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Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: A Gynecologic Oncology Group study

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Abstract

Objectives. To evaluate reasons for discontinuing intraperitoneal (IP) chemotherapy, and to compare characteristics of patients who did versus did not successfully complete six cycles of IP chemotherapy.

Methods. In a phase III trial, women with optimal stage III ovarian or peritoneal carcinoma were randomly allocated to receive IP therapy (paclitaxel 135 mg/m^2 intravenously (IV) over 24 h, cisplatin 100 mg/m^2 IP day 2, paclitaxel 60 mg/m^2 IP day 8) every 21 days for six cycles. Patients unable to receive IP therapy were treated with the alternate (IV) regimen. Variables compared included surgical procedures prior to enrollment, timing of IP catheter insertion, and primary and contributing reasons for discontinuing IP therapy.

Results. Among 205 eligible patients randomly allocated to the IP arm, 119 (58%) did not complete six cycles of IP therapy. Forty (34%) patients discontinued IP therapy primarily due to catheter complications and 34 (29%) discontinued for unrelated reasons. Hysterectomy, appendectomy, small bowel resection, and ileocecal resection were not associated with failure to complete six cycles. IP therapy was not initiated in 16% of patients who did versus 5% of those who did not have a left colon or rectosigmoid colon resection ($P = 0.015$). There was no association between timing of catheter insertion and failure to complete IP therapy.

Conclusions. In this multi-institutional setting, it was difficult to deliver six cycles of IP therapy without complications. There appears to be an association between rectosigmoid colon resection and the inability to initiate IP therapy. Catheter choice, timing of insertion, and how surgical treatment of ovarian cancer influences the successful completion of intraperitoneal chemotherapy require further study.

Keywords: Ovarian neoplasm; Intraperitoneal; Chemotherapy

Introduction

The adoption of potentially superior intraperitoneal (IP) chemotherapy for ovarian cancer has been hindered by technical challenges and toxicity, which physicians and their patients have found hard to overcome. Alberts et al. [1] in 1996, and Markman et al. [2] in 2001, reported improved outcome in women with optimally debulked stage III epithelial ovarian cancer when treated with IP chemotherapy. Markman noted that median overall survival (OS) was not significantly different between arms, 63 months for the IP regimen compared to 52 months for IV (RR = 0.81; $P = 0.05$), but that progression-free survival (PFS) was 28 months for the IP arm compared to 22 months for IV (RR = 0.78; $P = 0.01$). Alberts' study had a median OS of 49 months for the IP arm

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compared to 41 months for the IV arm; the risk of death was lower for IP (Hazard Ratio of 0.76; CI 0.61; 0.96; $P = 0.01$). Catheter-related complications and toxicities associated with the IP therapy itself were not thoroughly detailed in these reports. Both studies reported a significant increase in abdominal pain and gastrointestinal toxicity in the IP treatment arms. The successful delivery of six cycles of IP chemotherapy was seen in only 58% of the participants in the Alberts' trial and 71% of the participants in the Markman trial.

More recently, Gynecologic Oncology Group (GOG) 172 demonstrated significant improvement in PFS and OS with the IP regimen consisting of paclitaxel 135 mg/m^2 given by 24 h IV infusion on day 1, cisplatin 100 mg/m^2 IP day 2, and paclitaxel 60 mg/m^2 IP day 8, compared to paclitaxel 135 mg/m^2 day 1 IV over 24 h and cisplatin 75 mg/m^2 day 2 IV [3]. The median PFS for the IV and IP arms was 18.3 months and 23.8 months, respectively. The relative risk of progression was 0.8 (95% CI: 0.64, 1.00) for the IP group ($P = 0.05$, two-sided log-rank test). The median OS for the IV and IP arms was 49.7 months and 65.6 months, respectively. The relative risk of death was 0.75 (95% CI: 0.58, 0.97) for the IP group ($P = 0.03$, two-sided log-rank test).

The present report describes the complications reported in the IP arm of GOG 172, and their association with patient and clinical characteristics, to improve the design and patient selection methods in future trials utilizing IP chemotherapy with a goal of improving the tolerability, acceptance, and successful administration of this treatment modality.

Materials and methods

Eligibility for enrollment included a diagnosis of optimally surgically resected stage III epithelial ovarian or primary peritoneal adenocarcinoma. Participating institutions received approval from their institutional review boards prior to enrolling any patients, and all patients provided written informed consent consistent with federal, state, and local requirements prior to receiving any protocol therapy.

Women were required to be enrolled within 6 weeks of surgery and have ≤1 cm residual disease. Randomization was stratified by gross residual disease or no visible residual disease. The standard (control) treatment arm consisted of day 1 paclitaxel 135 mg/m^2 intravenous infusion (IV) over 24 h followed by day 2 IV cisplatin 75 mg/m^2 at a rate of one mg/min. The experimental arm consisted of day 1 paclitaxel 135 mg/m^2 24-h IV infusion followed on day 2 by cisplatin 100 mg/m^2 in 2 liters of saline infused into the peritoneal cavity followed by rolling the patient into four different positions every 15 min to disperse the drug throughout the peritoneal cavity. On day 8, paclitaxel 60 mg/m^2 was administered to the peritoneal cavity diluted in a liter of saline, followed by an additional liter of saline IP. Each cycle was repeated every 3 weeks for six cycles. Pretreatment steroids, antihistamine, cimetitdine, antiemetics, and hydration recommendations were contained in the protocol in general terms, and left to individual investigator discretion.

The specifications for intraperitoneal (IP) access were described in general terms in the protocol appendix, "Peritoneal Dialysis Catheter Implantation Procedure", as dictated by the GOG Surgical Procedures Manual. The catheter could be placed at the time of the original ovarian cancer resection, or delayed until after randomization. Tenckhoff or implanted port with attached fenestrated catheters or ports attached to venous catheters were allowed. The port was to be placed in a subcutaneous pocket overlying the inferior costal margin. The catheter was tunneled down through the subcutaneous tissue until parallel to the umbilicus, and then brought into the peritoneal cavity with a tonsil or tunneling device. Delayed insertion required mini-laparotomy or laparoscopy for catheter placement, but port placement was similar. A mini-laparotomy site several centimeters lateral to the umbilicus was used to identify the peritoneal cavity, into which the catheter was brought under direct visualization. Laparoscopy is described as an alternative. Patients who had peritoneal catheter failures were encouraged to have the IP access device replaced. Those who were unable to be treated using the IP route were treated with the IV regimen (the control arm).

Records were reviewed including operative reports, discharge summaries, pathology reports, GOG data forms, and communications. Data were categorized by extent of surgical procedures performed and whether the IP catheter was placed on the same day as the ovarian cancer resection surgery, or delayed until after randomization. Review of the operative reports and discharge summaries (not actual chart reviews) were used to inform this report; therefore, all complications associated with the initial surgery may not be taken into account. Each case was categorized as to the number of cycles of IP therapy received and, when prematurely discontinued, by the primary and contributing reasons reported. Six cycles of IP chemotherapy were considered successful and all others were considered failures. Reasons for failure were categorized as definitely, possibly, or not, catheter-related.

Quality of life data were prospectively collected from participating patients and will be reported elsewhere [3].

Results

Between March 1998 and January 2001, 214 women were enrolled onto GOG 172 and randomly allocated to receive IP protocol therapy. Nine of these patients were ineligible due to wrong stage ($n = 1$), second primary tumor ($n = 1$), wrong cell type ($n = 4$), inadequate surgery ($n = 1$), or tumor of low malignant potential ($n = 2$). The 205 remaining patients are the subject of this report. A comprehensive clinical report of GOG 172 will be presented elsewhere [3].

Eighty-six women (42%) completed all six cycles of IP chemotherapy and are thus categorized as having successfully completed IP therapy (of note, 83% of the 210 women on the control arm successfully completed six cycles of IV protocol therapy). Among 205 patients, 119 (58%) failed to complete all six cycles of IP therapy (Table 1) including 8% who received no IP therapy and 19% who only received one cycle. Two patients received IV treatment for one cycle due to temporary catheter problems and subsequently completed IP therapy. The remaining 117 patients who discontinued IP therapy were to be treated with the alternate (IV) regimen until they completed six cycles. Among them, 53 patients received IV treatment with cisplatin, 37 were treated with carboplatin, and one received only paclitaxel. Twenty-six patients went off study after discontinuing the IP regimen; in this group, the median number of cycles of IP chemotherapy received was one (range: 0–5). The median interval between primary surgery and the first

Table 1
Number of IP cycles completed ($n = 205$)

No. of IP cycles	No. of patients	% of patients
0	16	8
1	38	19
2	30	15
3	14	7
4	10	5
5	11	5
Failed: <6 cycles	119	58
Success: 6 cycles	86	42
Total	205	100

Table 2
Discontinuation of IP chemotherapy (n = 119)

Reason	Primary	Contributing
Catheter-related	40	10
IP catheter infection	21	4
IP catheter blocked	10	0
IP catheter leak	3	2
Access problems	5	3
Fluid leak out vagina	1	1
Not IP catheter-related	34	28
Nausea/vomiting/dehydration	16	16
Renal/metabolic	15	12
Disease progression	3	0
Possibly IP treatment-related	45	42
Other infection (not catheter)	7	5
Abdominal pain	4	16
Patient refusal	19	8
Bowel complication	4	4
Other	11	9

cycle of protocol chemotherapy were 25 days and 25.5 days, respectively, for patients who did versus did not complete six cycles of IP therapy.

Multiple reasons for discontinuing IP therapy were reported, and these were categorized as to whether or not they were related to the peritoneal access device (Table 2). In 34 (29%) patients, the reason for discontinuing IP treatment was clearly unrelated to the device itself and included nausea, vomiting, dehydration, and renal/metabolic disturbances. Three patients discontinued IP chemotherapy due to progression of disease. IP therapy was discontinued in 40 (34%) patients primarily for IP catheter complications including catheter infection (n = 21); blocked catheter (n = 10); leaking catheter (n = 3); IP infusion leaking from vagina (n = 1); and port access problems (n = 5). Other reasons for discontinuing therapy, which were considered possibly IP infusion- or catheter-related included major bowel complications (n = 4); infections possibly unrelated to the access device (n = 7); abdominal pain (n = 4); and patient refusal (n = 19). Eleven of the cases could not be reliably classified. Seven patients had a malfunctioning IP access device replaced, four of which successfully completed therapy. Sixteen patients never received any IP therapy, of whom nine never had an IP catheter placed. Reasons given for failure to place an IP catheter were disease progression (n = 3), adhesions (n = 2), patient refusal (n = 3), and inability of the radiologist to identify free peritoneal space (n = 1).

Table 3
Extent of surgical resection prior to study treatment

Extent of surgical resection	Failed to complete IP therapy			
	(n = 119)		(n = 86)	
	Yes	(%)	No	(%)
Hysterectomy	94	79	71	83
Appendectomy	40	34	32	37
Rt colon/cecum	9	8	7	8
Lt colon/rectosigmoid	33	28	17	20
Small bowel resection	11	9	6	7
Colostomy	7	6	2	2

Table 4
Cycles of IP chemotherapy completed if left colon resected (n = 205)

No. of cycles completed	Left colon resection				Total
	No	(%)	Yes	(%)	
0	8	5	8	16	15
1	30	19	8	16	39
2	20	13	10	20	30
3	11	7	3	6	14
4	8	5	2	4	10
5	9	6	2	4	11
6	69	44	17	34	86
Total	155		50		205

The primary surgical procedures performed to achieve optimal cytoreduction of ovarian cancer, which could potentially have contributed to catheter complications, are depicted in Table 3. A hysterectomy was performed in 165 (80%), appendectomy in 72 (35%), left colon or rectosigmoid resection in 50 (24.3%), right colon resection in 16 (8%), colostomy in 9 (4%), and small bowel resection in 17 (7%) patients. Bowel resections occurred in 32.2% of the women who were randomly allocated to the IP arm. The only surgery which was performed more often among patients who failed to initiate IP therapy was rectosigmoid or left colon resection. Of the patients who had left colon/rectosigmoid resection, 8/50 (16%) did not initiate the IP therapy compared to only 8/155 (5%) among those not having the procedure (Fisher's Exact Test, P = 0.012). Among patients who started IP therapy, the number of completed chemotherapy cycles was similar for patients who did versus did not undergo a left colon resection (Table 4).

Sixteen patients never initiated IP chemotherapy, of whom eight had left colon resections and three had right colon resections. Among the eight patients having left colon resection, reasons IP therapy was not initiated include: enterocutaneous fistula (n = 1); adhesions preventing catheter placement (n = 1); catheter malfunction (n = 4); brain metastases (n = 1); and patient refusal (n = 1).

The timing of the placement of the IP catheter was examined to see if delayed insertion improved tolerance of IP therapy, rather than at the same setting of the ovarian cancer resection surgery. Among 49 patients who had their catheters placed during primary surgery, 18 (37%) completed six cycles of IP chemotherapy compared to 55 (41%) of 133 patients whose catheter insertion was delayed (the timing of IP catheter placement was not provided for 23 patients). There was no association between timing of catheter insertion and failure to complete IP therapy.

Discussion

Three large randomized trials have shown the advantage of IP therapy over systemic therapy in stage III small volume ovarian cancer, but the toxicities and complications remain a concern and appear to be a serious obstacle to widespread implementation of this approach [1–7]. In GOG 172, only 42% of patients randomized to receive IP therapy completed the intended six cycles. It is possible that improvements in

technique and patient tolerance could result in a greater survival benefit. An alternative hypothesis is that less than six cycles of IP chemotherapy is adequate to achieve an improved survival.

Reasons for discontinuing IP therapy were categorized by whether or not they were related to the peritoneal access device, and took into account: (1) intolerance to the high doses of cisplatin, or inadequate hydration and supportive care (resulting in nausea, vomiting, dehydration, and renal and metabolic effects); (2) IP access device-related, demonstrated as either failure to place, or a complication/problem following insertion; (3) intolerance of the abdominal distention from the IP infusion of 2 liters of fluid or the drug it contained.

Gadducci et al. [8] described the challenges of IP chemotherapy following the closure of their trial due to inadequate enrollment (113 participants were enrolled out of the targeted accrual of 330). They reported that 22 patients (two from the IV arm and 20 from the IP arm) did not complete their assigned treatment. Of the IP patients, six refused further therapy, three had catheter obstruction, three had bowel perforations, two had abdominal pain, one experienced chemical peritonitis, and five had other reasons. The frequency of toxicity of IP therapy in the 46 evaluable participants was 8.7% catheter obstruction, 2% skin infection, 28.2% mild abdominal pain, and 21.7% moderate abdominal pain. The authors report that the surgeons participating in this trial mainly used temporary catheters, and that improved access and physician acceptance are necessary for IP therapy to be feasible.

Fujiwara et al. [9] reported on 165 patients who received IP carboplatin chemotherapy, of whom 16 (9.6%) had catheter-related complications and a total of 24 women terminated their IP chemotherapy early. The reasons for cessation of IP treatment included obstruction of catheter in eight patients, infection in four, pain in three, ileus in one, progressive disease in six (3.6%), and undefined in two.

Davidson et al. [10] evaluated 227 cases of IP chemotherapy and found that 20 (8.8%) patients had catheter obstruction, of whom 8 (3%) had bowel perforations. Catheter infection rates and complications increased when the catheters were replaced. They observed an association with increased IP toxicity in women who underwent gastrointestinal procedures (colectomy and appendectomy), that was not statistically significant. Catheter infections were found in 4.3% of women having small bowel surgery at the time of the ovarian cancer debulking, in 16% of those having large bowel surgery, and in 15.4% of the women who underwent appendectomy. They noted that, "optimally debulked ovarian cancer, which does not require contamination of the peritoneal cavity by bowel surgery, will have fewer complications". The recommendation based on that review was to place IP catheters a few weeks after the original laparotomy if a large bowel surgery was performed.

Bowel complications associated with IP catheters have been reported to occur at a rate of 3–5% and include fistulas, catheter migration into the bowel lumen, bowel obstructions, and perforations [11–16]. The original Tenckhoff peritoneal dialysis catheters had two major problems when used for ovarian cancer chemotherapy. First, the catheter fenestrations in the peritoneal cavity appear to cause a fibrous sheath formation that causes adhesions. Second, they have a Dacron cuff which was to be fixed into the abdominal wall to prevent catheter movement and leaking along the track. Reports of migration of the Dacron cuff into the peritoneal cavity have been thought to be a cause of some bowel obstructions. Catheters have been found in the bowel lumen and have been seen protruding through the rectum and vagina.

In the current study, there were eight major bowel complications on the IP arm, four of which were the primary reason for IP failure. The catheter type was not noted in these cases.

There was no relationship between appendectomy, small bowel resection or right colon resection, and IP failure. There appeared to be a problem initiating the first cycle of IP therapy in patients who had left colon resection, some were secondary to inability to place the infusion device. It was not possible to compare those cases where low rectal anastamosis was performed versus an end colostomy due to the small number of cases.

Women who are to have IP chemotherapy (when not on a randomized trial) may have the IP access device placed at the time of primary surgery as long as contamination has not occurred. IP catheters should be removed as soon as they are no longer required for current therapy. They should not be retained for future use, since the complication rates are high, even when not being used [15].

Delayed IP catheter insertion is a potential way to avoid introducing bacteria into the catheter in a contaminated field. Avoiding peritoneal dialysis catheters with fenestrated holes on the sides and implanting only ports developed as venous access devices for IP chemotherapy administration may also decrease complications. Makhija et al. [17] reported their experience with IP chemotherapy. To avoid contamination, they stopped inserting IP catheters during the ovarian cancer debulking surgery when a bowel resection was performed. A 9.6 Fr silicone venous access catheter is used to prevent kinking in the peritoneal cavity and is attached to an implantable subcutaneous port. It is pulled into the peritoneal cavity through the abdominal wall with a tonsil through a 3 mm perforation and left a minimum of 10 cm in the peritoneal cavity under direct visualization via a separate small laparotomy incision 6 cm lateral to the umbilicus. The wound needs to be closed in layers to prevent leaking of IP fluid during infusion, and treatment is not initiated for at least 24 h. The catheter is then tunneled 10 or more cm through the subcutaneous tissues above the fascia from the insertion site, and attached to a single lumen port. The port sutured to the lower rib is easy to place, easy to access, and can be removed without reentry into the peritoneal cavity. The port is sutured in four corners with prolene to the fascia overlying the lower ribs at the anterior axillary line. With these changes in technique, Makhija et al. [17] reduced their complication rate from 17.6% to 10%. There have been no intestinal obstructions or perforations since these changes were implemented

Table 5
Complications of IP access devices

	Piccart [14] fenestrated (n = 143)		Davidson [10] Port-A-Cath (n = 227)		Makhija [17] venous device (n = 301)		GOG 172 [3] (n = 205)	
	No.	%	No.	%	No.	%	No.	%
Port complications	6	11.1	40	17.6	30	10	40	19.5
Inflow obstruction	3	2	20	8.8	19	6.3	18	8.8
Infection	12	8	12	5.3	11	3.7	21	10.2
Bowel injury	2	1.4	8	3.5	0	0	4	2

(Table 5). This report cannot substantiate this proposed access device placement technique since it was not prospectively studied during this trial.

Delay of IP therapy allows opportunity for adhesion development, and may limit access of IP fluid to important locations of tumor spread. There is theoretical benefit of infusing the peritoneal cavity immediately following surgery, when the tumor is likely to be exposed and can be directly bathed by the chemotherapy drug. Segna et al. [18] demonstrated feasibility of immediate intraoperative chemotherapy for ovarian cancer with tolerable morbidity.

Table 5 lists the problems described by Davidson [10], Piccart [14], Makhija [17], and those encountered on GOG 172. Future trials must strictly specify peritoneal access device placement requirements for prospective data analysis, and documentation of surgical procedures and complications. Laparoscopic techniques [19] and percutaneous implantation [20] after fluoroscopically identifying the peritoneal cavity are well described and have reported successful peritoneal access device placement. These various techniques need standardization and monitoring on future trials.

Paclitaxel, when administered intravenously, has been reported by Seewaldt [21,22], Rose, and Piver [23] to contribute to bowel perforation approximately 2 weeks after the first or second cycle. They hypothesize an unmasking of a subclinical leak or bowel injury. They noted an event rate of 2.3% and a mortality rate of 43% when this complication occurred. It is possible that the addition of IV or IP paclitaxel therapy, rather than the IP cisplatin, is the etiology of these symptoms or complications. The survival advantage of this regimen may not be maintained if the IP paclitaxel was to be deleted from future regimens, so this theory must be considered with caution.

Supportive care related to high dose cisplatin could be improved with better hydration, new or improved schedules for antiemetics, and reassurance that long-term quality of life and survival are excellent. Some investigators did not prehydrate with saline and monitor urine output prior to cisplatin administered IP. The 2 liters of IP fluid does not replace the need for intravascular saline administration and documentation of adequate urine output. The 1 liter of saline hydration prior to cisplatin and 1 liter after cisplatin with at least 100 cm^3 of urine output per hour continues to be recommended. Alternatively, toxicity could potentially be overcome with the use of agents with less acute toxicity (i.e. carboplatin), or the use of alternate dose and schedule of the same drugs. However, since these changes could affect the survival advantage, they will need to be tested in phase III trials.

Successful IP administration requires alteration of surgical technique, device alterations, and selection of patients less prone to complications. Venous access devices (single lumen silicone Bardport or Deltec) should be utilized rather than Tenckhoff catheters or peritoneal “Port a Cath” (Deltec) designed for peritoneal dialysis. Avoiding insertion of access devices at the time of left colon/rectosigmoid bowel resections is appropriate if the peritoneal cavity is grossly contaminated. The use of IP chemotherapy after rectosigmoid colon resections requires further study, to consider delayed insertion of the access device, and to determine if time is needed for wound healing prior to initiation of IP chemotherapy.

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