

Intraoperative Normothermic Intraperitoneal Chemotherapy Following Optimal Cytoreduction in Advanced Ca Ovary: A Feasibility Study

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Introduction: Extrapolating the results from the studies using HIPEC, EPIC and normothermic intraperitoneal chemotherapy, we proposed that normothermic chemotherapy instilled after optimal cytoreduction will improve survival in patients who underwent optimal cytoreduction. We undertook this feasibility study with the aim of studying the effectiveness of intraoperative normothermic intraperitoneal chemotherapy in patients with advanced-stage epithelial carcinoma ovary.

Methods: This was a single institutional feasibility study. The primary objective was progression-free survival (PFS) following the instillation of normothermic chemotherapy following optimal cytoreduction in cases of advanced ovarian cancer after neoadjuvant chemotherapy. The secondary objective was to study tolerability and toxicity. The study received institutional ethical committee clearance.

Results: A total of 24 patients were included in the pilot study over two years. The short-term analysis was made by comparing 45 patients who underwent interval cytoreductive surgery (ICS) with CC 0 and 1 during the same period. The most common side effect was prolonged post-operative ileus which was seen in six patients. The median PFS among patients who received IP chemotherapy was significantly better in comparison to patients who received ICS alone (34.0 vs. 13.0 months, $p=0.018$).

Conclusion: Uniform state-of-the-art management of advanced epithelial ovarian cancer may not be accessible to all due to global resource limitations. Although the evidence is weak due to the small sample size and short follow-up of patients, the findings are encouraging. This feasibility study has provided substantial evidence to work further with this approach in our institute and plan an randomised controlled trial to gain more evidence.

Introduction

Epithelial carcinoma of the ovary primarily presents at an advanced stage, and most women recur within 1-2 years [1]. Optimal debulking surgery as interval cytoreductive surgery (ICS) or primary cytoreductive surgery (PCS) is the cornerstone in ensuring long term progression-free survival (PFS) in these patients. Many studies have shown ICS and PCS to have similar overall survival (OS) [2-4]. When compared to other chemotherapeutic medications, platinum-based chemotherapy has shown the greatest tumour regression when either cisplatin or carboplatin is combined with paclitaxel [5]. However, despite good response after optimal cytoreduction and chemotherapy, most patients recur, which signifies the inherent unfavourable nature of the advanced disease [6].

Various studies were undertaken to increase the PFS and OS of such patients. Studies conducted using Intraperitoneal Chemotherapy (IP) showed better survival than systemic chemotherapy alone [7-9]. The rationale for using IP chemotherapy has been based on the feasibility of IP instillation and the preponderance for intraperitoneal localization even in advanced stages, which makes it possible to bathe tumour cells with chemotherapy directly [10]. However, the benefit is only seen when the tumour has been optimally debulked, as IP chemotherapy does not diffuse in large bulky tumour nodules. Heated Intraperitoneal chemotherapy given immediately after surgery has been introduced and has shown to be of benefit both in the setting of PCS and ICS [11, 12].

Hyperthermia has been postulated to increase penetration of chemotherapy and sensitivity to chemotherapy by impairing DNA repair [13]. Intraoperative intraperitoneal chemotherapy has also been proposed to kill the floating tumour cells and prevent them from getting entrapped in the resection sites [14]. However, HIPEC is not freely available in most low-resource setting centres due to its high cost and requirement of specific types of equipment. Normothermic intraperitoneal chemotherapy (NIPEC) has also proven beneficial as adjuvant chemotherapy and when introduced in the early post-operative period [15-17]. Early postoperative intraperitoneal chemotherapy (EPIC) has certain conceptual benefits, as it is applied shortly after cytoreductive surgery when the tumor burden is minimal. Further-more, drug distribution is reduced as the adhesions are not formed and there is prevention of entrapment of residual cancer cells in postoperative fibrin deposits. EPIC does not entail hyperthermia and is administered in the postoperative period, usually on days 1 to 5, through an inflow catheter and outflow drains inserted during CRS. This approach can be employed with or without HIPEC [18]. Nevertheless, the drawbacks associated with EPIC, such as increased infection risks and postoperative complications, including catheter-related issues, have resulted in its diminished popularity compared to HIPEC [19].

Extrapolating the results from the studies using HIPEC and EPIC, we proposed that normothermic chemotherapy instilled after optimal cytoreduction will improve survival in patients who underwent optimal cytoreduction. We undertook this feasibility study with the aim of studying the effectiveness of modified EPIC using normothermic chemotherapy in patients with advanced-stage epithelial carcinoma ovary.

Materials and Methods

Methodology and study design

This was a single institutional feasibility study to evaluate the activity and tolerability of intraoperative normothermic intraperitoneal chemotherapy instilled as a modified EPIC regimen after optimal cytoreduction in advanced EOC after neoadjuvant chemotherapy. The study received clearance from the Institutional Ethical Committee. Recruitment of patients was done after ethical committee clearance. Patients who fulfilled the criteria were given patient information sheet and consent forms at the time of assessment for ICS, which was approximately 2-3 weeks before surgery.

The primary objective was to study the short-term efficacy by estimating the progression-free survival (PFS) following the instillation of normothermic chemotherapy following optimal cytoreduction in cases of advanced ovarian cancer after neoadjuvant chemotherapy.

The secondary objective was to study tolerability and toxicity.

Patients with advanced Ca Ovary (stage IIIC disease) were included in the study. A total of 24 patients were included in the study. Informed consent was taken from every patient. After optimal cytoreduction (defined by Cytoreductive scores 0 and 1) cisplatin (75 mg/m²) was instilled intraperitoneally with the help of intra-abdominal drains placed in Morrison's pouch and pelvis. Drains were unclamped after 24 hours for any unabsorbed fluid to be removed. Preloading with potassium chloride and magnesium sulphate was done. Adequate hydration was maintained.

Antiemetics were given for control of emesis associated with cisplatin. Monitoring and correcting dyselektrolytemia were done on the day of surgery for up to 3 days. Adverse effects were monitored and recorded per Common Terminology Criteria for Adverse Events (CTCAE) version 5 [20].

Eligibility criteria

Inclusion Criteria:

1. Patients with advanced (stage IIIC) epithelial carcinoma ovary, fallopian tube carcinoma or primary peritoneal cancer who received neoadjuvant chemotherapy.
2. Age: 20-70 years.
3. World Health Organization performance status 0-2.
4. Adequate organ function with the following criteria: White blood cell (WBC) $\geq 4,000/\text{ul}$; Absolute neutrophil count (ANC) $\geq 1,500/\text{ul}$; Platelet $\geq 100 \times 10^3/\text{ul}$; Aspartate aminotransferase (AST) ≤ 100 IU/L; Alanine aminotransferase (ALT) ≤ 100 IU/L; Serum total bilirubin ≤ 1.5 mg/dL; Creatinine clearance ≥ 60 mL/ min.

Exclusion Criteria:

1. Suboptimal debulking
2. Failure to give consent
3. Pre-existing renal disease
4. Benign ovarian disease, borderline ovarian malignancy, non-epithelial ovarian carcinoma or carcinosarcoma
5. Cirrhosis of liver
6. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation
7. Auditory impairment
8. Dehydration or intercurrent disease that contraindicates hyperhydration (including cardio-respiratory disease)
9. Other uncontrolled intercurrent diseases: diabetes; hypertension; symptomatic congestive heart or pulmonary failure; renal, hepatic or severe gastrointestinal (associated with diarrhoea) chronic disease
10. Any unresolved NCI-CTCAE Grade ≥ 2 toxicities from previous anticancer therapy (excluding alopecia). Being a feasibility study, the results were analyzed for

PFS at the end of one year of recruitment of the patients (Median followup 22 months). They were compared with patients who underwent interval cytoreductive surgery (ICS) as standard of care for stage IIIC epithelial ovarian cancer at our institute with a cytoreductive score of 0 or 1. PFS was calculated from the date of ICS till the recurrence of the disease.

Role of the funding source

There was no sponsor involved in the study design, in the collection, analysis, and interpretation of data, writing of the report, and in the decision to submit the paper for publication.

Results

A total of 24 patients were included in the pilot study over two years (Dec 2019 to Dec 2021). The median age of the patients undergoing ICS+ IP was 49 years. The short-term analysis was made by comparing 45 patients undergoing ICS only who underwent interval cytoreductive surgery (ICS) with CC 0 and 1 during the same period. The median age of the patients was 48 years. The predominant histopathology in the ICS+IP arm was high-grade serous carcinoma (24/24). In the patients who underwent ICS alone, the predominant HPE was high-grade serous carcinoma (40/45). The intraoperative parameters are shown in Table 1.

Intra-operative Parameters	
Number of surgical procedures performed	
Abdominal/pelvic peritonectomy	4
Bowel resection	0
Diaphragmatic stripping and or resection	6
Splenectomy	0
Aortic/pelvic lymphadenectomy/sampling	20
Cholecystectomy	1
Median operating time	6 hours
Completeness of cytoreduction	CC-0 (21)
	CC-1 (3)

Table 1. Table 1. Intraoperative Parameters of Patients Receiving IP Chemotherapy.

The mean PCI in the patients receiving intraoperative normothermic chemotherapy was 9.7 (range 0-28), whereas it was 6.48 (range 0-27) in patients undergoing ICS only.

There was acceptable tolerability and toxicity following intraperitoneal cisplatin instillation, with no grade IV toxicity or mortality. The most common side effect was prolonged post-operative ileus which was seen in 6 patients. Twelve patients received intraoperative blood transfusion of up to two units due to intraoperative blood loss. Although all patients received prophylaxis with dexamethasone and serotonin receptor uptake inhibitors, four patients had grade 2 nausea and vomiting lasting four days (Table 2).

Post-operative Parameters	Number of patients
Number of patients transfused	
Blood	12
Plasma	8
30-day mortality	0
Re-laparotomy	0
Post-operative ileus (>72 hours)	6

Table 2. Post-operative Parameters.

In post-procedural period, one patient had leakage of intraperitoneal fluid after 4 hours from the stitch line (required unclamping of the drains, and the wound redressing; there is no post-operative wound complications). None of the patients had post-operative wound sepsis following intraperitoneal chemotherapy instillation. There were no incidences of pleural effusion, fistula

(uretero-bowel), lung complication, arrhythmia, heart failure, tissue necrosis, central venous thrombosis, pulmonary embolism, septicaemia, intravenous line sepsis, wound seroma, urinary infections in the post-operative period.

Grade 2 anaemia was the most common haematological toxicity in the post-operative period, which developed in six patients, whereas grade 2 neutropenia was observed in one patient. One patient had grade 3 thrombocytopenia but recovered spontaneously (Table 3).

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Haematological:				
Leukopenia	0	0	0	0
Neutropenia	0	1	0	0
Anaemia	6	6	0	0
Thrombocytopenia	0	0	1	0
Non-haematological:				
Diarrhoea	0	0	0	0
Nausea	0	4	0	0
Vomiting	0	4	0	0

Table 3. Haematological and Non-haematological Toxicities.

With a median follow-up period of 22 months, nine patients (9/24) had disease recurrence in ICS plus intraperitoneal chemotherapy group, whereas 27 (27/44) patients had disease recurrence in ICS alone group (Table 4).

	Number of patients
Type of recurrence	
Single- site	3
Multiple-site	6
Diffuse carcinomatosis	0
Site of recurrence	
1) Intraperitoneal	1
2) Hepatic/splenic	0
3) Intraperitoneal + hepatic/splenic	3
4) Retroperitoneal Lymph nodes	2
5) Retroperitoneal Lymphnodes + with intraperitoneal/hepatic	1
6) Distant mets	2(Brain/SCLN)

Table 4. Patterns of Recurrence.

PFS in patients who received standard treatment (ICS alone) & IP chemotherapy was 52.0% & 83.3%, respectively (Table 5).

			1 Year				3 Year	
ICS alone			52.00%				22.00%	
ICS plus IP chemotherapy			83.30%				30.50%	
Means and Medians for Survival Time (PFS)								
Group			Meana				Median	
	Estimate	Std. Error	95%		Estimate	Std. Error	95%	

			Confidence Interval				Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
ICS alone	17.873	1.893	14.162	21.583	13	1.136	10.773	15.227
ICS + IP	26.56	2.338	21.977	31.143	34	7.532	19.238	48.762
Overall	21.17	1.612	18.011	24.329	18	2.046	13.989	22.011

Table 5. Progression Free Survival (PFS).

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

The median PFS among patients who received IP chemotherapy was significantly better in comparison to patients who recieved ICS alone (34.0 vs. 13.0 months, $p=0.018$) (Figure 1).

Figure 1. PFS ICS+IP Versus ICS Only.

Discussion

In patients with advanced epithelial ovarian cancer, the use of cisplatin-based chemotherapy, targeted therapy in the adjuvant setting, cytoreductive surgery with the goal of no residual disease, improved intensive care, and the use of HIPEC have resulted in modest improvement in overall survival [21, 22]. However, many factors affect the uniform delivery of optimal treatment, including high costs of newer drugs, specifically HIPEC and targeted therapy, lack of infrastructure, human resources, and ICU backup. Therefore, there is a need for innovative approaches in cancer treatment delivery aimed at improving survival at affordable costs. With the background knowledge and evidence from using normothermic intraperitoneal chemotherapy in adjuvant settings EPIC and HIPEC in intraoperative settings, this pilot project was undertaken to build up evidence for starting a randomized controlled trial. Our preliminary results show the feasibility of prolonged intraoperative instillation of normothermic cisplatin. The toxicity profile following intraperitoneal normothermic cisplatin was acceptable, with no grade IV toxicity or mortality. The most common side effect was prolonged postoperative ileus (25%), nausea and vomiting (16%). However, early feeds could be started in the majority of patients. The most common haematological toxicity was grade 2 anaemia in the postoperative period (25%). Grade 2 neutropenia and grade 3 thrombocytopenia (recovered spontaneously) were seen in one patient each. In the post-operative period, one patient had leakage at the stitch line after 4 hours, which was managed by unclamping the drain and redressing the wound. None of the patients had postoperative wound sepsis who received IP chemotherapy. Being a pilot project, we did a short follow-up (median 22 months) and compared the results with patients undergoing ICS only during the same period.

At the end of the follow-up, nine patients (37.5%) had a recurrence with ICS and intraperitoneal chemotherapy, whereas 27 (61.3%) had a recurrence with ICS only.

PFS in patients who received ICS alone versus ICS plus IP chemotherapy was 52.0% & 83.3%, respectively. The median PFS among patients who received ICS alone & ICS plus IP chemotherapy was 13.0 & 34.0 months, respectively ($p=0.018$).

Uniform state-of-the-art management of advanced epithelial ovarian cancer may not be accessible to all due to global resource limitations. Although the evidence is weak due to the small sample size and short follow-up of patients, the findings are encouraging. This feasibility study has provided substantial evidence to work further with this approach in our institute and plan an RCT to gain more evidence.

Disclosure

The authors declare no conflict of interest.

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