MEDDOCS Open Access Publisher

Annals of Gynecologic Cancer

Open Access | Research Article

Intraperitoneal Chemotherapy after Cytoreductive Surgery Improves Survival in Epithelial Ovarian Cancer: A Systematic Review and Meta-Analysis

Mercedes Jimenez-Heredia[1]*; Jose A Perez-Fidalgo[1,2,3]; Maria Morales-Suarez-Varela[4,5]; Andres Cervantes[1,2,3]

[1]Hospital Clinico Universitario de Valencia, Spain.

[2]INCLIVA Biomedical Research Institute, Valencia, Spain.

[3]CIBERONC, Spain.

[4]Department of Preventive Medicine and Public Health, Food Sciences, Universitat de Valencia, Spain.

[5]CIBER Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Spain.

***Corresponding Author(s): Mercedes Jimenez-Heredia**

Hospital Clínico Universitario de Valencia, Avenida Blasco Ibanez,17, CP: 46160, Valencia, Spain.

Tel: +34-633-376-176;

Email: jimenez_mercedes@hotmail.com

Received: Nov 26, 2020

Accepted: Dec 24, 2020

Published Online: Dec 30, 2020

Journal: Annals of Gynecologic Cancer

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Meta-analysis; Ovarian cancer; Intraperitoneal; Chemotherapy; Platinum.

Abstract

Introduction: Despite the magnitude of improvement in Overall Survival (OS) obtained in the GOG172, Intraperitoneal Chemotherapy (IPC) in advanced Epithelial Ovarian Cancer (EOC) has not been widely accepted as a standard procedure due to toxic effects. This together with negative results in recent Randomized Clinical Trials (RCTs) suggested a need for this meta-analysis.

Methods: A literature search of PubMed, Embase, MEDLINE and ClinicalTrials.gov between January 1990 and January 2018 was conducted to identify relevant RCTs comparing IPC vs. intravenous chemotherapy (IV CT) after cytoreductive surgery in women with a new diagnosis of primary EOC. Progression-Free Survival (PFS) and OS were primary outcomes and secondary outcomes were Complete Pathological Response (CPR) and adverse effects. Pooled Hazard Ratios (HRs) with 95% Confidence Intervals (CI) were calculated with fixed or random-effect models using the generic inverse-variance method. Statistical heterogeneity and publication bias were analyzed.

Results: Nine phase III trials and one phase II trial were included, involving 3688 patients in the pooled analyses. There was a significant improvement in PFS (HR= 0.86, 95% CI 0.77 to 0.95), in OS (HR= 0.81, 95% CI 0.73 to 0.90) and in CPR (RR= 1.28, 95% CI 1.08 to 1.51) in the IP arm. Infection, pain and cardiovascular, gastrointestinal and metabolic toxicity were more common in the IP arm.

Conclusions: The magnitude of the calculated benefit is clinically important, with an impact on OS. These results suggest that IPC is a valuable although more toxic strategy, that could be considered in EOC after complete upfront surgery.

Cite this article: Jimenez-Heredia M, Jose A, Perez-Fidalgo JA, Suarez-Varela MM, Cervantes A. Intraperitoneal Chemotherapy after Cytoreductive Surgery Improves Survival in Epithelial Ovarian Cancer: A Systematic Review and Meta-Analysis. Ann Gynecol Cancer. 2019; 1(1): 1003.

Introduction

Epithelial Ovarian Cancer (EOC) represents 3.4% of tumors in women and accounts for approximately 300,000 new cases and 180,000 deaths every year worldwide [1].

The disease is usually diagnosed and treated in advanced stages (stages III, IV), which affects its prognosis [2]. For more than 30 years the standard treatment of recently diagnosed advanced EOC has been optimal cytoreduction followed by systemic platinum-base chemotherapy [3,4]. However, despite significant rates of complete cytoreduction in front-line surgery this disease frequently relapses and long-term survival is poor. This has led to the emergence of numerous studies aimed at improving outcomes both in surgical techniques to minimize residual disease and in different ways of administering chemotherapy.

As far as surgical techniques are concerned, the optimal surgical cytoreduction established by Gynecologic Oncology Group (GOG) as residual disease ≤1 cm has evolved to no macroscopic residual disease [5], as patients with this latter status showed improved survival when compared to those with any visible residual implant [6].

Furthermore, Intraperitoneal Chemotherapy (IPC) emerged as a novel therapeutic strategy for patients with certain types of malignancy confined to the peritoneal area, such as advanced EOC. In 1978 it was reported that higher concentrations of intratumoral drugs were achieved when the exposure of the disease to chemotherapy drugs occurred in the peritoneum rather than through the intravenous route [7].

Since then, several clinical trials have documented the outstanding impact of IPC, reporting important survival benefits that outweighed toxicity limitations. Three large phase III trials [8-10] of the GOG (protocols 104, 114 and 172) showed that IPC resulted in approximately 25% decrease in the risk of death compared with systemic therapy. In fact the National Cancer Institute (NCI) communicated an announcement in January 2006 underlining the clinical utility of cisplatin-based IPC in advanced EOC based on the magnitude of benefit in Overall Survival (OS) obtained in the GOG172 [10]. This survival advantage conferred by IPC was validated in a large meta-analysis with over 10 years of follow-up that confirmed the substantial benefit of IPC in this setting [11]. Nevertheless, GOG172 [10] has received several criticisms, the main one being that the experimental arm included not only IPC but also a weekly schedule with higher doses than the thrice-weekly intravenous control arm.

Despite the positive results and the NCI announcement, IPC has not been adopted as a standard procedure in several countries, mainly due to the toxic effects of IPC and catheter complications. More recently, results from well-designed, prospective randomized trials [12,13] have shown no benefit from IPC administration over standard intravenous arm.

IPC has generated a high level of controversy, since the interpretation of these results has led to a discrepancy among oncologists over levels of recommendation in clinical guidelines.

In light of this, we identified a need to perform a meta-analysis including the latest negative results. The primary endpoint of this meta-analysis was to establish the benefit of IPC in terms of survival in primary EOC after cytoreductive surgery. Specifically, the research question was: How does IPC impact on survival of primary EOC after primary cytoreductive surgery compared to intravenous chemotherapy (IV CT)?

Secondary objectives were to evaluate the clinical response in both groups and to analyze the safety of IPC administration.

Methods

This meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [14]. The study protocol has been published in the Prospero registry (CRD42018104564).

Selection criteria

Studies were selected according to the following inclusion criteria: 1) Patient type: Patients recently diagnosed with a primary EOC after cytoreductive surgery; 2) intervention type: the intervention arm was Chemotherapy (CT) including a route of repeated IP administration while standard IV CT was considered as the control arm; 3) outcomes: the primary outcomes were Progression-Free Survival (PFS) defined as time to recurrence, and Overall Survival (OS) defined as the time to death or date of last follow-up. Secondary outcomes were Complete Pathological Response (CPR) defined as no evidence of disease in the pathological examination on a second-look surgery, and adverse events assessed by any recognized and validated scoring system; 4) study type: Randomized Clinical Trials (RCTs) with primary outcomes of PFS or OS. We excluded RCTs that evaluated intraperitoneal chemotherapy as a single administration during surgery under hyperthermic conditions.

Search strategy

We performed a literature search of PubMed, Embase, MEDLINE and ClinicalTrials.gov between January 1990 and January 2018 to find those RCTs comparing IPC vs. IV CT after cytoreductive surgery in epithelial ovarian cancer. We limited the search to those studies written in English language and in which the subject of the study were human. Additionally, abstracts from the annual meetings of the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) were screened in order to identify other potential RCTs. The reference lists of recruited trials and of previously published reviews and meta-analysis were also checked in order to identify potentially eligible studies. The search strategy for MEDLINE can be found in the published protocol.

Study selection and data extraction

Screened studies were examined by two independent investigators (MJ and JAPF) and selected separately by each investigator.

Assessment of methodological quality and risk of bias was carried out in accordance to the CONSORT (Consolidated Standards of Reporting Trials) [15] 2010 statement. A checklist of 25 items was analyzed, each item given a score ranging from 0 to 2 (0= no description, 1= inadequate description, 2= adequate description). The maximum score a RCT could obtain was 50 points. Clinical trials that obtained at least 65% of the maximum score were classed as high quality.

Statistical analysis

Statistical analysis was performed using the SPSS STATISTICS V.21 software. Pooled HRs for time-to-event data or pooled RRs for dichotomous data with two-sided 95% confidence intervals and P values were calculated with fixed (IV, fixed) or random-effect (IV, random) models using the generic inverse-variance

method. We used I^2 statistic for quantifying the impact of heterogeneity [16]. I^2 thresholds for low, moderate and high degrees of heterogeneity were 25%, 50% and 75% respectively [17]. If there was no or low heterogeneity, we used a fixed-effect model, in all other cases using a random-effect model [18]. Statistical significance was two-tailed P < .05. Begg's and Egger's tests were used in order to assess the potential publication bias [19,20]. Sensitivity analyses to evaluate the contribution of individual studies were also performed by estimating average HRs omitting one study each time and omitting lowest quality studies.

Results

We identified 92 papers in our initial literature search. One additional report presented at the 2016 ASCO annual meeting was also included. Out of 93 studies 23 were excluded based on abstract and title review and 60 were excluded after full text review. Finally 9 phase III RCTs [8-10,12,21-25] and one phase II trial [13] including 3688 patients were selected. (Figure S1) presents the PRISMA flow diagram.

In 9 RCTs [8-10,12,21-25] IPC was administered after upfront surgery and in one (OV21/PETROC) [13] it was given after Neoadjuvant Chemotherapy (NACT) and optimal debulking surgery. Patients were stratified according to the amount of residual tumor in four RCTs: Kirmani et al, compared patients with residual disease <= 1cm vs. >1 cm; Alberts et al., compared residual disease <= 0.5 cm vs. >0.5 to 2 cm; Polyzos et al, compared residual disease <2 cm vs. >= 2 cm, and Walker et al., compared residual disease <= 1 cm vs. no visible residual disease. Patients that had never received chemotherapy before were reported in five trials [8-10,21,23]. Three trials [9,12-13] were originally designed as three-arm trials but only one [12] of them managed this; in Markman et al., the third arm, based on a regimen of cisplatin 75 mg/m^2 plus cyclophosphamide 750 mg/m^2, was discontinued due to a poorer response compared with the combination of cisplatin 75 mg/m^2 and paclitaxel 135 mg/m^2 delivered over 24 hours; in Provencher et al., the study was designed to be a three-arm phase III trial but later it was amended to an expanded two-arm phase II trial with the primary endpoint of PD9 (proportion of patients with disease progression or death occurring within nine months of randomization) due to poor accrual and lack of efficacy of arm two compared with the IV regimen at the end of the first stage. (Table 1a & 1b) represent the characteristics of the selected studies.

Two independent investigators (MJ and JAF) analyzed nine trials [8-10,13,21-25] according to the checklist of 25 items of the CONSORT [15] 2010 statement. Only one trial [12] was excluded from the analysis of quality because it was not a full publication; nonetheless, it was considered high quality for survival analysis. Seven trials [8-10,13,26-28] were considered high quality clinical trials and two trials [21-22] were classed as low quality clinical trials after evaluation. The results of the quality analysis are shown in (Table 2).

OS and PFS data were extracted from the reports. Only one trial [22] was excluded for the survival analysis because it did not provide sufficient data to calculate HR; its results were only analyzed in the safety analysis.

HR and their 95% CI for OS were available in eight trials [8-10,13,21,23-25] (2217 patients). The pooled analysis showed a significant improvement in OS in the IP intervention group (HR=0.81, 95% CI 0.73 to 0.90, p= 0.0001; Figure 1). No heterogeneity (P= 0.727, I2= 0.0%) was detected among the trials. Begg's test (P= 0.458) and Egger's test (P= 0.231) revealed no significant publication bias. The effect was similar when only high quality trials were pooled [8-10,13,26-28] (HR= 0.80; 95% CI 0.72 to 0.89). One-way sensitivity analysis confirmed the aforementioned results (Figure S2).

HR and their 95% CI for PFS were available in seven RCTs [9-10,12-13,21,23,25] (2934 patients). Due to the moderate heterogeneity (χ^2=11.2, p=0.132, I2=37.3%) a random effect was used to PFS analyses. One trial [12] was double analyzed because it had two intervention arms (carboplatin intraperitoneal and cisplatin intraperitoneal). There was a significant improvement in PFS in the IP intervention group (HR=0.86, 95% CI 0.77 to 0.95, p=0.002; Figure 2). Begg's test (P= 0.621) and Egger's test (P=0.882) demonstrated no significant publication bias for PFS. The effect was similar when only high quality trials were pooled [9-10,12-13,26,28] (HR= 0.85; 95% CI 0.77 to 0.94). As for OS, a one-way sensitivity analysis confirmed the above PFS results (Figure S3).

CPR was evaluated in six trials [8,10,21-23,24] (575 patients) by second-look laparotomy in patients without clinical evidence of EOC at completion of therapy. In one trial [9] this end point was unreliable and likely biased because an important variability of procedures between the two arms. The overall analyses revealed that there was a statistically significant improvement in CPR in the IP intervention group (RR= 1.28, 95% CI 1.08 to 1.51, p= 0.005; M-H; Figure S4). This remained true even when one trial [8] with high relative weight was excluded (RR= 1.24, 95%CI 1.00 to 1.54, p= 0.047; M-H). No heterogeneity (P = 0.435, I^2 = 0.0%) was detected among the studies.

All included trials evaluated adverse effects but in one trial unpublished data was obtained from the review publication [11] (Table 3). The pooled toxicity analysis showed that there were no significant differences between interventions for anemia, leukopenia, thrombocytopenia, renal, pulmonary, fever, fatigue and neurologic. There was a significant increase in hearing loss in the IV intervention group (three trials, 781 patients; RR= 0.42, 95%CI 0.25 to 0.70, p= 0.001; IV, fixed). The most common adverse effects in the IP arm were infection (three trials, 1171 patients; RR=3.26, 95%CI 2.00 to 5.30, p<0.001; IV, fixed), metabolic (three trials, 1060 patients; RR= 3.69, 95%CI 1.45 to 9.38, p= 0.006; IV, random), cardiovascular (five trials, 2720 patients; RR= 1.41, 95%CI 1.15 to 1.73, p<0.001; IV, fixed), gastrointestinal (seven trials, 2907 patients; RR= 1.65, 95%CI 1.28 to 2.12, p<0.001; IV, random) and pain (four trials, 1422 patients; RR= 4.73, 95%CI 1.87 to 11.97, p<0.001; IV, random).

There were treatment-related deaths in five trials. In Alberts et al, two deaths related to respiratory complications occurred in the IP group. In Markman et al, two patients in the IV group with grade 4 gastrointestinal toxicity and one with concurrent grade 4 hematological toxicity died, and in the IP group there were two deaths associated with grade 4 hematological toxicity. In Yen et al, one patient died after suffering diffuse peritonitis despite intensive antibiotic treatment. In Armstrong et al, there were nine deaths all attributed to infection, four in the IV and five in the IP group. In Walker et al, fifteen potentially toxic deaths were distributed among treatment arms. Moreover there were catheter-related complications in six trials [10,13,21-24].

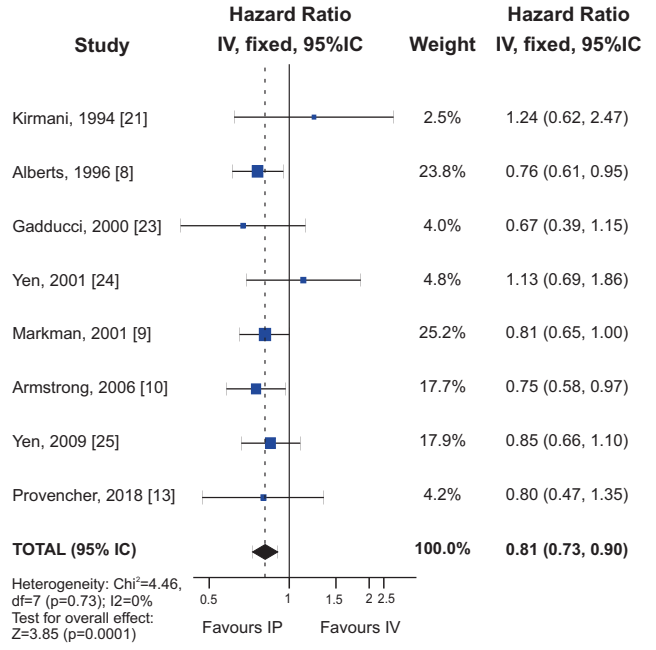

Figure 1: Pooled analysis of overall survival. 95% CI indicates 95% confidence interval; Chi2, chi-square test; df, degrees of freedom.

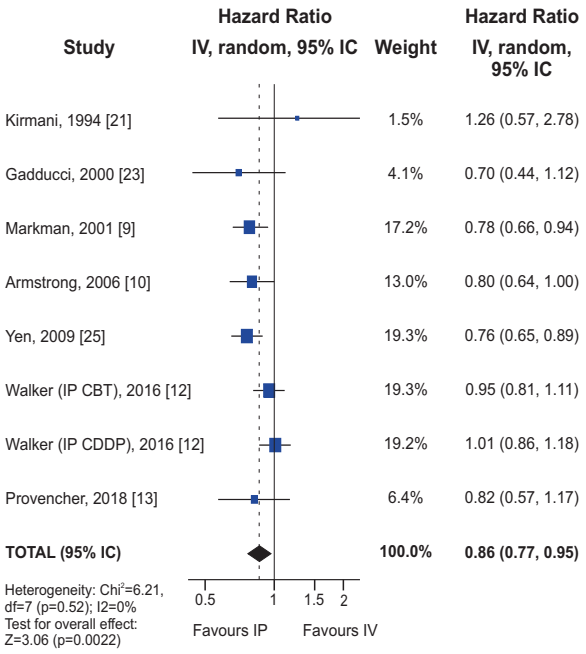

Figure 2: Pooled analysis of progression-free survival. 95% CI indicates 95% confidence interval; CBT, carboplatin; CDDP, cisplatin; Chi², chi-square test; df, degrees of freedom.

Table 1: Characteristics of eligible trials included in the meta-analysis.

Reference	PHASE	TYPE	OUTCOMES	SAMPLE SIZE		TREATMENT	CYCLE
Kirmani et al, 1994 [21]	PHASE III	SINGLE CENTRE	OS	IV	33	CYCLOPH IV 600 (MG/M2) + CDDP IV 100 (MG/M2)	q21d X6
			PFS				
			ADVERSE EFFECTS	IP	29	VP-16 IP 350 (MG/M2) + CDDP IP 200 (MG/M2)	q28d X6
Alberts et al, 1996 [8]	PHASE III	MULTICENTRIC	OS	IV	279	CYCLOPH IV 600 (MG/M2) + CDDP IV 100 (MG/M2)	q21d X6
			ADVERSE EFFECTS				
			PATHOLOGICAL CR	IP	267	CYCLOPH IV 600 (MG/M2) + CDDP IP 100 (MG/M2)	q21d X6
Polyzos et al, 1999 [22]	PHASE III	MULTICENTRIC	OS	IV	46	CYCLOPH IV 600 (MG/M2) + CBT IV 350 (MG/M2)	q21d X6
			PFS				
			ADVERSE EFFECTS	IP	44	CYCLOPH IV 600 (MG/M2) + CBT IP 350 (MG/M2)	q21d X6
Gadducci et al, 2000 [23]	PHASE III	MULTICENTRIC	OS	IV	56	4-EPI IV 60 (MG/M2) + CYCLOPH IV 600 (MG/M2) + CDDP IV 50 (MG/M2)	q28d X6
			PFS				
			ADVERSE EFFECTS	IP	57	4-EPI IV 60 (MG/M2) + CYCLOPH IV 600 (MG/M2) + CDDP IP 50 (MG/M2)	q28d X6
Markman et al, 2001 [9]	PHASE III	MULTICENTRIC	OS	IV	227	PACL IV 135 (MG/M2) 24H (d1) + CDDP IV 75 (MG/M2) (d2)	q21d X6
			PFS				
			ADVERSE EFFECTS	IP	235	CBT IV (AUC 9) q28dx2 à PACL IV 135 (MG/M2) 24H (d1) + CDDP IP 100 (MG/M2) (d2)	q21d X6
Yen et al, 2001 [24]	PHASE III	SINGLE CENTRE	OS	IV	55	CYCLOPH IV 500 (MG/M2) + ADRI IV 50 (MG/M2) + CDDP IV 50 (MG/M2)	q21d X6
			ADVERSE EFFECTS	IP	63	CYCLOPH IV 500 (MG/M2) + ADRI IV 50 (MG/M2) + CDDP IP 100 (MG/M2)	q21d X6
Armstrong et al, 2006 [10]	PHASE III	MULTICENTRIC	OS	IV	210	PACL IV 135 (MG/M2) 24H (d1) + CDDP IV 75 (MG/M2) (d2)	q21d X6
			PFS				
			ADVERSE EFFECTS				
			QOL (FACT-O)	IP	205	PACL IV 135 (MG/M2) 24H (d 1) + CDDP IP 100 (MG/M2) (d2) + PACL IP 60 (MG/M2) (d8)	q21d X6

Yen et al, 2009 [25]	PHASE III	SINGLE CENTRE	OS	IV	152	PACL IV 175 (MG/M2) 3H (d1) + CBT IV 300 (MG/M2) (d2)	q21d X6
			PFS				
			NOMOGRAMA	IP	146	PACL IV 175 (MG/M2) 3H (d1) + CDDP IP 100 (MG/M2) (d2)	q21d X6
Walker et al, 2016 [12]	PHASE III	MULTICENTRIC	PFS	IV	461	PACL IV 80 (MG/M2) 1H (d1, 8, 15) + CBT IV (AUC 6) (d1)	q21d X6
						+ BEV IV 15 (MG/KG) (d1) on cycles 2 -22	
				IP CBT	464	PACL IV 80 (MG/M2) 1H (d1, 8, 15) + CBT IP (AUC 6) (d1)	q21d X6
						+ BEV IV 15 (MG/KG) (d1) on cycles 2 -22	
				IP CDDP	456	PACL IV 135 (MG/M2) 3H (d1) + CDDP IP 75 (MG/M2) (d2) + PACL IP 60 (MG/M2) (d8)	q21d X6
						+ BEV IV 15 (MG/KG) (d1) on cycles 2 -22	
Provencher et al, 2018 [13]	PHASE II	MULTICENTRIC	PD9	IV	101	PACL IV 135 (MG/M2) (d1) + CBT IV (AUC 5-6) (d1) + PACL IV 60 (MG/M2) (d8)	q21d X6
			OS				
			PFS				
			ADVERSE EFFECTS				
			QOL	IP	102	PACL IV 135 (MG/M2) (d1) + CBT IP (AUC 5-6) (d1) + PACL IP 60 (MG/M2) (d8)	q21d X6

Os: Overall Survival; Pfs: Progression-Free Survival; Iv: Intravenous; Ip: Intraperitoneal; Cycloph: Cyclophosphamide; CDDP: Cisplatin; q21d X 6, every 21 days for a total of six cycles; VP-16, etoposide; q28d X6, every 28 days for a total of six cycles; CBT, carboplatin; 4-EPI: Epidoxorubicin; PACL: Paclitaxel; ADRI: Adriamycin; QOL: Quality of Life; BEV: Bevacizumab; PD9: Proportion of patients with disease progression or death due to any cause occurring within 9 months of randomization.

Table 1b: Characteristics of eligible trials included in the meta-analysis.

									PFS		OS	
Reference	**Sample Size**		**Stage**	**PS**	**Median Age**	**Median follow-up (months)**	**Residual Mass**	**N° Pts (%) received all cycles of assigned CT**	**Median (months)**	**HR (95% CI)**	**Median (months)**	**HR (95% CI)**
Kirmani et al, 1994 [21]	IV	33	IIC-IV	0-2	61	46	>1 cm or <=1 cm	60%	14	1.26 (0.57-2.78)[a]	-	1.24 (0.62-2.47)[a]
	IP	29			60			76%	12		-	
Alberts et al, 1996 [8]	IV	279	III	0-2	56	-	<=2 cm	58%	-	-	41	0.76 (0.61-0.96)
	IP	267			59			58%			49	
Polyzos et al, 1999 [22]	IV	46	III	0-3	55	-	>2 cm or <=2 cm	-	19	-	25	-
	IP	44			58				18		26	
Gadducci et al, 2000 [23]	IV	56	II-IV	< 2	53	-	< 2 cm	96%	25	0.70 (0.44-1.12)[b]	51	0.67 (0.39-1.15)[b]
	IP	57			56			65%	42		67	
Markman et al, 2001 [9]	IV	227	III	0-2	-	-	<=1 cm	86%	22.2	0.78 (0.66-0.94)	52.2	0.81 (0.65-1.00)
	IP	235						71%	27.9		63.2	
Yen et al, 2001 [24]	IV	55	III	0-2	52.8	74	< 1 cm	32%	-	-	48	1.13 (0.69-1.86)
	IP	63			54.6			25%			43	
Armstrong et al, 2006 [10]	IV	210	III	0-2	-	48.2	< 1 cm	83%	18.3	0.80 (0.64-1.00)	49.7	0.75 (0.58-0.97)
	IP	205				52.6		42%	23.8		65.6	
Yen et al, 2009 [25]	IV	152	III	0-2	56.6	62.4	<=1 cm	-	-	0.76 (0.65-0.89)[c]	-	0.85 (0.66-1.10)[c]
	IP	146			58.1			49,3%				
Walker et al, 2016 [12]	IV	461	II-IV	-	58	-	<=1 cm or no visible residual tumor	90%	26.8		-	-
	IP CBT	464						91%	28.7	0.95 (0.81-1.11)		
	IP CDDP	456						84%	27.8	1.01 (0.86-1.18)		
Provencher et al, 2018 [13]	IV	101	IIB-IVA	0-2	62	33	<=1 cm	-	11.3	0.82 (0.57-1.17)	38.1	0.80 (0.47-1.35)
	IP	102			62				12.5		59.3	

PS indicates GOG Performance Status; Pts: Patients; CT: Chemotherapy; PFS: Progression-Free Survival; OS: Overall Survival; IV: Intravenous; IP: Intraperitoneal; CBT: Carboplatin; CDDP: Cisplatin.

[a]HR estimated from the Kaplan-Meier survival curve

[b]HR estimated using Parmar's methods

[c]Data obtained from the review publication [8]

Table 2: CONSORT 2010 checklist [10].

Section/Topic		Item N°	Kirmani 1994 [21]	Alberts 1996 [8]	Polyzos 1999 [22]	Gadducci 2000 [23]	Markman 2001 [9]	Yen 2001 [24]	Armstrong 2006 [10]	Yen 2009 [25]	Walker 2016 [12]	Provencher 2017 [13]
	Title and abstract	1	1	1	1	1	2	1	1	1	-	2
	Background and objectives	2	2	2	2	2	2	2	2	2	-	2
Methods	Trial design	3	1	1	1	1	2	1	2	1	-	2
	Participants	4	2	2	2	2	2	2	2	2	-	2
	Interventions	5	2	2	2	2	2	2	2	2	-	2
	Outcomes	6	1	2	2	2	2	2	2	2	-	2
	Sample size	7	0	2	0	2	2	2	2	0	-	2
	Randomisation:											
	Sequence generation	8	0	0	0	2	2	0	2	0	-	2
	Allocation concealment mechanism	9	0	0	0	2	0	2	2	0	-	2
	Implementation	10	0	0	0	2	0	0	2	0	-	2
	Blinding	11	0	0	0	0	0	0	1	0	-	0
	Statistical methods	12	2	2	2	2	2	2	2	2	-	2
Results	Participant flow	13	2	2	1	2	2	2	2	2	-	2
	Recruitment	14	2	2	1	2	2	2	2	2	-	2
	Baseline data	15	2	2	2	2	2	2	2	2	-	2
	Numbers analysed	16	2	2	2	2	2	2	2	2	-	2
	Outcomes and estimation	17	1	2	1	1	2	2	2	2	-	2
	Ancillary analyses	18	1	2	1	0	2	2	2	2	-	2
	Harms	19	2	2	2	2	2	2	2	2	-	2
Discussion	Limitations	20	2	2	2	2	2	2	2	1	-	2
	Generalizability	21	2	2	2	2	2	1	2	2	-	2
	Interpretation	22	2	2	2	2	2	2	2	2	-	2
Other information	Registration	23	0	0	0	0	0	0	0	0	-	2
	Protocol	24	0	0	0	0	0	0	0	0	-	2
	Funding	25	0	2	0	0	2	0	2	2	-	2
	TOTAL SCORE CONSORT		29 (58%)	36 (72%)	28 (56%)	37 (74%)	40 (80%)	35 (70%)	44 (88%)	33 (66%)	-	48 (96%)

The score for each item ranged from 0 to 2 (0: No Description; 1: Inadequate Description; 2: Adequate Description). Maximum score: 50 points.

Table 3: Grade 3/4 Adverse Events.

Reference	No. of pts	Arm	Anemia	Leukop	Thrombo	Renal	Pulmon	CV	Fever	Fatigue	GI	Infec-tion	Metab	Neurol	Pain	Hearing Loss
Kirmani et al, 1994 [21]	36	IV	19.40%	58.30%	13.90%	5.60%					30.60%			8.30%		16.70%
	32	IP	9.40%	59.40%	0.00%	0.00%					18.80%			3.10%		12.50%
Alberts et al, 1996 [8]	276	IV	25.00%	50.00%	9.10%		0.40%		5.10%					21.00%	2.20%	15.20%
	250	IP	26.00%	40.00%	8.00%		3.20%		6.00%					16.00%	18.00%	5.20%
Polyzos et al, 1999 [22]	46	IV		39.10%	21.70%											
	44	IP		11.40%	6.80%											
Gadducci et al, 2000 [23]	54	IV	5.60%	18.50%	1.90%	0.00%		0.00%	1.90%		25.90%			0.00%		0.00%
	46	IP	8.70%	23.90%	0.00%	0.00%		0.00%	0.00%		39.10%			0.00%		0.00%
Markman et al, 2001 [9]	227	IV		61.70%	2.60%	1.30%		2.60%	1.30%	1.30%	17.60%	1.80%	1.30%	8.80%		
	235	IP		76.60%	48.90%	4.30%		3.40%	3.00%	3.00%	36.60%	4.70%	9.80%	11.90%		
Yen MS et al, 2001 [24]	63	IV	19.00%	33.30%	15.90%											
	55	IP	12.70%	18.20%	12.70%											
Armstrong et al, 2006 [10]	210	IV		63.80%	3.80%	2.40%	2.40%	4.80%	3.80%	4.30%	24.30%	5.70%	7.10%	8.60%	1.40%	
	201	IP		75.60%	11.90%	7.00%	3.50%	9.50%	9.50%	17.90%	45.80%	16.40%	27.40%	19.40%	11.40%	
Yen et al, 2009 [25]	152[†]	IV	19.7%[a]	27.6%[a]	19.1%[a]	7.2%[a]	7.6%[a]	4.2%[a]	10.5%[a]	21.1%[a]	9.2%[a]	2.6%[a]		3.9%[a]	3.9%[a]	
	146[†]	IP	20.5%[a]	24.0%[a]	17.8%[a]	5.5%[a]	1.4%[a]	2.9%[a]	12.3%[a]	30.8%[a]	19.2%[a]	14.4%[a]		4.8%[a]	25.3%[a]	
Walker et al, 2016 [12]	461	IV			17.60%	2.70%		11.90%			5.10%			5.70%		
	464	IP CBT			15.10%	3.10%		13.80%			4.70%			4.50%		
	456	IP CDDP			6.10%	1.60%		20.50%			11.20%			5.50%		
Provencher et al, 2018 [13]	95	IV					0.00%	7.40%	5.30%	4.20%	2.10%	0.00%	2.10%	0.00%	4.20%	1.10%
	92	IP					3.30%	7.60%	1.10%	0.00%	4.30%	0.00%	1.10%	0.00%	2.20%	1.10%

Pts indicates patients: Leukop: Leukopenia; Thrombo: Thrombocytopenia; Pulmon: pulmonary; CV: Cardiovascular; GI: Gastrointestinal; Metab: Metabolic; Neurol: Neurologic; CBT: Carboplatin; CDDP: Cisplatin; IV: Intravenous; IP: Intraperitoneal.

[a]Data obtained from the review publication [11].

Discussion

Despite the significant impact on survival in randomized clinical trials, the benefit of IPC has been under debate for years. As a consequence of this controversy, its toxic profile and complexity of administration, the use of this therapeutic alternative has not been widely accepted. In this context, two recent randomized trials [12-13] have increased doubts about the benefit of IPC. Firstly, OV21/PETROC [13] attempted to evaluate the benefit of IP/IV chemotherapy in following NACT but this trial was underpowered to draw firm conclusions about OS and PFS. Secondly, the initial findings of GOG252 [12] showed no improvement in PFS with IPC, although survival data are not yet mature and available data have been presented only as a communication.

The results of our pooled analysis confirmed that IPC obtained a statistical survival benefit, increasing both PFS and OS. These results were statistically homogeneous despite the fact that the treatment regimens were different. Most of the trials [8-10,21,23-25] included cisplatin-containing IPC regimens but in the latest two trials [12-13] cisplatin was replaced with carboplatin, most likely due to the results of numerous studies documenting the potential benefits of carboplatin over cisplatin, such as lower toxicity and better tolerance [26]. It was also hypothesized that including OV21/PETROC [13] designed to evaluate the role of IPC after NACT could be a cause of heterogeneity, but it was considered important to include this trial to assess how its negative results influenced the meta-analysis, and because its results provide data both supporting the use of IP carboplatin and showing non-inferiority of NACT vs. upfront surgery in EOC.

Moreover, GOG252 [12] added bevacizumab during chemotherapy and as maintenance in all arms, probably based on reports of significantly improved PFS in several clinical trials such as GOG-0218 [27], but this fact has triggered the non-significant results as predicted by the GOG262 [28] trial. GOG262 [28] showed that dose-dense paclitaxel improved PFS over three-weekly paclitaxel without bevacizumab.

Additionally, the most recent included trials [12,13] have also shown that reduced doses of cisplatin IP (75mg/m^2) to decrease the toxicity could have an impact on efficacy. After the first stage in OV21/PETROC [13], arm 2 (cisplatin IP) was discontinued due to lack of effectiveness.

Regarding the secondary objectives, it is worth mentioning that the pooled analysis revealed a statistically significant improvement in CPR in the IP intervention group. This positive result should be treated with caution, however, due to the low frequency of second-look surgical procedures in most clinical trials.

In terms of toxicity, pooled analysis showed that the most common adverse events in the IP arm were infection, pain and cardiovascular, gastrointestinal and metabolic toxicity. It should be noted that the cardiovascular effects could be explained due to the weight of the GOG252 [12], in which bevacizumab was used. On the other hand, use of less toxic schedules or carboplatin instead of cisplatin is reflected in reduced toxicity compared to the initial trials. These modifications have led to increases in the percentage of patients who received all cycles of assigned chemotherapy, increasing from 42% in GOG172 [10] to between 80-90% in GOG252 [12].

After the results of the GOG252 [12] trial many oncologists decided not to continue with IPC, on the basis that bevacizumab would overcome the benefit of IPC with less toxicity. However, until these results are mature and published, and while awaiting the results of the ongoing iPocc trial (GOTIC-001/JGOG-3019), the data from this meta-analysis confirm the survival benefit of IPC as consistent and robust, within the limitations of this statistical tool.

The magnitude of the calculated benefit, with a HR 0.86 and 0.81 for PFS and OS respectively, although more marginal, is clinically relevant with an impact on OS. Nevertheless, IPC's toxic profile should be not underestimated in clinical decision-making. These results suggest that IPC is a valuable, if more toxic strategy, that could be considered in EOC after complete upfront surgery.

Disclosure statement

Jiménez-Heredia M reports non-financial support from MSD, outside the submitted work.

Perez-Fidalgo JA reports personal fees and other from AstraZeneca, personal fees and other from Roche, personal fees from Pharmamar, personal fees from Clovis, personal fees and other from Pfizer, personal fees from Tesaro, during the conduct of the study; personal fees from Ipsen, personal fees from Clinigen, personal fees from Lilly, outside the submitted work; In addition, Dr. Pérez-Fidalgo has a patent EP18382390 pending.

Morales-Suárez-Varela M has nothing to disclose.

Cervantes A reports grants from Genentech, grants and personal fees from Merck Serono, grants from BMS, grants from MSD, grants and personal fees from Roche, grants from Beigene, grants from Bayer, grants and personal fees from Servier, grants from Lilly, grants from Novartis, grants and personal fees from Takeda, grants and personal fees from Astelas, grants from Fibrogen, during the conduct of the study.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68: 394-424.
2. Olson SH, Mignone L, Nakraseive C, Caputo TA, Barakat RR, et al. Symptoms of ovarian cancer. Obstet Gynecol. 2001; 98: 212-217.
3. Piver MS, Lele SB, Marchetti DL, Baker TR, Tsukada Y, et al. The impact of aggressive debulking surgery and cisplatin-based chemotherapy on progression-free survival in stage III and IV ovarian carcinoma. J Clin Oncol. 1988; 6: 983-989.
4. Delgado G, Oram DH, Petrilli ES. Stage III epithelial ovarian cancer: the role of maximal surgical reduction. Gynecol Oncol 1984; 18: 293-298.
5. Chang SJ, Bristow RE. Evolution of surgical treatment paradigms for advanced-stage ovarian cancer: redefining 'optimal' residual disease. Gynecol Oncol. 2012; 125: 483-492.
6. Chi DS, Eisenhauer EL, Lang J, Huh J, Hadded L, et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? Gynecol Oncol. 2006; 103: 559-564.
7. Dedrick RL, Myers CE, Bungay PM, DeVita VT. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep. 1978; 62: 1-11.

8. Alberts DS, Liu PY, Hannigan EV, O'Toole R, Williams SD, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med. 1996; 335: 1950-1955.

9. Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, 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: 1001-1007.

10. Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med. 2006; 354: 34-43.

11. Jaaback K, Johnson N, Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database Syst Rev 2016; 11: CD005340.

12. Walker J, Brady MF, DiSilvestro PA, et al. A phase III trial of bevacizumab with IV versus IP chemotherapy for ovarian, fallopian tube, and peritoneal carcinoma: An NRG Oncology Study (abstract). Gynecol Oncol 2016; 141(Suppl 1): P208.

13. Provencher DM, Gallagher CJ, Parulekar WR, Ledermann JA, Armstrong DK, et al. OV21/PETROC: A randomized Gynecologic Cancer Intergroup phase II study of intraperitoneal versus intravenous chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer. Ann Oncol. 2018; 29: 431-438.

14. Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009; 6: e1000097.

15. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010; 340: c332.

16. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002; 21: 1539-1558.

17. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327: 557-560.

18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7: 177-188.

19. Egger M, Davey Smith G, Schneider M, Minder C, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315: 629-634.

20. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50: 1088-1101.

21. Kirmani S, Braly PS, McClay EF, Saltzstein SL, Plaxe SC, et al. A comparison of intravenous versus intraperitoneal chemotherapy for the initial treatment of ovarian cancer. Gynecol Oncol. 1994; 54: 338-344.

22. Polyzos A, Tsavaris N, Kosmas C, Giannikos L, Katsikas M, et al. A comparative study of intraperitoneal carboplatin versus intravenous carboplatin with intravenous cyclophosphamide in both arms as initial chemotherapy for stage III ovarian cancer. Oncology. 1999; 56: 291-296.

23. Gadducci A, Carnino F, Chiara S, Brunetti I, Tanganelli L, et al. Intraperitoneal versus intravenous cisplatin in combination with intravenous cyclophosphamide and epidoxorubicin in optimally cytoreduced advanced epithelial ovarian cancer: a randomized trial of the Gruppo Oncologico Nord-Ovest. Gynecol Oncol. 2000; 76: 157-162.

24. Yen MS, Juang CM, Lai CR, Chao GC, Ng HT, et al. Intraperitoneal cisplatin-based chemotherapy vs. intravenous cisplatin-based chemotherapy for stage III optimally cytoreduced epithelial ovarian cancer. Int J Gynaecol Obstet. 2001; 72 55-60.

25. Yen MS, Twu NF, Lai CR, HHorng HC, Chao KC, et al. Importance of delivered cycles and nomogram for intraperitoneal chemotherapy in ovarian cancer. Gynecol Oncol. 2009; 114: 415-419.

26. Fujiwara K. Can carboplatin replace cisplatin for intraperitoneal use? Int J Gynecol Cancer. 2008; 18(Suppl 1): 29-32.

27. Burguer RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Eng J Med. 2011; 365: 2473-2483.

28. Chan JK, Brady MF, Penson RT, Huang H, Birrer MJ, et al. Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer. N Engl J Med. 2016; 374: 738-748.