

Intraperitoneal Chemotherapy in Patients Pretreated for Ovarian Cancer Matched with Patients Treated with Parenteral Chemotherapy

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Abstract. *Background:* Our aim was to analyze the impact of intraperitoneal chemotherapy (IPC), administered with direct peritoneal puncture, on the survival of patients with pretreated ovarian cancer in a real-life setting. *Patients and Methods:* This was a retrospective study comparing patients with advanced ovarian cancer treated with IPC (N=33) and patients treated with standard intravenous (i.v.) chemotherapy matching cases for known prognostic factors (age, platinum sensitivity, histological subgroup and grade). Data were then analyzed for survival with nested Cox multivariate regression. *Results:* The case matching resulted in two homogeneous cohorts by age, platinum sensitivity, resistance to therapy and histology. When analyzed by hazard ratio (HR), the number of previous treatments and IPC vs. i.v. therapy were significant (HR=1.97 for i.v. and HR=1.90 for each incremental previous treatment line, multivariate $p < 0.001$). When analyzing the patients with fewer than three previous treatment lines, IPC conferred a survival advantage of about 2.2 months (IPC=10.0 vs. i.v.=7.8 months, $p=0.011$). However, the survival advantage in heavily pre-treated patients (with three or more previous treatments) was not significant. One case, pre-treated with more lines of chemotherapy, with renal failure after intraperitoneal cisplatin was followed by death. None of the patients had bowel sub-

occlusions and we recorded a lower incidence of local toxicity, such as cellulite, with IPC (two out of 33 cases). Two patients thereafter refused IPC due to abdominal pain. *Conclusion:* Our findings confirm that IPC is an effective approach compared to systemic chemotherapy for advanced ovarian cancer, even in pre-treated patients, including platinum-resistant cases. The survival benefit appears to be confined to non-heavily treated patients. Overall, direct intraperitoneal drug injection (without permanent devices) appears to be feasible, safe and possibly advantageous.

Ovarian cancer is the eighth most common cancer among women, and is the fifth leading cause of cancer-related death among women, hence it is the deadliest of gynecological cancers. Mortality rates are slightly higher for Caucasian women than for African-American women (1). Most patients with advanced cancer have a 70% probability of recurrence and death because of disease progression. Therefore, more effective therapies are needed for this aggressive cancer, especially for pre-treated patients.

The peritoneum is the most frequent site of disease spread and treatment failure in the majority of advanced ovarian cancers (2). The treatment of ovarian cancer by intraperitoneal chemotherapy (IPC) was performed in several phase II trials with cisplatin/paclitaxel, showing the feasibility of the procedure and leading to an overall survival spanning from 8 months for patients with less than 2 cm residual disease to 43 months for patients with minimum residual disease (smaller than 0.5 cm) (3-6). Moreover, when IPC was tested in patients with no residual mass greater than 1.0-2 cm after first surgery in phase III trials, it showed significant survival benefit

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compared to intravenous (*i.v.*) chemotherapy (7-10). However, since patients with minimal residual disease are the minority and this issue is still the object of debate, neoadjuvant *i.v.* chemotherapy followed by interval surgery is currently recommended (11), despite the results obtained with IPC. Moreover, another article by Markman *et al.* showed that IPC after neoadjuvant and interval surgery conferred an advantage of 5 months in overall survival and 9 months in progression-free survival (12).

Concerns about local toxicity and permanent catheter complications or malfunctioning have led to a cautious introduction of the IPC procedure in European clinical practice (13-15). With the exception of trabectedin, which demonstrated an overall survival improvement of 6 months in partially sensitive patients, new therapies for advanced ovarian cancer in inoperable and relapsed disease, such as bevacizumab and poly ADP-ribose polymerase inhibitors have only improved disease-free survival, without consistent impact on overall survival (16-18). Of note, there are no data for direct intraperitoneal puncture applied in a non-drug-naïve setting, in particular for heavily pre-treated patients. The aim of the present study was to assess both efficacy and tolerability of IPC performed with direct puncture (as an alternative approach to permanent catheter) (19-20) for the treatment of previously treated patients with advanced ovarian cancer in a real-life setting.

Patients and Methods

Patients. Patients with advanced ovarian cancer (intraperitoneal disease or ascites) who received IPC between January 2006 and June 2015 (N=33) were retrospectively identified from the prospectively maintained database of our Institution. For each IPC case, the database was also queried to identify two patients who received *i.v.* chemotherapy (N=66) and matched IPC cases in terms of age, platinum sensitivity after first-line chemotherapy, histology, grade according to the International Federation of Gynecology and Obstetrics (FIGO) criteria and the World Health Organisation (WHO) system (22), year of first diagnosis as date of first surgery (medium interval of 12 months). We administered IPC as cisplatin on day 1 followed by paclitaxel on day 8 every 21-28 days for 3-4 cycles. Before they could receive a subsequent cycle of IPC, patients were required to have an absolute neutrophil count of 1,500 cells/mm³ or greater, a platelet count of 100,000 cells/mm³ or greater, and a creatinine level of 2.0 mg/dl or less. Treatment modifications for hematological toxic effects included cycle delay and dose reduction. Treatment was postponed in cases of creatinine level greater than 2.0 mg/dl (N=1). Patients in whom treatment was delayed for more than three weeks were removed from IPC (39.4%). Among patients in the IPC group, the dose of intraperitoneal drugs was reduced in the case of grade 2 abdominal pain and if these were persistent after dose reduction, they did not receive further IPC.

In the IPC arm, 14 patients had platinum-sensitive disease which became platinum resistant, and 12 had platinum-sensitive and seven platinum-resistant disease from the outset. Clinical response was considered the disappearance of ascites or stabilization of the ascites for over 45 days.

The survival observation starting point was the date of first IPC administration versus the date of the first corresponding *i.v.* treatment in the matched cases (*i.e.* if the patient received IPC as third line of treatment, the observation start for survival comparison was the date of the third *i.v.* therapy regimen for the two matched *i.v.* cases).

Treatment. The infusion used a set comprising a Veress needle (15 gauge, 100 mm), a bag with drain-tap and a 3-way stopcock 360°. The interventional radiologist inserted the Veress needle in the peritoneum smiled by ultrasound scan. The ascites, if present, was drained and collected within the bag. The patients were then transferred to the Medical Oncology Department for peritoneal drainage and IPC.

An infusion bag of 500-1000 cc of 0.9% saline solution was heated to a temperature between 30 and 35°C using a waterbath Argolab WB 12 (Corato SAS, Verona, Italy) and was connected to the 3-way stopcock. The stopcock was opened and the saline solution was infused in 30 minutes to prepare the peritoneum to receive the treatment. At the end of the saline infusion, the bag containing the drug was connected to the 3-way stopcock and infused as fast as possible.

The procedure was performed with local anesthesia (5 ml of bupivacaine or lidocaine diluted with 5 ml of 0.9% saline solution) and monitoring of vital signs. On the first day of the cycle, cisplatin was administered at a fixed dosage of 100 mg for pre-treated patients. The drug was diluted in 500 cc of 0.9% saline solution and infused into the peritoneum as rapidly as possible. Parenteral *i.v.* was infused in 2 litres of glucose solution with normal saline with 3 g of magnesium sulfate and 40 g of mannitol (7), with premedication with corticosteroids and antiemetic, according to standard institutional procedures (7-9). We added hydration on the days following IPC to avoid nephrotoxicity. In the case of mild renal impairment, we administered carboplatin (22) at a fixed dosage of 4 areas under the curve (AUC) for pre-treated patients.

The second part of the cycle was administered after 7 days. This consisted of the administration of IPC paclitaxel at a fixed dose of 90 mg in 250 cc of 0.9% saline solution, due for pre-treatment.

At the end of IPC infusion, a further peritoneal washing with 500 cc of 0.9% saline solution was administered (7-9). The Veress needle was removed at the end of the procedure and compressive medication was applied. In the days after treatment, creatinine, ionemia and vital signs were monitored daily for 1 week.

Intravenous chemotherapy was by clinician's choice, according to international guidelines (23-25), and in the case of allergy to taxol or platin salts, premedication was required according to Castells and Reeves (26, 27).

Adverse events were recorded according to Common Toxicity Criteria for Adverse Events (CTCAE) v. 4.03. (28).

Statistical analyses. The power of the study was not pre-planned as the aim of the project was exploratory and descriptive. There was no selection of patients outside the inclusion and matching criteria. Patients were eventually grouped according to the number of previous chemotherapy lines, by grouping criterion of fewer than three and three or more lines. Data analysis was performed by means of nested Cox regression, interaction was designed for investigational treatment (IPC vs. *i.v.*) and number of previous therapy lines. Wald test with analysis of variance was used after the building of the regression model, the proportional hazard assumption was verified by means of Schoenfeld residuals. Observation time started from the date of the corresponding line of *i.v.* chemotherapy. Survival was estimated with the Kaplan-Meier method, and differences in the studied cohorts were calculated

Table I. Comparison of complication reports.

	Author (Ref)	No. of patients	Catheter dysfunction	Infection
Peritoneal catheter	Walker <i>et al.</i> (15)	189	26.4%	13.2%
	Sakuragi <i>et al.</i> (13)	78	6.4%	20.5%
	Landrum <i>et al.</i> (14)	83	6%	4.8%
Direct puncture of abdomen	Lan <i>et al.</i> (19)	194	1%	0
	Benedetti-Panici <i>et al.</i> (20)	38	1.5%	0
	Present study	33	1%	0

Table II. Characteristics of patients according to intraperitoneal (IPC) and intravenous (IV) therapy.

Variable	IPC, n (%)	IV, n (%)	HR	p-Value
Median age (years)	62.6	66.7	1.0	0.332
Platinum-sensitivity	25 (75.7%)	50 (75.7%)	1	0.003
Platinum-resistance	7 (21.2%)	14 (21.2%)	1.8	
Platinum-refractory	1 (3%)	2 (3%)	8.9	
Histological grade				
2	2 (6.1%)	6 (9.1%)	1	0.976
3-4	31 (93.1)	60 (90.9%)	1.1	
Histology				
Undifferentiated	5 (15.1%)	11 (16.7%)	1	0.275
Clear cell	1 (3%)	2 (3%)	3.7	
Other epithelial subtype	6 (18.2%)	9 (13.6%)	10.0	
Serous	21 (63.6%)	44 (66.7%)	2.7	
Median no. of previous treatments	3	2	1.9*	<0.001
Administration route				
IPC	33 (100%)	0	1	0.010
IV	0	66 (100%)	1.97	

HR: Hazard ratio. *For each incremental treatment.

with log-rank test. Comparison of variables was performed by means of Chi-square, Fisher or Wilcoxon-Mann-Whitney test according to the nature and numerosity of the variable. Two-sided *p*-values are reported. Statistical analyses were performed with R 3.2.2 (survival and rms libraries; R Foundation for Statistical Computing, Vienna, Austria).

Patients gave consent to use their data for scientific purposes, and the study was performed under local Ethic Committee approval (number 15/2015).

Results

The case-by-case matching resulted in two homogeneous cohorts, IPC *vs.* *i.v.*: by age group (62 *vs.* 65 years), platinum sensitive [25 (75.8%) *vs.* 50 (75.8%)], resistant [7 (21.2%) *vs.* 14 (21.2%)], refractory [1 (3%) *vs.* 2 (3%)], histology [serous: 21 patients (63.6%) *vs.* 44 (66.7%); undifferentiated: 5 (15.1%) *vs.* 11 (16.7%); epithelial-mixed: 6 (18.2%) *vs.* 9 (13.6%); clear cell: 1 (3%) *vs.* 2 (3%)], histological grade [grade 2: 2 (6%) *vs.* 6 (9%); grade 3-4: 31 (93.1%) *vs.* 60 (90.9%)].

The treatment was well tolerated. The main adverse event observed was in patient with severe ascites and seven lines of prior chemotherapy; the patient developed progressive renal

failure after first intraperitoneal cisplatin, deteriorating until death, occurred on day 8. Three patients stopped IPC because of pain (two after second cycle, responsive to treatment, and one after the third cycle, without response to treatment) consequent to grade 2 cellulite (caused by the shift of the needle in two cases, as a result of abrupt needle dislocation during the transfer from stretcher to bed, and which resolved spontaneously). Table I provides a comparison of adverse events observed with IPC in published series and in our cohort.

Table II summarizes patient characteristics according to treatment group, and the impact of these features on the hazard of death. At Cox regression analysis, histology, grade and age did not impact on the hazard of death, while platinum sensitivity status (HR=1.8 and HR=8.9 for platinum resistance and refractoriness, respectively; *p*=0.003) and administrative route (HR=1.97 for *i.v.*, *p*=0.010) significant. In addition, the number of previous treatments had an impact on the hazard of death (HR=1.9 for each incremental line, *p*<0.0001). After Wald analysis, only administrative route (*p*=0.007) and the number of previous treatments (*p*<0.001) maintained significance. We then repeated the analysis selecting covariates that were

Table III. Survival in intraperitoneal (IPC) and intravenous (IV) therapy groups according to pretreatment.

Group	Study treatment	N	Deaths, n (%)		Overall survival
				At 1 year (%)	Median (months)
Not-heavily pre-treated (<2 previous lines)	IPC	16	13 (81%)	48.1	10.0
	IV	45	40 (88.8%)	40.2	7.8
Heavily pre-treated (≥3 previous lines)	IPC	17	16 (94%)	36.4	4.4
	IV	21	21 (100%)	10.6	4.2

significant (platinum sensitivity at the beginning of the disease, number of previous treatments and treatment with IPC or *i.v.* chemotherapy) and hypothesized an interaction between the route of administration and number of previous treatments. IPC treatment had a positive impact on the hazard of death only in the subgroup of not heavily pre-treated patients [HR=0.21, 95% confidence interval (CI)=0.09-0.48, $p<0.001$], while in patients who had previously received three or more treatment lines, the benefit was unimportant (HR=0.55, 95% CI=0.27-1.12, $p=0.101$). When analyzing the patients with fewer than three previous treatment lines, IPC had a survival advantage of 2.2 months (IPC=10.0 *vs.* *i.v.*=7.8 months, $p=0.011$). The prognostic advantage in heavily pretreated patients (with three or more previous treatments) was not significant. The significant impact of platinum sensitivity status on prognosis was confirmed, as patients with refractory and platinum-resistant disease had an HR of 5.7 (95% CI=1.62-20.14, $p=0.038$) and 1.8 (95% CI=1.03-3.16, $p=0.006$), respectively.

Four (12.1%) patients in the IPC arm were alive after a median follow-up of 22 months and five (7.57%) patients were alive in the *i.v.* group after a median follow-up of 16 months. Table III summarizes the survival data for the two treatment cohorts according to pretreatment group, and Figure 1 reports the survival curve for IPC and *i.v.* cohorts for not-heavily pretreated patients.

Within the IPC group, 27 patients had ascites, and six patients had peritoneal carcinomatosis only. Fourteen (51.8%) out of 27 patients had a clinical response, with disappearance or significant reduction of ascites for more than 45 days after IPC. Information on ascites was not available in the *i.v.* group.

The cost of standard intravenous regimens for advanced ovarian cancer, including bevacizumab, pegylated liposomal doxorubicin plus oxliplatin and pegylated liposomal doxorubicin plus trabectedin, catumaxomab and IPC are compared in Table IV. As may be seen, the expense savings are of the order of up to 12 times in favor of IPC (16, 18, 29).

Discussion

The efficacy of first-line IPC with cisplatin/paclitaxel in ovarian epithelial cancer is well documented in phase III studies (7-9, 30, 31). Of note, striking survival data have been

recorded for patients with responsive disease, with a consistent number of patients alive after 120 months in this group (31). As consequence, the toxicities, issues and cost of IPC appears justified from the survival benefit. This retrospective case-matched report endorses a significant role in previously treated patients, such as in second and third line (*i.e.* for patients with fewer than three previous therapy lines), partly confirming the experience of Markman and colleagues about intraperitoneal treatment after neoadjuvant chemotherapy and interval surgery (12).

Pre-treated patients represent the majority of the ovarian cancer population; moreover, they are often candidates for palliative treatment only and excluded from clinical trials with new drugs. Therefore, studies for effective and possibly not expensive second and third line treatments can be considered a priority for patients despite age and platinum sensitivity. Intraperitoneal catumaxomab, a monoclonal antibody designed to reduce ascites production in patients with cancer, can prolong the interval between peritoneal drainage, but a clinical objective response was not reported (32). On the contrary, more than half of the patients in the IPC group in our study experienced significant improvement of ascites and, of consequence, a reduction of the need for ascites drainage, with intervals of longer than 45 days.

According to our results, IPC was well-tolerated. In particular, direct intraperitoneal puncture, avoiding permanent catheterization, was associated with minor toxicities when compared with historical series of IPC administered by permanent catheter, confirming the reports of Lan *et al.* (19) and Benedetti-Panici *et al.* (20) in a first-line setting. In particular, we recorded one possible toxic death but the clinical impression was of multi-organ failure, in the context of heavily pretreated disease not responding to last-resort therapy. No bowel obstructions and infections (considering cellulite an inflammatory adverse event) with IPC were registered, as opposed to other studies that used permanent devices (7-9). As confirmation of the tolerability and feasibility of IPC, the procedure was safe, even in elderly pretreated patients. As confirmation of the procedure's safety and feasibility, there is a report of IPC administered during pregnancy. In fact, a primiparous woman received four cycles

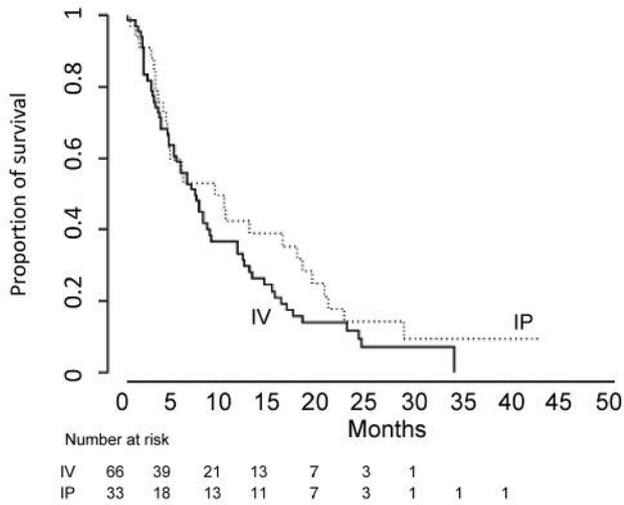


Figure 1. Overall survival curve for patients treated with intraperitoneal (IP) or intravenous (IV) chemotherapy.

Table IV. Costs of intraperitoneal (IPC) and intravenous (IV) therapy.

Chemotherapy regimen (Ref)	One cycle (€)	Six cycles (€)
Trabectedin–pegylated doxorubicin (18)	3,956	23,739
Pegylated doxorubicin–oxaliplatin (32)	639	3,838
Carboplatin–gemcitabine–bevacizumab (17)	3,284	19,767
Catumaxomab	1,225	7,350
Cisplatin–paclitaxel IPC	309	1,858

of IPC from about the 14th gestational week (33), followed by successful caesarean delivery in the 37th week.

Moreover, according to our results, IPC was associated with a survival advantage when compared with standard *i.v.* chemotherapy in unselected patients, even if the advantage was only significant for not heavily pretreated patients. Of note, the influence of platinum sensitivity still appears important as an independent prognostic factor, even if not discriminatory for the benefit from IPC.

In order to avoid needle dislocations and its consequences, as demonstrated by our experience, the positioning of the peritoneal needle should occur under ultrasound guidance directly at the patient’s bed.

One of the disadvantages of IPC, it could be argued, would be the necessity for referral to a specialized center. However, multidisciplinary approaches and effective networks between peripheral and referral centers are already a priority of ovarian cancer patient management in modern oncology.

In conclusion, the issue of costs for expensive new cancer drugs that can offer limited advantage of overall survival is a

topic of current debate. We confirm a benefit in terms of overall survival and costs for IPC and would foster further studies to improve feasibility and toxicity management to encourage the implementation in daily practice of this treatment approach for not-heavily pre-treated patients.

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