Intraperitoneal Chemotherapy for Epithelial Ovarian Cancer – Single Center Experience

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Abstract Majority of intraperitoneal (IP) chemotherapy complications were related to the chemoport. Aim of our study was to find the means of reducing complications of IP chemoport, to increase the benefits of IP chemotherapy. During January 2007 to December 2010, hundred consecutive patients of stage III epithelial ovarian cancer who had optimal cytoreduction underwent chemoport insertion during laparotomy. Initial 20 cases had 14.3Fr Bard IP chemoport, and later cases had 9.6Fr single lumen venous port inserted intraperitoneally. Entry point into the peritoneum was single, 6 cm lateral to the umbilicus and double purse-string suture taken around the catheter to prevent pericatheter backflow of ascitic fluid or drug. Modified IP chemotherapy regimen (SWOG-9912 trial) was used. Age of the patient ranged from 34 years to 76 years. In total 600 cycles, 516 cycles (86 %) were completed. Seventy patients (70 %) received all the 6 cycles by IP route. Two in the initial 10 patients had vaginal leak, for whom first 2 cycles were given by IV route and then shifted to IP route. Subsequently all cases had double layer closure of vaginal vault. Nine patients (9 %) had port related complications, in which 8 were transient. Catheter block was seen in 5 cases, of which 4 salvaged by heparin injection lock for 2 h and in subsequent cases IV port access catheter with valve replaced the fenestrated IP catheter. None of the IV catheters had the block. Four cases had backflow of fluid around catheter collecting around the port chamber site. Two patients had severe abdominal pain due to dense adhesions and further

cycles were completed by IV route. Cisplatin was replaced with carboplatin in 5 cases with severe toxicity. Longest follow-up is 4 years with median follow up of 1.8 years. 70 % are disease free on follow up. Local recurrence rate was 18 and systemic in 8 cases. Mortality rate is 4 %. Complications of IP ports are low when insertion is done meticulously with a dedicated team. With modified IP dose and drug regimen, side effects are less and most patients can complete all the desired cycles.

Keywords Intraperitoneal chemotherapy · Ovarian cancer · Chemotherapy

Introduction

Intraperitoneal (IP) chemotherapy is considered superior method to standard intravenous (IV) chemotherapy in stage III epithelial ovarian carcinoma after three major randomized trial reports [1–3]. Walker et al. reported in their study, 58 % of patients failed to complete all six cycles of IP therapy and 34 % discontinued primarily because of catheter related complications [4]. Nearly 6 years have passed since the Armstrong publication [3], but still this method is not widely practiced. We undertook this study with the goal of reducing complications related to IP port, and to increase the successful administration of this treatment modality for superior patient benefit.

Patients and Methods

Patients

Between January 2007 and December 2010, one hundred consecutive patients of stage III epithelial ovarian cancer

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with ECOG performance status of 0–1, who had optimal cytoreduction at Manipal Comprehensive Cancer Center, Manipal Hospital, Bangalore were included in the study. Optimal cytoreduction was defined as leaving no residual mass greater than 1 cm in diameter after surgery. Institutional review board approval was taken.

IP Chemoport Insertion Technique

All patients underwent chemoport insertion during optimal cytoreduction. It was done by experienced oncosurgeons and also by oncosurgery residents under training after observing 5 insertions. A transverse incision slightly larger than the port was made for chamber placement in subcutaneous pocket at the midclavicular line, overlying the inferior costal margin. Catheter is tunneled under the subcutaneous tissue, above the fascia, to a point 6 cm lateral to the umbilicus with a tunneling device. Tunneling of the catheter was meticulous, single thrust without great disturbance to subcutaneous tissue. At this point, catheter is pulled into the peritoneal cavity through a single small hole, and double purse-string suture taken around the entry point to prevent peri-catheter backflow of ascitic fluid or drug. The catheter was cut to a length of 15 cm and left free in the peritoneal cavity. Catheter is connected to the port and chamber was fixed to the underlying fascia with 2–0 prolene. Initial 20 cases had 14.3Fr Bard IP port (Bard access systems, Inc. Salt Lake City, UT 84116 USA, product code 0603000), and later cases had 9.6Fr venous port inserted. Non-coring winged infusion set 20 gauge needle of 1 inch length is used to access the port.

Treatment Plan

Modified IP chemotherapy regimen with day1- paclitaxel IV (135 mg/m² over 3 h), day 2-cisplatin (75 mg/m²) and on day 8- paclitaxel IP (60 mg/m²) was given 3 weeks after cytoreductive surgery with patient in supine or semi-Fowler's position with her head no higher than 30° above the bed. Adequate hydration and premedications were given. For intraperitoneal therapy, 1 l of warmed saline is infused first, which confirms the intact vaginal vault and volume tolerability, followed by paclitaxel or cisplatin was reconstituted in 1 l of warmed normal saline and infused by gravity through IP port. After completing the infusion, patients are asked to change position at 15 min intervals for 2 h to ensure adequate intra-abdominal distribution. Treatment was given every 3 weeks for 6 cycles. All ports were removed 3 weeks after completion of last cycle of chemotherapy.

Results

Age of the patient ranged from 34 years to 76 years, with a median age of 58 years. Most (46) of the patients were in their fifth decade, followed by sixth decade (30 patients) of life. In the present study we left no visible residual disease after cytoreduction. Side of insertion was routinely on the left and only 13 % had it on the right. Patients who had extensive disease or bowel resection and anastomosis on the left side, were chosen for right side insertion. Out of a total of 600 cycles, 516 cycles (86 %) were completed. Seventy patients (70 %) received all the 6 cycles by IP route (Table 1).

Catheter related complications were seen in the initial period of our study (Table 2). Two of the initial ten patients had vaginal leak. It was a surprise for us in the beginning when patient started passing large amount of involuntary fluid per vaginum. In these patients first two cycles were given by IV route allowing gap in the vault to close by healing and IP chemotherapy was started from third cycle. All cases subsequent to this had double layer closure of vaginal vault with 2–0 vicryl and we never had any further complications. Infusion of 1 l of normal saline into the peritoneal cavity prior to the drug was reassuring.

Catheter block was seen in five cases. In four cases it was salvaged by locking the catheter with heparin injection for 2 h. Filling the catheters with heparin is known as locking. In subsequent cases single lumen IV port access (9.6Fr Bard venous access) catheter with Groshong tip replaced the fenestrated IP catheter (14.3Fr Bard IP access). None of the IV catheters had the block.

Two cases had backflow of fluid around the catheter and fluid tracked to collect around the port chamber site. Development of ascites or the presence of large amount of infusate itself may create increased pressure in the intra-abdominal compartment for fluid to track out along the gaps available. Double purse-string suture around the intraperitoneal entry point of catheter in subsequent cases helped in alleviating this complication. Two cases had needle displacement and extravasation of drug around the port chamber. Patient had local pain associated with erythema on the overlying skin. Immediate aspiration of fluid with wide bore needle and

Table 1 Number of chemotherapy cycles completed

Sl.No	Cycles completed	Number of patients
1	6	70 %
2	5	4 %
3	4	13 %
4	3	5 %
5	2	1 %
6	1	7 %

Table 2 Complications of IP chemotherapy

Complications	Number of patients
Cisplatin induced toxicity	5 % (<i>n</i> =5)
Vaginal leak	2 % (<i>n</i> =2)
Catheter block	5 % (<i>n</i> =5)
Extravasation/back flow	4 % (<i>n</i> =4)
Bowel complications	Nil
Infection	Nil
Severe abdominal pain	2 % (<i>n</i> =2)

anti-inflammatory drugs enabled patient to recover. Subsequently access of port was made only by trained staff.

Two patients had severe abdominal pain (grade 3 of Common Terminology Criteria for Adverse Events version 4.0) after infusion of saline. This was due to dense adhesions and unequal distribution of drug confirmed on radionuclide scan. Further cycles were completed by IV route. Cisplatin was replaced with carboplatin in five cases with severe toxicity. No dose modifications were done. There were no bowel complications or catheter related infections. Longest follow-up was 4 years with median follow up of 1.8 years. 70 % were disease free on follow up. Local recurrence rate was 18 and systemic in 8 cases. Mortality rate was 4 %.

Discussion

Toxicities and catheter related complications remain the major obstacle for wide spread implementation of intraperitoneal chemotherapy. The successful delivery of six cycles of IP chemotherapy was seen in only 42 % of the participants in the Armstrong's trial and major reason for discontinuation of IP chemotherapy was due to catheter complications [3]. In our study, 70 % of the patients completed six cycles.

Optimal timing of catheter insertion has not been established. In our study, port was placed during cytoreductive surgery. Delayed insertion necessitates a second surgical procedure and many patients are reluctant to have second operation for port placement. It is easier to remove a device that is not required than it is to place one at a second surgery and chemotherapy can be started in time. Delay of IP therapy allows opportunity for adhesion development, and may limit access of IP fluid to important locations of tumor spread. Transverse colon will be adherent to anterior abdominal wall after omentectomy and delayed insertion is associated with difficulty in identifying free IP space to avoid injury to bowel. It can be done by mini-laparotomy or laparoscopic method, but peritoneum should be entered under direct vision. Delayed insertion is done when peritoneal cavity is grossly contaminated [4]. Analysis of data

from GOG 172 suggests that delayed placement of an IP port did not decrease the likelihood of complications [4].

GOG 172 trial reported one case of vaginal leak and we too had two cases. It never required additional treatment but to give adequate time for the vault to heal. In 34 % of patients catheter related complications contributed to discontinuation of IP chemotherapy in GOG172 trial [4]. Though we had nine patients with catheter related problems, only one patient had to permanently discontinue further cycles and rest of the patients received less than six cycles. Catheter infection rate was very high (17.85 %) in that trial but we never had one. Davidson et al. [5] reported catheter infection in 4.3 % of women having small bowel surgery, in 16 % of those having large bowel surgery and 15.4 % of the women who underwent appendectomy. Makhija et al. [6] stopped inserting IP catheters when bowel resection was performed to avoid contamination. Eight patients in our series underwent bowel resection and primary anastomosis guiding us to place the port on the opposite side but it never made any difference in the final outcome. Preoperative bowel preparation was routine in all the cases. There was no relation between initiation of IP therapy and left colon or rectosigmoid resection as against reported in GOG172 trial. Walker et al. [4] also reported catheter block in 8.5 %, access problem in 4.2 % and catheter leak in 2.5 % of patients.

In our study, there were no complications related to bowel, though reported to occur at a rate of 3–5 % and include fistulas, catheter migration in to the bowel lumen, bowel obstruction and perforations [7–12]. In our study, none of the venous catheters had obstruction but in the initial 20 fenestrated catheters five had obstruction, indicating that venous catheters are less prone for obstruction. Fenestrated catheter causes fibrous sheath formation that can cause adhesions [2, 4], though recent studies have reported low complication rates [13–15]. Formation of adhesions or obstruction is not related to the experience of the surgeon or technique of insertion, as most of initial insertions were done by experienced oncosurgeons and technique is standardized. In four cases, heparin for 2 h, helped on unblocking the catheter. The exact cause of obstruction and mechanism of action of heparin is unknown. Resistance was only for the first cycle to begin with, and subsequently there was easy flow. Probably heparin had some indirect action on not so dense fibrin or continued contact of fluid dissolved the block or it was an evolving clot. It needs further evaluation. One catheter which could not be salvaged was removed and was found to be blocked with fibrin. Potential benefits of adhesion barriers have not been validated in a randomized trial. IP catheters should be removed after completion of current therapy, as complication rates are high, on retaining for longer period [11]. It is removed under local anesthesia on outpatient basis.

In our study, IP chemotherapy was started on an average 3 weeks after the cytoreductive surgery, with median 21 days (range between 19 days to 25 days). Delay in IP therapy allows opportunity for adhesion development and may limit access of IP fluid spread. Abdominal pain is thought to be related to stretching and distension of bowel-to-bowel adhesions. The symptom of pain is an evidence that the distribution of drug is likely to be less than ideal. Low grade abdominal pain can usually be treated with opioids [16]. GOG trial 172 mandated dose reduction with grade 2 abdominal pain and change over to IV chemotherapy for those with grade 3 abdominal pain.

There has been an active interest in developing alternative treatment regimens to reduce toxicities and tolerability without compromise of the survival benefit [17]. Southwest Oncology Group (SWOG-9912) trial used 3 h infusion of paclitaxel at 135 mg/m² on day 1 IP cisplatin 75 mg/m² on day 2 and IP paclitaxel 60 mg/m² on day 8. By switching to 3 h infusion, the myelosuppressive activity of IV paclitaxel is greatly diminished and the 135 mg/m² dose (as compared with the 175 mg/m² dose) has less potential to cause neurotoxicity when combined with IP cisplatin [18]. It is reasonable to reduce IP cisplatin to 75 mg/m² as tolerability is substantially improved, without interfering with documented benefits of regional drug delivery. Major justification for this statement comes from the fact that with IP administration, the 10–20 fold higher concentration of the cytotoxic agent will still be in direct contact with the tumor within the peritoneal cavity, even though the systemic exposure is reduced modestly [19–22]. Berlin JN et al. has reported that by modifying the GOG 172 treatment regimen, convenience, toxicity, and tolerability appear improved, with survival outcomes similar to those of GOG 172 [23]. GOG 9916 and 9917 were opened to evaluate IP carboplatin. Konner et al. [24] reported on a phase II trial from Memorial Sloan-Kettering Cancer Center using a modified regimen as used in our study but with cycle 2, bevacizumab at 15 mg/m² was included on day 1 of treatment. At interim analysis, 80 % of patients either had completed 6 cycles or were continuing on protocol with this IP regimen. Grade 3–4 toxicities occurred in approximately 10 % of patients, with the exception of neutropenia which occurred in 26 % of patients. These data suggest that addition of bevacizumab to this IV/IP regimen is feasible and preliminarily indicates a high rate of successful completion of IP therapy with limited toxicity. The currently open GOG 252 trial takes into account issues pertaining to dose dense therapy, IP therapy and the inclusion of bevacizumab in front-line treatment in order to establish the most effective approach. It has arm 1- IV paclitaxel and IV carboplatin with bevacizumab, arm 2- IV paclitaxel and IP carboplatin with bevacizumab and arm 3 – IV paclitaxel, IP cisplatin and IP paclitaxel with bevacizumab. This study will include stage II and III patients with

ovarian, fallopian tube, and peritoneal adenocarcinoma, and it is expected to accrue 1,500 patients. The bevacizumab will be dropped if the results of the GOG 218 study are not supportive of the control arm as a new standard. The primary objective is to determine if IP chemotherapy demonstrates improved progression free survival to IV administration and if either IP cisplatin or IP carboplatin demonstrates improved progression free survival. Secondary objectives include analysis of the reduction of death with IP chemotherapy and adverse events.

Simple techniques at port placement like adequate incision, limited subcutaneous dissection, meticulous tunneling of catheter, single entry hole in the peritoneum, double purse-string suture at the catheter entry point into the peritoneum, use of single lumen venous access catheter, vaginal vault closure in double layer and placing port on right side when extensive dissection is done on left side resulted in few complications.

Precautions observed during infusion of IP chemotherapy were access of port by well trained staff, use of large plain tegaderm dressing to hold the needle in place after access and above all complete aseptic precaution. With the use of modified drug regimen, tolerance was good in our study, with minimal toxicity. We conclude that it is possible to administer more number of cycles by improving port placement techniques, careful delivery of drugs with trained staff and selecting modified chemotherapy regimen, which provides superior benefit to the patient than IV chemotherapy.

Conflict of interest The authors declare that they have no conflict of interest

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