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Phase II study of Intraperitoneal Chemotherapy in patients with inoperable Ovarian and Primary Peritoneal Cancers

KEYWORDS

Abdul Majeed K
Additional Professor, Division of Haematology & Medical Oncology. GovtMCH, Kozhikode

GanesanTS
Professor, Department of Medical and Paediatric oncology Cancer Institute (WIA) Chennai

Pavithran K
Professor, Head of Department of medical oncology Amrita institute Of Medical science Cochin

Vijaykumar D. K
Professor, Surgical Oncology Amrita institute Of Medical science Cochin

ABSTRACT

BACKGROUND: *Epithelial ovarian cancer is the leading cause of death from gynecologic cancer world wide. As most patients present with advanced disease, chemotherapy is a crucial adjunct to surgical cytoreduction. In the last 10 years, three large prospective phase III clinical trials have shown survival advantages for patients receiving IP versus IV chemotherapy for the treatment of optimally cytoreduced, advanced ovarian cancer. Despite this demonstrated survival advantage, IP chemotherapy continues to await universal acceptance as first-line treatment for advanced epithelial ovarian cancer.*

PATIENTS AND METHODS: *Between November 2007 and June 2009, total of 25 patients with histology proven inoperable stage IIIC or IV epithelial ovarian and primary peritoneal cancers were offered the IP therapy but only 18 patients gave consent for study. The age varied from 29 to 67 median age 54yrs.Selected patients were initially treated with six cycles of systemic chemotherapy with Paclitaxel and Carboplatin, responding patients underwent optimal cytoreductive surgery and catheter placement. Intraperitoneal chemotherapy with cisplatin 75 mg/M2 was given for three cycles every 3 weeks. Patients with catheter block were treated with direct puncture technique.*

RESULTS : *A total of 29 cycles were administered. 14 cycles were given with IP catheter and 15 cycles with direct puncture technique. 8/11 patients received all planned cycles of IP therapy. Major toxicities noticed in patients with IP catheter include blocked catheter, sepsis and abdominal pain. Direct puncture technique was without any toxicity related to the procedure. Quality of life assessment by using global health status scale was better in patients who received IP chemotherapy through direct puncture (n=7) compared to chemotherapy using IP catheter [n=8]. (P value less than 0.001).*

CONCLUSIONS : *Intraperitoneal chemotherapy by direct puncture technique is feasible without any major catheter related toxicities even in the post operative setting after six cycles of chemotherapy. IP therapy by silastic catheter is associated with catheter related toxicities in a majority of patients. IP chemotherapy by Cisplatin can be safely administered on an out patient basis which will reduce the cost of therapy and the need for hospitalization.*

INTRODUCTION

- Epithelial ovarian cancer is the leading cause of death from gynecologic cancer world wide. In India, estimated number of carcinoma ovary in 2009 is 29,929 and for 2015 it is estimated that there would be 33,218 new cancer cases of ovary in the country [1].In the United States it is the fifth most common causes of mortality in women. In the year 2009 there will be an estimated 21550 new diagnoses and an estimated 14600 deaths from neoplasm in the United States; less than 40% of women with ovarian cancer are cured [2]. As most patients present with advanced disease, chemotherapy is a crucial adjunct to surgical cytoreduction. The combination of a platinum and taxane agent has proven effective in improving the overall survival in these patients [3] and the intravenous (IV) regimen of carboplatin and paclitaxel is currently the most frequently used treatment. This regimen is used widely as it has equal efficacy and less toxicity when compared with a combination of IV cisplatin and paclitaxel [4]. Besides the intravenous route, chemotherapy can be instilled directly into the peritoneal cavity, the principal site of disease in ovarian cancer. Intraperitoneal (IP) chemotherapy was first proposed in the 1970s as a way to maximize drug delivery to the tumor while avoiding systemic toxicities associated with IV administration of the same agents [5-8] Owing to the unique properties of the peritoneum, IP chemotherapy affords the opportunity to use higher concentrations of drugs for prolonged periods of time to directly bathe resected tumor beds, lymph node basins, and residual tumor nodules. Many chemotherapeutic agents used in the treatment of ovarian cancer, including cisplatin and paclitaxel, have been found to be effective and safe for intraperitoneal administration [5,8].In the last 10 years, three large prospective phase III clinical trials have shown survival advantages for patients receiving IP versus IV chemotherapy for the treatment of optimally cytoreduced, advanced ovarian cancer [9-11].Despite this demonstrated survival advantage, IP chemotherapy continues to await universal acceptance as first-line treatment for advanced epithelial ovarian cancer. Recognized barriers to its widespread use include increased cost, inconvenience of inpatient administration, and the potential for increased toxicities and catheter complications. Also, there has been concerns expressed by certain authors as to whether the benefits seen in the IP therapy trial was due to higher doses of cisplatin used and the weekly scheduling. A well-designed study of intraperitoneal therapy has completed enrolment and should report soon. (NCT00951496))

PATIENTS AND METHODS

Women with inoperable histology proven epithelial ovarian cancer stage III, & IV and primary peritoneal cancers with ECOG performance status of 2 or less, with absolute neutrophil count >1.5 X 109/L,platelet count > 100 X 109/L, haemoglobin > 10 gm./dL,creatinine clearance estimated with Cockcroft–Gault>60 ml/min, aspartate aminotransferase (AST) < 2 X upper limit of normal (ULN), alanine aminotransferase (ALT) <

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2 X ULN, in case of liver metastasis, < 5 X ULN ,total bilirubin < 1.6 mg/dl, competent to comprehend, sign and date an Institutional ethical committee approved informed consent form where included in the study. Patients with operable cases of ovarian cancer,other comorbid conditions which prevent the use of chemotherapy, performance status ECOG III & IV, patients who are refractory or progress during first line chemotherapy where excluded from the study. Patients should have optimal debulking after six cycles of chemotherapy.All the patients selected for the study had their complete blood examination, liver function test, renal function test, CA 125, CEA, X ray chest, USG abdomen/CT Scan abdomen done.

Selected patients were treated with six cycles of intravenous Paclitaxel and Carboplatin followed by surgery, which will include TAH, BSO and omentectomy as the minimum and with intraperitoneal Cisplatin 3 weeks following surgery. The treatment comprised of 3 cycles at 3 weekly intervals of Cisplatin at 75mg/m2 administered intraperitoneally. The catheter used was silastic catheter which was placed inside the peritoneal cavity at the time of cytoreductive surgery with distal end kept outside. Chemotherapy was started 3weeks after optimal cytoreductive surgery. Patients were hydrated with 500 ml of normal saline and 500 ml of Isolyte M administered in 4 hours as intravenously. Premedication consisted of Dexamethasone 20 mg, Ondansetron 8 mg and Ranitidine 150 mg orally given 30 minutes before starting chemo therapy.Cisplatin 75mg /m2 were administered in one litre of normal saline Intraperitoneally. One litre of saline was administered through the IP catheter over one hour. After infusion all patients were asked to lie in three different positions. All patients were given 500 ml of normal saline with 20 milli equivalents of KCl in 3 hrs and 500 ml of normal saline with 1 ml of magnesium sulphate 25% in 2 hrs. Patient should have absolute neutrophil count greater than 1500cells/micro-litre, platelet count greater than 100000 cells/ micro litre and creatinine clearance greater than 50 ml /mt to begin a new cycle of IP therapy. Patients who had catheter block or needed intraperitoneal catheter removal due to any reason were given intraperitoneal therapy by direct puncture technique with 16 G peripheral IV canula. Cisplatin dose modification was done for toxicity. For neurotoxicity grade 2, a 50% of Cisplatin dose was given and drug was not given for grade 3 and 4 toxicity. For abdominal pain - Grade 2 severity a dose reduction of 20 % of Cisplatin and 40% for grade 3 or 4 abdominal pain. Cisplatin was not given if the creatinine clearance decreased below 40ml/minute, and on recovery, dose adjustments to 75% of initial dose was given for that and subsequent cycles. Patients are monitored with physical examination, complete blood counts, and serum creatinine serum bilirubin, and CA125 analysis before the initiation of each cycle of therapy.

RESULTS

Patients

Between November 2007 and June 2009, total of 25 patients with inoperable stage IIIC or IV epithelial ovarian and primary peritoneal cancers were offered the IP therapy but only 18 patients gave consent for study. The age varied from 29 to 67 with a median age of 54 yrs. Performance status varied from ECOG PS 0 to 2.16/18 patients presented with abdominal distension, 14/18 had vague abdominal pain and 5 patients presented with abdominal mass as presenting symptom. There were 15 patients with epithelial ovarian cancer and 3 patients with primary peritoneal cancer. 14 patients had FIGO stage III C and 4 with stage IV cancer. Serum CA 125 ranged from 13 u/ml to 150000 u/ml, with two patients had normal CA 125 (below 36 U/ml).13 patients had papillary adenocarcinoma and four patients had adenocarcinoma. (Table-1)

Neoadjuvant chemotherapy

Of the 18 patients who received neoadjuvant chemotherapy, 14 patients completed all 6 cycles of chemotherapy. 12 patients received paclitaxel and carboplatin as chemotherapy for all 6 cycles and 2 patients had single agent carboplatin after cycle 1 due to financial reasons. 14/18 who had 6 cycles of neoadjuvant chemotherapy underwent surgery. Three patients (3/18) opted for surgery after 3 cycles of neoadjuvant chemotherapy and were not given intraperitoneal chemotherapy. One patient (1/15) died after first cycle of chemotherapy. Planned treatment was possible only in 15 patients.

Neoadjuvant chemotherapy Toxicity (NCI toxicity criteria)

Vomiting (grade 2) was observed in 3/18 patients and grade 3 in 3/18. All patients had grade 2 alopecia. Neutropenia was observed in 3/18 patients (grade 3=2; grade 2=1).One patient had grade 3 anemia. 3/18 patients had grade 1 neuropathy.

Pathologic response at surgery

Out of 18 patients 14 patients underwent surgery after 6 cycles of chemotherapy.13 /14 had optimal cytoreduction (optimal cytoreduction defined as no visible tumor at any one site more than 1 cm) and four of them had pathological complete response. (pCR). The remaining one patient had inoperable disease. No patient had bowel resection during surgery.

Intraperitoneal chemotherapy

IP catheter was inserted at surgery in 13/14 patients. The remaining one patient, catheter was not inserted due to inoperable disease. In one patient catheter was displaced before starting chemo. One patient had severe phobia following the IP catheter placement and catheter was removed. One patient excluded from the study due to low performance status and delayed recovery following cytoreductive surgery. 11/14 patients were given intraperitoneal chemotherapy. In view of difficulties of administering chemotherapy via the catheter infection, catheter block, abdominal pain) during the course of treatment an option for direct administration using 16 G IV canula was given to the patients.

8/11 patients were given treatment with IP catheter. Only one patient completed all 3 cycles of IP chemotherapy with IP catheter, 4/8 patients received 2 cycles and 3/8 patients received only 1 cycle through IP catheter.

In 7/11 patients IP treatment was given through direct puncture technique.3/11 patients received all the 3 cycles and 2/11 patients had 2 cycles and another 2/11 patients received one cycle each [figure 1,2] by direct puncture mentod.4/11 patients received IP treatment both through the catheter and direct puncture technique. A total of 29 cycles were administered. 14 cycles were given with IP catheter and 15 cycles with direct puncture technique. 8/11 patients received all planned cycles of IP therapy.

Procedural toxicity related to catheter/Direct puncture technique.

Major toxicities noticed in patients with IP catheter include blocked catheter, sepsis and abdominal pain. One patient had intestinal obstruction on the 4th postoperative day. She required laparotomy and removal of catheter. Two patients had catheter-induced sepsis after surgery which needed hospitalization and intravenous antibiotics. 5 patients had blocked catheter. Peritoneovaginal fistulae developed in one patient and she was given all 3 cycles by direct puncture technique. Three patients had grade 3 abdominal pain following IP catheter and needed catheter removal in one patient (Table – 3).Direct puncture technique was without any toxicity related to the procedure.

Toxicity due to IP Cisplatin (by either method)

Three patients had grade 2 abdominal distension during 1st cycle of IP Therapy. All other patients had grade 1 abdominal distension during IP Therapy. Two patients developed chills during IP therapy. Three patients had serous discharge from the catheter site. Seven patients had vomiting during IP chemother-

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apy; two had grade 3 and three patients with grade 2. Other two patients developed delayed grade 2 vomiting (Table 4).

One patient had grade 2 anemia. No patients had neutropenia or thrombocytopenia.

Two patients had moderate constipation during IP treatment. One patient had grade 1 renal toxicity. There was no grade 3 or above toxicities noted in patients receiving IP therapy through direct puncture technique.

Quality of life analysis by using global health status scale QLQ-C 30 version 3.0 scoring system analysis in all patients showed deterioration of quality life during and 3 weeks following IP therapy [n=11]. [figure 4&5]

Quality of life assessment by using global health status scale was better in patients who received IP chemotherapy through direct puncture (n=7) compared to chemotherapy using IP catheter [n=8]. (P value less than 0.001).

DISCUSSION

In this study we assessed the safety of intraperitoneal intraperitoneal chemotherapy with cisplatin in women with advanced ovarian and primary peritoneal cancers. Three major randomized trials demonstrate a significant improvement in survival for women with, optimally debulked, stage III EOC treated with cisplatin based IP/IV chemotherapy [12, 13, 14]. Debate continues over individual trial design and the statistical reporting of these studies, nevertheless, IP chemotherapy remains a valid treatment option for a select group of women. Across the three trials, a survival benefit was seen even though the number patients completing the planned cycles of IP chemotherapy was only 42% to 71% [12, 13, 14]

Randomized trials have shown that patients in the intraperitoneal group had more toxic events than women in the intravenous group. The toxic effects are attributed to IP catheter and higher dose of cisplatin used for IP therapy. [12, 13, 14]

A National Cancer Institute clinical announcement recommended intraperitoneal therapy for women with optimally debulked ovarian cancer on the basis of a summary of eight randomized controlled trials and two systematic reviews, which appear to indicate benefit of IP therapy. [15]

Our patients were given 6 cycles of neoadjuvant chemotherapy with Paclitaxel and carboplatin. In Vergotes study the actuarial 3-year survival rate was higher for the group of patients treated during the selective neoadjuvant chemotherapy time period (42%) compared to the standard surgery time period (26%, P=0.0001)[16] .A study by Kumar et al showed patients in neoadjuvant chemotherapy arm showed higher optimum debulking rate, p<. 0001, decreased blood loss during surgery (mean vol 520 verses 373 ml p<0.003) and reduced postoperative infections (14.8 % vs. 2.5%, p<0.04.)[17]. Study by Zamagni et al [18] in 35 patients with stage III C- IV, unsuitable for optimal upfront surgery were treated with 6 cycles of carboplatin AUC 5 and paclitaxel 175 mg/m2, every 3 weeks before surgery.

The intraperitoneal paclitaxel weekly administration combined with intravenous carboplatin administration prior to radical surgery/peritonectomy with hyperthermic intraoperative intraperitoneal chemotherapy is a safe and effective option in the treatment of ovarian peritoneal carcinomatosis. This study shows the possibility to investigate other forms of intraperitoneal chemotherapy and their combinations thoroughly [19]. The National Cancer Institute of Canada Clinical Trials Group has developed a protocol for a randomized phase ii/iii study which will examine whether IP platinum-taxane-based chemotherapy benefits women who have received neoadjuvant chemotherapy before optimal surgical debulking. To address whether the less systemically toxic carboplatin can be substituted for cisplatin IP, the first phase of the study will have 3 arms: 1 intravenous-only, and 2 IP-containing regimens. At the end of the first stage, and provided that IP therapy is feasible to administer in this patient population, one of the IP regimens, either IP carboplatin or IP cisplatin, will proceed into a phase iii comparison with the intravenous arm. This exciting new study has gathered international support.[20]

Of 33 patients who completed 6 courses of neoadjuvant chemotherapy (NACT) 18 patients (51%) had a pathological response. In this study an optimal pathological response occurred in 51% of cases after 6 cycles of carboplatin-paclitaxel, doubling the results described in the literature with 3 courses of NACT. Given that an optimal pathological response correlates with a longer survival compared to a sub-optimal one, a randomized study of 6 verses 3 courses of NACT in order to verify if the increase in pathological response rate will translate into a survival benefit is warranted.

We used silastic tube as IP catheter in our study which was placed inside the peritoneal cavity during surgery. In those patients who had catheter block or needed catheter removal, IP therapy was delivered using direct puncture technique with 16 G peripheral IV canula. In one patient with catheter blockage we were able to demonstrate localization of fluid around the catheter due to fibrous sheet formation by x ray abdomen after radio opaque dye injection. [Figure-11, 12]

Different types of catheters are used in different trials. Some trails have not specified about catheter type and timing of catheter placement in the study design [13]. Chin et al [21] used the Bard 9.6 [1.6mm lumen] single lumen venous access port. Catheter insertion was done at the time of surgery and they recommended delayed insertion of catheter by an interventional radiologist using image guidance in case of bowel resection occurred during sugery. 13 patients [27%] in their group-developed catheter related complications, mostly minor. A separate evaluation in Armstrong study for catheter related outcomes showed that patients who had left colonic or recto sigmoid resection at the time of initial surgery were less likely to receive all planned doses of IP therapy [22].The single lumen venous access catheter attached to an implanted subcutaneous port has been reported to be superior to the fenestrated catheter designed for intraperitoneal use with minimal fibrous sheet formation and markedly reduced risk of small bowel obstruction or perforation[23].Emily et al in their review reported 37% of patients discontinued IP chemotherapy secondary to port and catheter complications, many of which contributed to treatment-related hospitalizations and delays.[21]The standardization of the devise to be used and the technique and timing of implantation could improve the success of intraperitoneal therapy.Our reason for using silastic catheter was easy availability and low cost when compared to Bard venous access port.

IP therapy using direct puncture technique was not associated with any catheter related complications. The patients in our study who received IP chemotherapy by this technique had better quality of life compared to patients who had IP therapy with IP catheter. There was no abdominal pain or infection reported in these patients.

Lan et al [24] retrospectively reviewed the clinical records of all patients with stage II-IV epithelial ovarian, fallopian tube, and primary peritoneal cancer at Sun Yat-sen University Cancer Center from 01/1995 to 11/2006 to identify patients who had received IP therapy via direct puncture after primary cytoreduction and identified 194 patients, and 121 (62.4%) of them successfully completed six or more cycles of IP chemotherapy, whereas 73 (37.6%) failed. Two (1%) patients ceased IP therapy directly due to IP access related complications and 35 (18.1%) discontinued IP therapy for reasons unrelated to IP

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access.

IP access via direct puncture using a peripheral venous needle could be an alternative and safe way to deliver IP chemotherapy in the primary treatment of ovarian cancer and primary peritoneal cancers.

Although 100 mg/m2 cisplatin IP was the common feature of GOG 104, GOG 114 and GOG 172, debate continues over the optimal dosing of IP cisplatin in clinical practice. [12, 13, 14] Given the 10–20 fold higher concentration of cisplatin in contact with the tumor as a result of IP administration some have argued that the modest reduction in systemic exposure resulting from reducing the IP dose to 75 mg/m2 is unlikely to effect efficacy [25]. Conversely, cisplatin related toxicity (particularly emesis and neurotoxicity) exhibits a steep "dose response" effect [26]. Whilst less intensive regimens have the advantage of improving completion rates it remains to be seen whether this translates into equivalent or improved efficacy and requires evaluation in randomized clinical trials.

In the study by Chin et al, 21% of patients intended to receive 6 cycles of IP chemotherapy cisplatin was initiated at a dose of 75 mg/m2.Furthermore, 27% of women commenced at 100 mg/m2 required a dose reduction due to toxicity.

The peripheral neuropathy observed in GOG 172 study was 19% and for GOG 114 10% and study by Chin et al was 9%.In our study there was no grade 2 neuropathy reported with Cisplatin given at a dose of 75 mg /m2.

IP carboplatin appears to offer an effective and well-tolerated alternative to cisplatin and is currently under active investigation [27].In our study the hematological toxic profile was favourable. There was no grade 3 or 4 thrombocytopenia, anemia or neutropenia. Abdominal pain was observed in 4 patients and in three it was grade 3.The incidence of grade 3 abdominal pain reported in the literature range from 11 to 20% [12, 13,14]. Two patient who had severe abdominal discomfort during infusion was given only 1.5 litres of fluid during next cycles. They did not experience any discomfort with 1.5 litres .By using a slightly lower volume of intraperitoneal fluid 1.5 litre compared to the 2 litre used in most studies, the resulting reduction in abdominal distension may have contributed to the reduction in abdominal pain. It remains to be seen whether reducing the volume impacts on efficacy.

Nausea and vomiting, particularly delayed emesis, represents a particular challenge when administering IP cisplatin. Eight patients had vomiting and two of them was grade 3 (11.1%).Use of IV palanosetron in these patients resulted in reduction in vomiting in one patient. Two patients had moderate constipation and were treated with prophylactic laxatives. Nausea and vomiting remains a significant problem for cisplatin containing regimens. Use of neurokinin inhibitors may reduce the cisplatin induced vomiting and requirement of hydration which may improve the quality of life in these patients.

Gastrointestinal and metabolic toxicities were noted among 46% and 27% of all patients receiving IP chemotherapy on the GOG 172 protocol, respectively.

In our study 44.4% of patients had catheter related complications. In a study by Barakat et al. an overall catheter complication rate of 22.6% was reported in 433 patients participating in phase II trial of IP chemotherapy with a 3.4% rate of catheter related sepsis and 0.2% rate of bowel perforation [28].Study by SN Chin et al. showed over all catheter complication rates of 27%.

Initially we treated the patients with IP therapy as in patients. As these patients tolerated the procedure well without immediate complications we continued the procedure on an out patient basis. The whole procedure take only 6hrs.This allows the therapy to be given on outpatient basis. Chin et al. reported a median time spent in the ambulatory chemotherapy unit by patients was approximately 7 hrs and more cost effective than other published IP cisplatin based regimens. In a small study Emily et al demonstrated the feasibility of an outpatient IP chemotherapy regimen designed as a modification of the GOG 172 protocol [29]. The use of granulocyte-colony stimulating factors, multiple anti-emetics, scheduled home hydration and IV docetaxel reduced toxicities associated with their protocol.

The cost of therapy was reasonable as the direct puncture technique dose not add to any extra cost of catheter and there is no catheter related infections. The complications that can occur with direct puncture technique are bowel perforation, injecting in to the vessels and extravasations.

No cases of bowel perforation occurred in our study. Extravasations of fluid can be made out easily as it causes pain and abdominal swelling and most characteristically lack of rapid flow of fluid through the IV canula. This will not produce a major problem as initial fluid given is normal saline without cisplatin.

Puncturing the vessel and injecting directly in to the vessel can be avoided by continuous aspiration with a syringe while introducing the needle in to the peritoneum.

On follow up till July 2014, a total of five patients who received IP chemotherapy wasdied in our series. Mortality free survival in our patients were 64.5 months (54.1 to 74.8 months 90% confidence interval) and progression free survival were 55.9 months(41.8 to 70.05 , 90% confidence interval). Despite the results of several phase III randomized trials that have demonstrated improved survival with IP therapy, standard front-line therapy has remained largely unchanged for nearly 15years. This has, in part, been due to the lack of training of healthcare personnel at all levels concerning the modern methods of IP therapy and perception of increased toxicity and related costs associated with some IP regimens. The advances in therapy of stage III, optimally debulked disease have been translated only marginally into the everyday practice setting, and progress in the treatment of ovarian cancer has unnecessarily been slowed.

The improvement in toxicity and quality of life can be achieved by dose modification of intraperitoneally delivered cisplatin and by using direct puncture technique for intraperitoneal chemotherapy in patients with stage IIIC and stage IV epithelial ovarian and primary peritoneal cancers.

As the new drugs evolve for IP chemotherapy and techniques of administering the IP therapy improves, the intraperitoneal chemotherapy will definitely become the front line treatment in advanced ovarian and primary peritoneal cancers after cytoreductive surgery.

Conclusions

Intraperitoneal chemotherapy by direct puncture technique is feasible without any major catheter related toxicities even in the post operative setting after six cycles of chemotherapy. IP therapy by silastic catheter is associated with catheter related toxicities in a majority of patients. IP chemotherapy by Cisplatin can be safely administered on an out patient basis which will reduce the cost of therapy and the need for hospitalization.Cisplatin dose of 75 mg/m2 was not associated with grade 3 or 4 renal or neurologic toxicities.Randomized studies are needed to evaluate the better complete pathological response after 6 cycles of neoadjuvant chemotherapy compared to 3 cycles and also whether this can translate in to a better over all survival.

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Table 1
Patient Characteristics **n=18**

Characteristics	
Age	
Median	54
Range	29-67
Symptoms	
Abdominal Distension	16
Abdominal pain	14
Abdominal Mass	5
Stage	
Stage IIIC	14
Stage IV	4
Tumor type	
Ovarian	15
Primary Peritoneal	3
CA 125	
Normal	2
Elevated	16
Histopathology	
Papillary Adenocarcinoma	14
Adenocarcinoma	4
Neoadjuvant Chemotherapy- Cycles	
6 cycles	14
3 cycles	3
1 cycle	1
Neoadjuvant Chemotherapy Toxicity	
Alopecia	17. (Grade 2)
Vomiting	5. (Grade 2=3; Grade)3=2
Anemia	1 (Grade 2)
Neutropenia	3 (Grade 2 =1; Grade 3=2)
Neuropathy	3 (Grade 1)
Surgery Total	14
No disease	4
Optimal cytoreduction	9
Inoperable	1
Ca theter placement done	13
Pathological	
pCR	4
Disease present	10
IP Therapy delivery	
No of patients through IP catheter	8
No of patients through Direct method	7
Total cycles through IP catheter	14
Total cycles through Direct method	15
Complications of IP catheter	
Intestinal Obstruction	1
Peritoneovaginal fistula	1
Sepsis	2
Abdominal Pain	3
Blocked catheter	5
Leaking entry site	1
Serous discharge catheter site	3
Toxicity due to IP Cisplatin	
Abdominal distension	3 (Grade 2)
Vomiting	7. (Grade 2=5;Grade3=2)
Chills	2
Constipation	2 (Grade =2)
Anemia	1 (Grade =2)

Table -2
Total [n = 18]

Died- 1

↓ Consent withdrawn-3
Inoperable-1

IP catheter [n =13]

↓ Catheter Displacement-1
Catheter removal due to Phobia – 1
Low performance status-1
Blocked catheter-2

Direct. Puncture (n=7; 3 cycles 3, 2 cycles 2, 1 cycle 2) →
IP catheter treatment [n = 8]
(3 cycles 1, 2cycles 4 and 1 cycle 3)

Blocked Catheter-3

Intestinal obstruction	1
Peritoneovaginalfistula	1
Sepsis	2
Abdominal pain	3(grade III)
BlockedCatheter	5
Leakat entry site	1
Dischargefromcatheter site	3

(Port related complications in patients with IP catheter – Table 3)

	Grade 2	Grade3	Grade 4
Abdominal distension	3		
Vomiting	5	2	
Constipation	2		
Anemia	1		
Chills	2		

(Toxicity due IP Cisplatin by either route – Table 4)

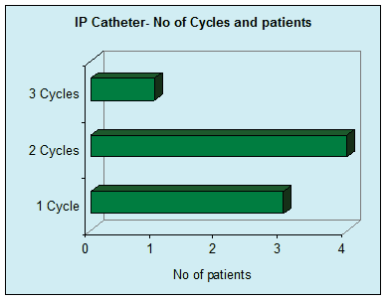

Figure: 1 No of patients and IP Cycles received through catheter

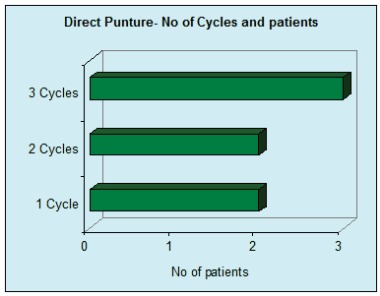

Figure: 2 No of patients and IP Cycles received through Direct Puncture

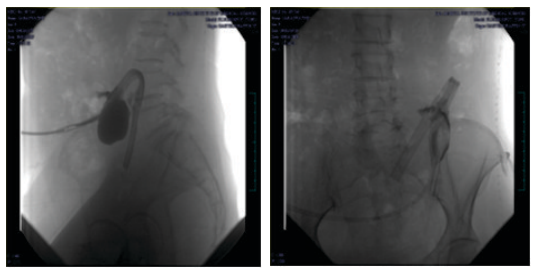

Figure: 3 Loculation of fluid due to fibrous septae formation– Gastrograffin series 10 minutes after contrast and 30 minutes after. Contrast fluid was aspirated after 30 minutes.

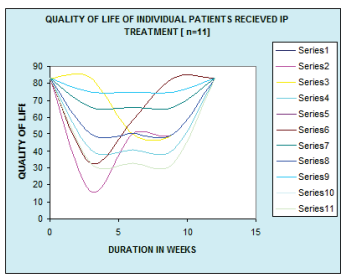

Figure: 4

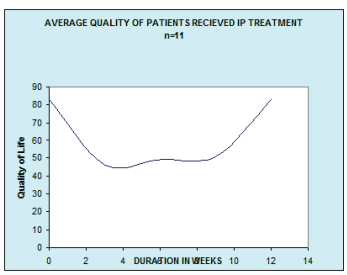

Figure: 5

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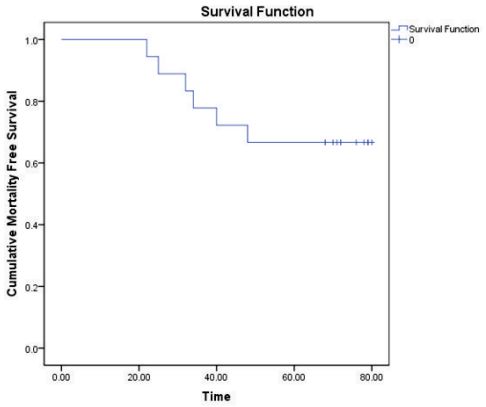
Means and Medians for Survival Time

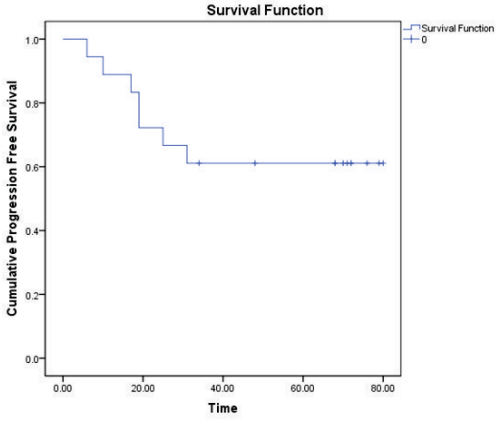
Mean			
Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound
64.500	5.302	54.108	74.892



Means and Medians for Survival Time

Meana			
Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound
55.944	7.200	41.832	70.057

a. Estimation is limited to the largest survival time if it is censored.



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