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A meta-analysis of the efficacy of intraperitoneal cisplatin for the front-line treatment of ovarian cancer

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Abstract. Hess LM, Benham-Hutchins M, Herzog TJ, Hsu C-H, Malone DC, Skrepnek GH, Slack MK, Alberts DS. A meta-analysis of the efficacy of intraperitoneal cisplatin for the front-line treatment of ovarian cancer. *Int J Gynecol Cancer* 2007;**17:**561–570.

Ovarian cancer is the fourth leading cause of cancer death among women in the United States. First-line chemotherapy offered to patients with ovarian cancer generally consists of an intravenous (IV) platinum plus taxane regimen and has remained virtually unchanged for the past 10 years. A number of recently completed phase III randomized trials in the United States have reported improved progression-free survival (PFS) and/or overall survival (OS) with the intraperitoneal (IP) administration of cisplatin. The purpose of this study was to pool the published data to perform a meta-analysis of randomized trials of IP cisplatin in the initial chemotherapy treatment of ovarian cancer patients. This study was initiated to obtain a more valid estimate of the therapeutic impact of IP treatment for these patients. A search strategy was initiated that searched published findings of randomized trials of IP cisplatin therapy from multiple sources from January 1990 through January 2006. Six randomized trials of 1716 ovarian cancer patients were identified and included in this analysis. The pooled hazard ratio (HR) for PFS of IP cisplatin as compared to IV treatment regimens is 0.792 (95% CI: 0.688–0.912, $P = 0.001$), and the pooled HR for OS is 0.799 (95% CI: 0.702–0.910, $P = 0.0007$). These findings strongly support the incorporation of an IP cisplatin regimen to improve survival in the front-line treatment of stage III, optimally debulked ovarian cancer.

KEYWORDS: cisplatin, intraperitoneal, meta-analysis, ovarian cancer, survival.

Ovarian cancer was projected to occur in approximately 20,180 women and to cause an estimated 15,310 deaths in 2006[1]. Despite aggressive surgical and chemotherapy management, most women who are diagnosed with ovarian cancer will not be cured; these women will experience disease recurrence and will eventually die from the disease.

The standard treatment regimen for all advanced ovarian cancers generally consists of six courses of carboplatin plus paclitaxel therapy[2]. Since the mid-1990s, there have been more than 400 publications that focus on clinical trial results from phase I–III clinical trials in ovarian cancer patients. Despite the financial investment in clinical research, numerous published data, and the development and continuation of phase II–III research trials, the standard front-line treatment regimen has remained virtually unchanged for nearly 10 years. Death rates have not demonstrated significant improvement over time since establishment of the taxane era, particularly with regard to women aged 65 and older[3].

A number of phase II and III trials have investigated the role of intraperitoneal (IP) administration of a variety of chemotherapeutic agents to improve survival outcomes in ovarian cancer patients. The rationale for the IP administration of cisplatin and other agents is

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based on the ability to reach higher peak concentrations in the peritoneal cavity than is possible when delivered intravenously. In an early study by Howell *et al.*[4], IP cisplatin (90 mg/m^2) was shown to result in extremely high concentrations of cisplatin bathing the ovarian cancer tumor bed (97.1 μg·h/mL), while also delivering relatively high concentrations of cisplatin into the plasma (7.2 μg·h/mL). This was a 15-fold greater exposure of the peritoneal cavity than was achieved by intravenous (IV) administration of 100 mg/m^2 cisplatin. Theoretically, if there is only minimal residual cancer volume following surgery, IP cisplatin therapy can attack the tumor cells from both the outer core (by direct contact) and the inner core by recirculation through the bloodstream into small tumor arterioles. However, if bulky tumor (eg, >2 cm) remains, IP administration is thought to have little or no advantage; in preclinical models, cisplatin molecules are only able to penetrate approximately 4 mm from the outer tumor surface, and bulky disease will interfere with the distribution of the agent throughout the peritoneal cavity[5]. Alternative hypotheses are related to the overall less favorable prognosis of all ovarian cancer patients with suboptimal disease[6].

Three recently completed phase III randomized trials in the United States have all documented improved progression-free survival (PFS) and/or overall survival (OS) with IP administration of cisplatin. These studies, led by the Gynecologic Oncology Group (GOG), Southwest Oncology Group (SWOG), and the Eastern Cooperative Oncology Group (ECOG), include SWOG-8501[7], GOG-114[8], and GOG-172[9]. As discussed in an editorial in the *Journal of Clinical Oncology*[10], the results of these studies alone have not significantly altered the community standard of care for patients diagnosed with ovarian cancer. A need exists for an objective evaluation of the published data to guide both clinical practice and patient decision making, as women and their physicians are faced with treatment decisions that will impact both quality and quantity of life before such changes are implemented.

Unlike a systematic review, which summarizes research trial data individually while making summary conclusions, a meta-analysis mathematically combines data to produce a statistical analysis of a set of published research results[11]. This methodology enables a summary of the results of multiple studies and an increase in the power to detect significant changes while taking into account between-study variations. This allows "a more objective appraisal of the evidence than traditional narrative reviews, provides a more precise estimate of a treatment effect, and may explain heterogeneity between the results of individual studies"[12]. When conducted properly, meta-analyses can provide a summary of research to benefit the clinician, patient, and the research community.

The purpose of this study was to perform a meta-analysis of randomized trials of IP cisplatin in the initial adjuvant chemotherapy treatment of ovarian cancer. This meta-analysis was designed to more accurately quantify the effect of IP cisplatin treatment in the setting of newly diagnosed ovarian cancer. The primary outcomes of interest include PFS, OS, and toxicity.

Materials and methods

Identification of trials

An article search was conducted in Medline, PubMed, and the Cochrane Register of Controlled Trials. In addition, abstract databases from the Society of Gynecologic Oncologists and the American Society of Clinical Oncology were reviewed. Clinicaltrials.gov and clinicaltrialresults.org were searched to identify trials that may have not been published. Searches were limited to the time period of January 1, 1990, through August 31, 2006, with the exception of Society of Gynecologic Oncologists and American Society of Clinical Oncology, which each provided abstracts from 2000 through 2006. The search terms ovarian neoplasms, ovarian carcinoma, or ovarian cancer were combined with IP, IP injections, or injections, IP. Studies to be considered for study inclusion were required to contain at least one ovarian and one IP term as well as the term cisplatin. All terms were expanded to include all subcategories in an attempt to obtain all published research that fit inclusion criteria; no language restrictions were made. Inclusion criteria included randomized trials of front-line ovarian cancer treatment with IP cisplatin as at least one agent on at least one treatment arm. Exclusion criteria included nonrandomized trials, trials that did not include IP cisplatin in at least one of the treatment regimens, case reports or review articles, post–front line treatment regimen trials, studies of nonovarian/nonperitoneal cancers or multiple disease sites, and studies that involved hyper- or hypothermia. All resulting citation abstracts were reviewed for potential eligibility; in the case that the abstract did not provide enough detail for the determination of eligibility, the full article text was obtained for further evaluation.

Study quality

Study quality was evaluated using the PEDro Scale[13], which contains elements designed to assess randomized controlled trials as well as all key features

of other frequently used, validated quality scales (Delphi and Jadad). Quality factors included specified eligibility criteria; concealed allocation to study groups; study groups similar at baseline, subject, physician, and outcome assessor blinding; outcome data for greater than 85% of those allocated to treatment groups; intention-to-treat design; and between group, point measures, and variability data reported for at least one key outcome. Each of the 11 factors is awarded "1" when the criterion is clearly satisfied. As blinding is not readily feasible in chemotherapy trials comparing administration routes, the highest possible quality score for the trials included in this meta-analysis is 8.

Data abstraction

The following data were independently abstracted by two reviewers (L.M.H. and M.B.H.) for this meta-analysis: publication year; number of patients; mean age; percent presenting with stage IV disease; definition of optimal cytoreduction, agents, dosage, and prescribed administration schedule of agents administered in each treatment arm; median PFS; median OS; OS and PFS hazard ratio (HR) and confidence intervals (CIs); percent presenting with optimal disease; percent of each grade 3 or greater toxicity; and treatment-related deaths. The two reviewers compared results of the abstraction for accuracy and came to an agreement on any discrepancies. In the case of disagreement, a third reviewer (D.S.A.) served as the "tiebreaker".

Statistical analysis

For those studies that did not report the HR, the method of Parmar *et al.*[14] was used to calculate log HR. All HRs were calculated with associated 95% CIs. PFS, OS, and toxicity outcomes were analyzed using Comprehensive Meta-Analysis version 2.2.023 (New York, NY) using a random-effects model. Planned sensitivity analyses were conducted for the following: to exclude studies with less than and greater than 100 mg/m^2 IP cisplatin, respectively; to exclude studies with poor study quality[15]; and to exclude studies that included patients with less than stage III disease. Additional sensitivity analyses were conducted to systematically remove individual trials from the survival analyses to ensure that any one study did not bias the overall summary.

Meta-analyses are designed to pool independent research trials, but results could be biased if there is significant between-study variance. A test of homogeneity (the Q statistic) was conducted prior to analysis of survival outcomes. This test assesses if the variability around the mean between studies is larger than that would be expected from sampling error alone[16], and essentially tests whether the various trials included in a meta-analysis are testing a common parameter, or if there is random variation among trials that may be due to population or design issues[17]. Therefore, a statistically significant Q statistic would require that the meta-analysis use a random-effects model to include both within-study variance and between-study variance in the pooled analyses and may additionally require that analyses be undertaken to investigate the sources of heterogeneity[17]. Given the bias in the literature for studies that demonstrate significant findings, the concept of a "fail-safe N" was developed[18]. The fail-safe N refers to the number of unpublished, negative study results that would be needed to lower the results of a meta-analysis to a nonsignificant level, or that would bring the probability of a type I error to 0.05[19]. The fail-safe N analysis was conducted as part of this meta-analysis. Two additional methods of assessing publication bias were included: Egger's regression intercept (a test for significance is conducted to evaluate the null hypothesis of symmetry)[20] and a rank correlation test for publication bias (statistical presentation of a funnel plot for bias)[21].

Results

Search strategy

Based on the above search criteria, six articles were identified for inclusion in the meta-analysis (Fig. 1 and Table 1). Three of the studies were conducted by cooperative groups in the United States (GOG-172, GOG-114, and SWOG-8501/GOG-104)[7–9], one was a single institution study (University of California at San Diego [UCSD])[22], one trial was conducted in Taiwan[23], and another study was completed in Italy by the Northwest Oncology Group (NWOG)[24]. The United States cooperative group trials were larger (>200 patients per treatment arm) than the other studies, which each enrolled less than 100 patients per treatment arm. Median OS of each trial is presented in Figure 2. No data used in this meta-analysis required the need for a tiebreaker; the two reviewers (L.M.H. and M.B.H.) were able to agree on all data abstracted.

Patient and treatment characteristics

Patient and treatment characteristics of the 1716 patients from these six studies are shown in Table 2. Each study was individually balanced between

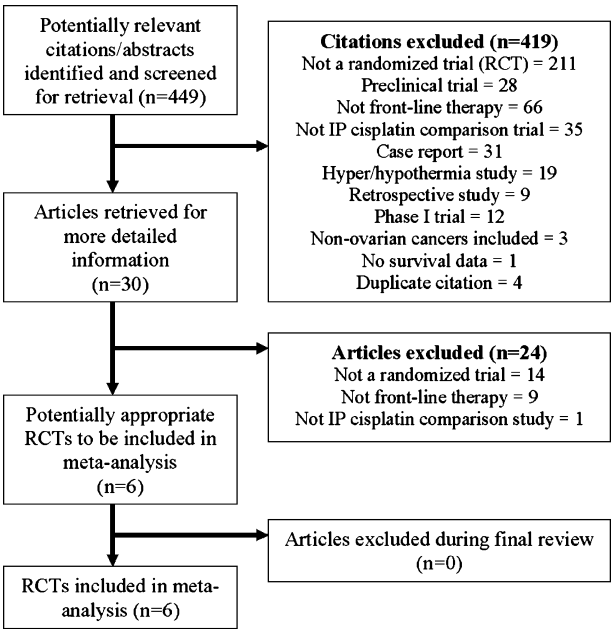


Figure 1. QUOROM (Quality of Reporting of Meta-Analyses) statement flow diagram.

treatment arms in terms of baseline prognostic factors. The OS meta-analysis is based on summary data from 1716 ovarian cancer patients (868 randomized to IV regimens and 848 randomized to IP cisplatin-containing regimens). The PFS meta-analysis is based on summary data from 1052 ovarian cancer patients (526 randomized to IV therapy and 526 randomized to IP cisplatin-based therapy).

Homogeneity of trials

Tests of homogeneity found that there was no significant between-study variation ($Q = 1.596$, $P = 0.66$ for PFS; $Q = 4.262$, $P = 0.512$ for OS). Despite the homogeneity of trials in this meta-analysis, all analyses were conducted with a random-effects model as planned.

Survival

OS data were available for each of the six studies; GOG-114 reported 90% CIs, so these data were

Table 1. Studies included in meta-analysis

Primary author (year)	Study	Number eligible IV	Number eligible IP	IV regimen	IP regimen
Alberts (1996)	SWOG-8501/ ECOG/GOG-104	279	267	Cisplatin 100 mg/m^2 IV + cyclophosphamide 600 mg/m^2 IV every 3 weeks for six cycles	Cisplatin 100 mg/m^2 IP + cyclophosphamide 600 mg/m^2 IV every 3 weeks for six cycles
Armstrong (2006)	GOG-172	210	205	Paclitaxel 135 mg/m^2 over 24 h IV day 1 + cisplatin 75 mg/m^2 IV day 2 every 3 weeks for six cycles	Paclitaxel 135 mg/m^2 over 24 h IV day 1 + cisplatin 100 mg/m^2 IP day 2 + paclitaxel 60 mg/m^2 IP day 8 every 3 weeks for six cycles
Gadducci (2000)	NWOG	57	56	Cisplatin 50 mg/m^2 IV + epidoxorubicin 60 mg/m^2 IV + cyclophosphamide 600 mg/m^2 IV every 4 weeks for six cycles	Cisplatin 50 mg/m^2 IP + epidoxorubicin 60 mg/m^2 IV + cyclophosphamide 600 mg/m^2 IV every 4 weeks for six cycles
Kirmani (1994)	UCSD	33	29	Cisplatin 100 mg/m^2 IV + cyclophosphamide 600 mg/m^2 IV every 3 weeks for six cycles	Cisplatin 200 mg/m^2 IP + etoposide 350 mg/m^2 IP every 4 weeks for six cycles
Markman (2001)	SWOG/ECOG/ GOG-114	227	235	Paclitaxel 135 mg/m^2 IV over 24 h on day 1 + cisplatin 75 mg/m^2 IV day 2 every 3 weeks for six courses	Carboplatin (AUC = 9) IV every 4 weeks for two courses, followed 4 weeks later by paclitaxel 135 mg/m^2 IV over 24 h on day 1 + cisplatin 100 mg/m^2 IP on day 2 every 21 days for six courses
Yen (2001)	Veterans General Hospital, Taipei (Taipei study)	63	55	Cyclophosphamide 500 mg/m^2 IV over 1 h day 1 + adriamycin or epirubicin 50 mg/m^2 over 1 h IV day 1 + cisplatin 50 mg/m^2 IV every 3 weeks for six courses	Cyclophosphamide 500 mg/m^2 IV over 1 h day 1 + adriamycin or epirubicin 50 mg/m^2 over 1 h IV day 1 + cisplatin 100 mg/m^2 IP rapid infusion every 3 weeks for six courses

AUC, area under the curve.

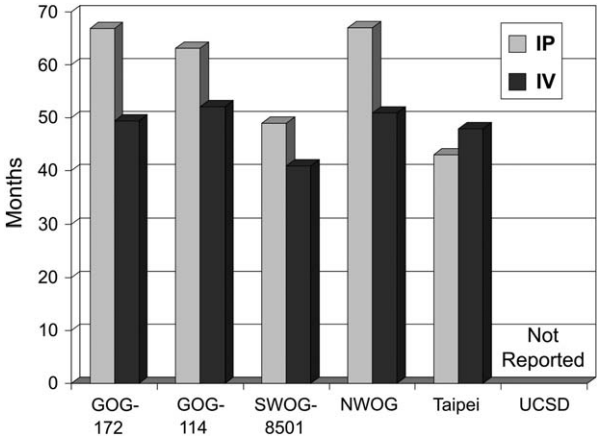


Figure 2. Median OS (months).

adjusted to be consistent with the 95% CIs reported in the other studies. The NWOG study provided the number of observed and expected events, which were transformed into HRs using the method of Parmar *et al.*[14]. The UCSD PFS and OS data provided were limited (eg, OS data were only available from the survival curves); therefore, the summary statistics for this study were obtained from Jaaback and Johnson using the Parmar method[14,25]. Two studies (SWOG-8501 and Taipei) did not report PFS, thus four studies were included in the PFS analysis. Summary data for each study and the pooled values for PFS and OS are shown in Tables 3 and 4, respectively. These tables demonstrate the HRs for each study and the pooled results of the analyses both in numeric and in graphic formats, with values below 1.0 indicating results in favor of IP therapy and values above 1.0 in favor of the IV regimen. The pooled HR for PFS of IP cisplatin treatment as compared to IV treatment regimens is 0.79 (95% CI: 0.69–0.91, $P = 0.001$). The pooled HR for OS of IP cisplatin treatment compared to IV treatment is 0.80 (95% CI: 0.70–0.91, $P = 0.0007$).

Study quality and publication bias

Study quality was similar among all trials (quality = 7 for all trials but the UCSD trial, which had a quality score of 6 because less than 85% of those enrolled to the trial were available for the endpoint survival analysis). The fail-safe N analysis concluded that six negative studies would be needed to bring the P value of the OS pooled analysis to nonsignificance (eg, to bring the P value >0.05). There was no evidence of publication bias (Begg and Mazumdar rank correlation test, Kendall's tau = 0.067, $P = 1.0$).

Sensitivity analyses

When the study that involved an IP cisplatin dose less than 100 mg/m^2 (NWOG study) was removed from the OS analysis, the resulting HR was 0.808 (95% CI: 0.707–0.923, $P = 0.002$). When the two studies that included stage II disease (NWOG and UCSD studies) were removed from the analysis, the resulting HR was 0.794 (95% CI: 0.693–0.910, $P = 0.0009$). When the study with greater than 100 mg/m^2 of IP cisplatin dose was removed from the analysis (UCSD study), the HR for OS was 0.786 (95% CI: 0.689–0.898, $P = 0.0004$).

Sensitivity analyses of PFS removing the study with less than 100 mg/m^2 IP cisplatin (NWOG study) resulted in a PFS HR of 0.802 (95% CI: 0.692–0.930, $P = 0.003$). When the two studies that included stage II disease (NWOG and UCSD studies) were removed from the analysis, the resulting PFS HR was 0.789 (95% CI: 0.679–0.917, $P = 0.002$). When one study that used greater than 100 mg/m^2 dose of IP cisplatin (UCSD Study) was removed, the resulting HR for PFS was 0.781 (95% CI: 0.676–0.901, $P = 0.001$).

For OS, removing SWOG-8501 from the analysis had the greatest impact on lessening the strength of the pooled HR, yet this still did not reduce the results to the point of nonsignificance (HR = 0.819, 95% CI: 0.699–0.960, $P = 0.01$). For PFS, removing GOG-114 had the greatest impact on lessening the significance of the results, yet again remained statistically significant in favor of the IP cisplatin regimens (HR = 0.804, 95% CI: 0.662–0.977, $P = 0.028$). Additional sensitivity analyses based on study quality could not be performed due to similarities in PEDro Scale values among the six studies.

Toxicity

The primary grade 3 or greater toxicities reported by the six trials included in this meta-analysis are shown in Table 5. The random-effects model analyses of toxicities found no statistically significant pooled risk for grade 3 or greater leukopenia (six studies, OR = 1.07, 95% CI: 0.66–1.75), hemoglobin toxicity (four studies, OR = 0.88, 95% CI: 0.58–1.35), platelet toxicity (six studies, OR = 1.5, 95% CI: 0.32–7.04), neurotoxicity (five studies, OR = 1.21, 95% CI: 0.59–2.49), or treatment-related death (three studies, OR = 1.4, 95% CI: 0.50–3.97).

However, there was a significant increased risk among those treated with IP cisplatin of grade 3 or greater gastrointestinal symptoms (four studies, OR = 1.95, 95% CI: 1.17–3.24, $P = 0.01$) and fever (four studies, OR = 1.7, 95% CI: 1.02–2.84, $P = 0.04$). There was

Table 2. Patient and treatment characteristics

	SWOG-8501	NWOG study	GOG-114	Taipei study	GOG-172	UCSD study
% ineligible after randomization						
IV	15.7	0	12.7	10.6	2.3	15.4
IP	17.3	0	10.6		4.2	23.7
Residual tumor status, %						
IV	No gross: 26	None: 12.3	No evidence: —	NR	No gross: 36	≤1 cm: 62.1
	Minimal residual: 72	Microscopic: 8.8	Microscopic: 36		Gross residual: 64	>1 cm: 37.9
		Macroscopic: 78.9	Gross residual: 64			
IP	No gross: 25	None: 10.7	No evidence: —	NR	No gross: 38	≤1 cm: 45.5
	Minimal residual: 73	Microscopic: 17.9	Microscopic: 35		Gross residual: 62	>1 cm: 51.5
		Macroscopic: 71.4	Gross residual: 65			Unknown: 3
Mean age, years						
IV	54.5	53.3	[a]	54.6	[a]	57.6
IP	55	54.7	[a]	52.8	[a]	58.7
Stage, %						
IV	I: —	I: —	I: —	I: —	I: —	I: —
	II: —	II: 12.3	II: —	II: —	II: —	II: 15.2
	III: 100	III: 86.0	III: 100	III: 100	III: 100	III: 72.7
	IV: —	IV: 1.7	IV: —	IV: —	IV: —	IV: 12.1
IP	I: —	I: —	I: —	I: —	I: —	I: —
	II: —	II: 19.6	II: —	II: —	II: —	II: 13.8
	III: 100	III: 76.8	III: 100	III: 100	III: 100	III: 69
	IV: —	IV: 3.6	IV: —	IV: —	IV: —	IV: 17.2
% completed all assigned courses						
IV	58	96.5	86	31.7	83	60
IP	58	64.3[b]	71	25.5	42[c]	76
Mean number of treatment cycles completed						
IV	4.6	NR	5.6	4.6	5.4	4.9
IP	5.0	NR	4.9	4.1	3.7	5.0
Median PFS, months						
IV	NR	25	22.2	NR	18.3	14
IP	NR	42	27.9	NR	23.8	12
Median OS, months (95% CI)						
IV	41 (34–47)	51 (NR)	52.2 (NR)	48 (37–59)	49.7 (NR)	NR
IP	49 (42–56)	67 (NR)	63.2 (NR)	43 (31–54)	65.6 (NR)	NR

NR, not reported.
[a]Categorical data reported only; greater than 60% younger than 60 years.
[b]Twenty patients crossed over from IP to IV during trial; mean number of cycles before crossover = 1.65.
[c]Eighty-four patients crossed over from IP to IV during trial; mean number of cycles before crossover unknown.

a significant increased risk of ototoxicity those randomized to IV therapy (OR = 0.38, 95% CI: 0.19–0.73, $P = 0.004$); however, only two studies (SWOG-8501 and UCSD study) provided data for this analysis.

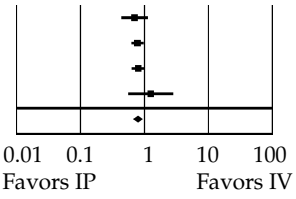
Based on the fail-safe N analysis, the number of additional negative studies that would be needed to change the significant results of the significant pooled toxicity results was 18 for gastrointestinal toxicities and 4 for fever. Publication bias statistics could not be run on ototoxicity because of the few studies reporting this toxicity.

Discussion

The treatment of ovarian cancer has been a challenge for gynecological oncologists due to the relatively rapid emergence of platinum resistance following initial therapy and the subsequent high recurrence rates, as well as the number of patients who present with advanced, unresectable, bulky disease. Despite the results of several phase III randomized trials that have demonstrated improved survival with IP therapy, standard front-line therapy has remained largely unchanged for nearly 10 years. This has, in part, been due to the lack of training of healthcare personnel at all levels concerning the modern methods of IP therapy and perception of increased toxicity and related costs associated with some IP regimens. The advances in therapy of stage III, optimally debulked disease have been translated only marginally into the everyday practice setting, and progress in the treatment of ovarian cancer has unnecessarily been slowed.

Table 3. Pooled PFS

Study name	Statistics for each study				HR and 95% CI	*P* Value
	HR	Lower limit	Upper limit	*Z* value		
NWOG	0.704	0.443	1.120	−1.483		0.138
GOG-114	0.780	0.636	0.957	−2.383		0.017
GOG 172	0.800	0.640	1.000	−1.960		0.050
UCSD	1.260	0.571	2.783	0.572		0.568
Random effects	0.792	0.688	0.912	−3.233		0.001



Although IP therapies in general are of interest to the scientific community, IP cisplatin was selected as the focus of this meta-analysis due to the number of patients enrolled on trials that could potentially be included in this study. Future meta-analyses should be conducted to assess the value other agents, respectively, that have been administered intraperitoneally in the randomized trial setting. Unlike the Cochrane review, which assessed route of administration for ovarian cancer[25], this meta-analysis specifically assesses the value of IP cisplatin in the front-line setting of ovarian cancer treatment.

The present meta-analysis has summarized the data from six randomized trials of IP cisplatin and found a consistent, highly statistically significant improvement in both PFS and OS, particularly among patients with stage III disease. When studies were assessed individually, this consistent, significant relationship is not as clearly evident—only three of six studies showed significant improvement in OS. However, the strength of a meta-analysis is that the analysis provides the ability to increase the statistical power to detect a difference between treatments or interventions. The three studies that did not demonstrate a significant improvement in survival all enrolled less than 100 patients per treatment arm, and each of the three negative studies were either closed earlier than anticipated due to lack of accrual (NWOG and UCSD studies) or failed to meet stated accrual goals for adequate power (Taipei study). These studies alone could not make a decisive statement about survival related to IP cisplatin therapy, but when combined with other trials, the results of the nonsignificant trials did not cancel out the effect of the larger trials, but rather further supported the findings of the larger trials. This suggests that if sufficient power had been reached in these trials, they also would have demonstrated significant improvement in survival among those patients randomized to IP cisplatin.

Sensitivity analyses indicate that when trials with lower stage disease were included, the HR was virtually unchanged (HR of 0.799 when all studies were included, 0.794 when stage II patient studies removed) and remained significant in favor of the IP regimens. This could in part be due to the small number of stage II patients included in these studies (20% in the NWOG study and 14% in the UCSD study were stage II).

Calculation of the fail-safe N and other publication bias statistics demonstrated that there was minimal risk of publication bias for this meta-analysis. Due to the fact that the findings are highly significant, six additional negative trials would be needed to reduce

Table 4. Pooled OS

Study name	Statistics for each study				HR and 95% CI	*P* Value
	HR	Lower limit	Upper limit	*Z* value		
SWOG 8501	0.760	0.606	0.953	−2.372		0.0177
NWOG	0.670	0.389	1.155	−1.441		0.1497
GOG 114	0.810	0.627	1.047	−1.609		0.1076
Taipei	1.130	0.688	1.855	0.483		0.6290
GOG 172	0.750	0.580	0.970	−2.193		0.0283
UCSD	1.240	0.621	2.475	0.610		0.5418
Random effects	0.799	0.702	0.910	−3.383		0.0007

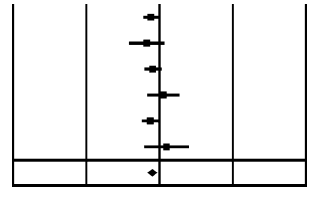


Table 5. Percent (*n*/*N*) grade 3 or greater toxicities

	SWOG-8501/ECOG/GOG-104	NWOG study	SWOG/ECOG/GOG-114	Taipei study	GOG-172	UCSD study
Neutropenia/granulocytopenia						
IV	69 (190/276)					42 (63/151)[a]
IP	56 (140/250)					42 (55/132)[a]
Other hematologic toxicities						
IV			88.5 (201/227)		90.5 (190/210)	
IP			92.8 (218/235)		93.5 (188/201)	
Leukopenia/white blood cells						
IV	50.0 (138/276)	18.5 (10/54)	61.7 (140/227)	33.3 (21/63)	63.8 (134/210)	21 (35/167)[a]
IP	40.0 (100/250)	23.9 (11/46)	76.6 (180/235)	18.2 (10/55)	75.6 (152/201)	19 (29/154)[a]
Thrombocytopenia/platelets						
IV	9 (25/276)	1.9 (1/54)	2.6 (6/227)	15.9 (10/63)	3.8 (8/210)	5 (8/164)[a]
IP	8 (20/250)	0 (0/46)	48.9 (115/235)	12.7 (7/55)	11.9 (24/201)	0 (0/154)[a]
Anemia/hemoglobin						
IV	25 (69/276)	5.6 (3/54)		19.0 (12/63)		7 (12/165)[a]
IP	26 (65/250)	8.7 (4/46)		12.7 (7/55)		3 (5/153)[a]
Gastrointestinal						
IV		25.9 (14/54)	17.6 (40/227)		24.3 (51/210)	30.6 (11/36)
IP		37 (17/46)	36.6 (86/235)		45.8 (92/201)	18.8 (6/32)
Cardiovascular						
IV		0 (0/54)	2.6 (6/227)		4.8 (10/210)	
IP		0 (0/46)	3.4 (8/235)		9.5 (19/201)	
Infection/febrile neutropenia						
IV			1.8 (4/227)		5.7 (12/210)	NR (2/NR)[a]
IP			4.7 (11/235)		16.4 (33/201)	NR (1/NR)[a]
Fatigue						
IV			1.3 (3/227)		4.3 (9/210)	
IP			3.0 (7/235)		17.9 (36/201)	
Fever						
IV	5 (14/276)[b]	1.9 (1/54)	1.3 (3/227)		3.8 (8/210)	
IP	6 (15/250)[b]	0 (0/46)	3.0 (7/235)		9.5 (19/201)	
Metabolic						
IV			1.3 (3/227)		7.1 (15/210)	
IP			9.8 (23/235)		27.4 (55/201)	
Ototoxicity						
IV	15 (41/276)[b]	0 (0/54)				16.7 (6/36)
IP	5 (13/250)[b]	0 (0/46)				12.5 (4/32)
Pain						
IV	2 (6/276)[b]				1.4 (3/210)	
IP	18 (45/250)[b]				11.4 (23/201)	
Pulmonary						
IV	0.4 (1/276)[b]				2.4 (5/210)	
IP	3 (8/250)[b]				3.5 (7/201)	
Renal/genitourinary						
IV		0 (0/54)	1.3 (3/227)		2.4 (5/210)	
IP		0 (0/46)	4.3 (10/235)		7.0 (14/201)	
Neurology/neuromuscular						
IV	21 (58/276)[b]	0 (0/54)	8.8 (20/227)		8.6 (18/210)	8.3 (3/36)
IP	16 (40/250)[b]	0 (0/46)	11.9 (28/235)		19.4 (39/201)	3.1 (1/32)
Treatment-related death						
IV	0 (0/276)		0.9 (2/227)		2.0 (4/210)	
IP	0.8 (2/250)		0.9 (2/235)		2.4 (5/205)	

NR, not reported.
[a]Number of courses, not number of patients.
[b]Grade 2 or greater; not reported for grade 3+.

these findings to a level of nonsignificance. The likelihood of this many negative trials having been completed but unpublished is quite low. Furthermore, tests of homogeneity demonstrated no evidence of statistical heterogeneity between trials ($P > 0.50$). Therefore, despite the relatively small number of trials

included in this meta-analysis, this meta-analysis demonstrated a consistent, highly significant improvement in survival under a variety of sensitivity analyses.

Toxicity analyses, unlike the survival analyses, did demonstrate a "canceling-out" effect between the significant and nonsignificant differences among trials (eg, leukopenia and thrombocytopenia). This suggests that it is not IP cisplatin alone causing these toxicities, but rather other features unique to the specific therapeutic dose, schedule, and agents used in the IP regimen. Similarly, had there been a canceling out of the IP cisplatin survival findings, one would further investigate other aspects of the treatment that would have led to differential survival between the trials. Few reported toxicities were consistently increased with IP treatment; however, there were significant differences within individual studies that may be due to the specific regimen than to IP treatment in general. The randomized trials included in this meta-analysis did not report sufficient data to include catheter complications among the toxicity analyses. However, two of the trials (NWOG and GOG-172) published their experiences with IP catheters[24,26]. The NWOG study reported that four patients (8.7%) experienced a catheter obstruction. GOG-172 found that of the 205 patients randomized to IP therapy, 40 (19.5%) experienced catheter-related complications. These complications included infection ($n = 21$), blockage ($n = 10$), access problems ($n = 5$), and leakage ($n = 1$). There was no association with the timing of the catheter placement or colon resection[26]. These complications are consistent with published experiences outside of the randomized trial setting[27,28].

Hematologic toxicities (eg, anemia and neutropenia) could not be assessed for all six trials, as GOG-114 and GOG-172 used the general definition of "other hematologic toxicities" to include a variety of toxicities. Therefore, toxicities such as anemia and granulocytopenia/neutropenia were combined for GOG-114 and GOG-172 and could not be teased out for this meta-analysis. Only gastrointestinal toxicities and fever showed a significant, consistent positive association with IP cisplatin-containing treatment regimens. The most instructive studies in this regard are SWOG-8501 and the NWOG study, wherein the only difference between the two study arms was the administration route for cisplatin, which was used in a dose of 100 mg/m^2 on both study arms for SWOG-8501 and 50 mg/m^2 on both study arms for the NWOG study. In SWOG-8501, IP cisplatin was associated with significantly less grade 3–4 leukopenia and neutropenia, as well as less grade 2–3 tinnitus, and clinical hearing loss related to the well-documented lower peak plasma levels achieved with IP drug administration. No significant differences in toxicity were found between treatment groups in the NWOG study.

In GOG-172, a quality of life (QOL) assessment found that despite the significantly higher toxicity in the IP treatment arm and QOL disruption during treatment, patient-reported QOL was equivalent between both treatment arms 1 year posttreatment, suggesting that these side effects were manageable for the patient and short term in nature[29].

Each of the prospective, randomized trials included in this meta-analysis used an intention-to-treat design. This is considered the "gold standard" for randomized trials, so that all patients assigned to a treatment regimen are included in the analysis regardless of adherence to the prescribed regimen or the subsequent therapies received. In combination with concealed allocation procedures during the randomization process limits the potential bias that could be introduced. For advanced ovarian cancer patients, there is furthermore no reason to believe that the treatment assignment in this trial had any bearing on the patients' future care; therefore, the likelihood of differential treatment in the second- or third-line setting leading to improved survival is highly unlikely.

This analysis provides a strong argument in favor of the use of IP cisplatin therapy for the front-line treatment of optimal stage III ovarian cancer due to the significantly improved survival associated with IP cisplatin in this population. The toxicities consistently associated with IP therapy in this meta-analysis include gastrointestinal toxicities and fever. Future research should assess methods to reduce these toxicities associated with regimens containing IP cisplatin, and should focus on reducing the additional toxicities specific to the dose and combination of agents used with IP cisplatin, and should focus on minimizing catheter complications, which were experienced in nearly 20% of patients receiving IP cisplatin in GOG-172.

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