Bevacizumab (or placebo) was added in cycle 2 rather than cycle 1 to decrease the risk of wound-healing complications. The maintenance treatment time of 15 months was selected to exceed the anticipated median PFS and to ensure feasibility. The bevacizumab dose of 15 mg/kg every 3 weeks was selected based on the approved combination with carboplatin and paclitaxel for advanced non–small cell lung cancer.
- Most adverse events were reported during chemotherapy. All but one gastrointestinal (GI) perforation/fistula occurred during chemotherapy. Exceptions included hypertension, proteinuria, and pain, which were more commonly reported during the extended phase in patients receiving maintenance bevacizumab.
- This cohort had relatively poor prognosis with 40% with suboptimal stage III and 26% with stage IV disease.
- The maximum separation in the PFS curves (PC vs PCB+B) occurred at 15 months with convergence of the curves 9 months later. This convergence of PFS curves was also seen in the ICON7 trial (which used 12 months of maintenance bevacizumab). There was no convergence of PFS curves in the OCEANS trial (for recurrent ovarian cancer) in which bevacizumab was used until disease progression and not discontinued at a predefined time. This suggests that the magnitude of benefit may correlate directly with treatment duration and is consistent with preclinical studies that demonstrate regrowth of tumor upon discontinuation of anti-VEGF therapy (Bagri et al. 2010).
- The improvement in PFS was consistent across different subgroup analyses (Figure 2C in manuscript).

- There was no reduction in quality of life with the addition of bevacizumab.
- There was no improvement in OS, but the ability to detect a difference may be limited by later crossover to receiving bevacizumab or other anti-VEGF agents.
- Bevacizumab increased the risk of hypertension, which appeared to be cumulative, but this tended to be controlled with medical therapy and did not lead to many treatment discontinuations.
- The lack of survival difference between control and bevacizumab initiation suggests that bevacizumab must be continued as a maintenance therapy to delay disease progression.
- The change in primary endpoint from OS to PFS is a major limitation of this study. The authors note that the GCIG supports the use of PFS as a primary endpoint for trials evaluating front-line therapy because of the influences of postprogression therapy on OS (Stuart et al. 2011).

MITO-7 (Pignata, Lancet Oncol 2014)

REFERENCE

- Pignata S, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2014;15(4): 396-405. PMID: 24582486. (Pignata et al. 2014)

TRIAL SPONSORS

- MITO-7 (Multicentre Italian Trials in Ovarian Cancer)
- ENGOT-OV-10 (European Network of Gynaecological Oncological Trial Groups)
- GCIG (Gynecologic Cancer InterGroup) Trial

RATIONALE FOR TRIAL

- Standard paclitaxel-carboplatin chemotherapy every 3 weeks is toxic and causes alopecia, neurotoxicity, and fatigue.
- Weekly paclitaxel may reduce toxicity by decreasing the peak concentrations and increase efficacy by reducing tumor regrowth and providing an antiangiogenic effect.
- Weekly paclitaxel in patients with recurrent ovarian cancer resulted in fewer hematologic and neurologic side effects.

- This trial sought to investigate whether weekly carboplatin and paclitaxel is more effective than the every 3-week regimen.

PATIENT POPULATION

- N = 822.
- Recruited from 67 institutions in Italy and France from November 2008 to March 2012.
- Women older than 18 years.
- Stage IC to IV epithelial ovarian, fallopian tube, or peritoneal cancer.
- ECOG performance status 0 to 2.
- Life expectancy of at least 3 months.
- Adequate bone marrow, kidney, and liver function.
- Excluded if clinically relevant heart disease or other contraindication to treatment.
- Randomization after initial surgery and staging.

TREATMENT DETAILS

Arm 1: Standard Regimen Every 21 Days

- Paclitaxel starting dose 175 mg/m^2 infused over 3 hours.
- Carboplatin AUC 6 mg/mL per minute, Calvert formula, creatinine clearance estimated by Cockcroft-Gault formula.
- Hematologic parameters to treat were more restrictive than in the weekly treatment with WBC >3000//μL, ANC >1500/μL, platelets >100,000/μL.
- Dose reduction of all drugs by 20% if ANC <500/μL or platelets <50,000/μL for 7 days or longer.
- Dose reduction by 25% for grade 2 neuropathy.
- Treatment discontinuation for prolonged toxic effects causing treatment delay of 2 weeks or longer.

Arm 2: Weekly Regimen

- Paclitaxel 60 mg/m^2 infused over 1 hour weekly for 18 weeks.
- Carboplatin AUC 2 mg/mL per minute infused over 30 minutes for 18 weeks.
- Hematologic parameters to treat—WBC >3000/μL, ANC >1000/μL, platelets >75,000/μL.
- Dose reduction of all drugs by 20% if ANC <500/μL or platelets <50,000/μL for 7 days or longer.
- Dose reduction by 25% for grade 2 neuropathy.

- Treatment discontinuation for prolonged toxic effects causing treatment delay of 2 weeks or longer.

Surgery

- Interval debulking surgery was allowed after 3 cycles.

ASSESSMENTS

- Baseline CT or nuclear magnetic resonance (NMR) and CA125.
- Imaging after 3 and 6 cycles of chemotherapy, response assessed by RECIST version 1.0 (French centers did not image after 3 cycles if clinical suspicion of progression was absent).
- Quality of life assessed by FACT-O version 4.
  - FACT-O/TOI (trial outcome index) calculated by adding scores from physical, functional, and ovarian cancer-specific subscales.
- Neurotoxicity assessed by FACT/GOG-Ntx.
- Adverse events graded according to CTCAE version 3.0.

ENDPOINTS

- Quality of life, measured by FACT-O/TOI score (primary endpoint).
- PFS (co-primary endpoint). In 2010, PFS was added as co-primary endpoint after publication of the JGOG NOVEL trial showed 11-month prolongation of PFS.
- Overall survival.
- Toxic effects.
- Proportion of patients who achieved an objective response (complete or partial response).

STATISTICAL CONSIDERATIONS

Sample Size

- Sample size of 350 patients calculated to find a difference between arms in FACT-O/TOI changes between baseline and 9 weeks of 0.30 with α of 0.05 and power of 80%.
- Sample size adjusted to 810 patients to detect a 0.75 hazard ratio of progression (median PFS from 18 to 24 months) with α of 0.05 and an interim analysis of efficacy after half of events had occurred.

CONCLUSION OF TRIAL

- Weekly carboplatin and paclitaxel.
  - Does not improve progression-free survival.

Table 2.23 Results of MITO-7

Treatment arm	Every 3 weeks N=404	Weekly N=406	Statistics
Patient characteristics			
Median age (range)	59 (29-83)	60 (23-87)	
No residual	41%	41%	
≤1 cm residual	12%	12%	
>1 cm residual	23%	23%	
No surgery	25%	24%	
Stage IC	6%	8%	
Stage II	8%	8%	
Stage III	63%	58%	
Stage IV	23%	27%	
Serous	72%	67%	
Endometrioid	8%	12%	
Clear cell	6%	5%	
Mucinous	2%	2%	
Other	12%	14%	
Grade 3	71%	66%	
Treatment delivery			
Interval debulking	20%	17%	
Received all treatment	90%	83%	
Stopped for toxicity	4%	8%	
At least 1 delay	62%	79%	
Dose reduction	36%	19%	
Carboplatin dose intensity	82.7%	76.6%	
Paclitaxel dose intensity	86.8%	79.1%	
Efficacy			
PFS (95% CI)	17.3 months (15.2-20.2)	18.3 months (16.8-20.9)	HR 0.96, *P*=NS
24-month survival	78.9%	77.3%	HR 1.20, *P*=NS
Objective response rate	58.8%	56.2%	
Toxicity			
FACT-O/TOI	QOL scores declined after every chemotherapy cycle	QOL scores declined after week 1, then stabilized	
Deaths	N=3	N=5	
Worse with q 3 weeks			
G3-4 neutropenia	50%	42%	
Febrile neutropenia	3%	0.5%	
≥G2 neuropathy	17%	6%	
≥G2 hair loss	59%	29%	
Worse with weekly			
≥G2 pulmonary	3%	5%	

CI, confidence interval; FACT-O/TOI, Functional Assessment of Cancer Therapy—Ovarian/Trial Outcome Index; HR, hazard ratio; NS, not significant; PFS, progression-free survival; QOL, quality of life.

- Better toxicity profile and better quality of life.
- Less adherence to treatment schedule, challenging regimen.

- Carboplatin and paclitaxel every 3 weeks.
  - More frequent and severe hematologic toxicity, vomiting, neuropathy, hair loss.

COMMENTS

- Differences between NOVEL and MITO-7 every 3-week treatment arms.
- Frequency and severity of toxicities were higher in NOVEL trial.
  - G3-4 neutropenia—88% vs 50%.
  - Thrombocytopenia—38% vs 7%.
  - Anemia—44% vs 8%.
- Suggests possible genetic reasons for drug sensitivity.
- Similar PFS for q 3-week treatment arm across studies, but PFS differed in the weekly regimens.
- Dose of weekly paclitaxel was 80 mg/m^2 in NOVEL compared to 60 mg/m^2 in MITO-7. Dose density may be needed to improve outcomes.
- Carboplatin every 3 weeks may be more efficacious than carboplatin every week; weekly carboplatin may antagonize the effects of paclitaxel.