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ROLE OF CYTOREDUCTIVE SURGERY WITH HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY IN OVARIAN CANCER

Oncology

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ABSTRACT

Introduction Ovarian cancer is the most lethal gynecologic malignancy. Approximately 75% of ovarian cancer patients are diagnosed in the advanced setting, when the disease has spread in the peritoneal cavity.1 Complete cytoreduction followed by HIPEC improves not only survival but also quality of life of patients. We assessed the feasibility, perioperative outcomes and short-term oncological outcomes of this procedure in our set up. **Methods** This prospective observational study was conducted in Indraprastha Apollo hospital, New Delhi, between June 2018 and May 2020 and included 24 patients of ovarian cancer who underwent cytoreductive surgery and HIPEC. **Results** 24 patients of carcinoma ovary were included in this study. Median age was 53.4yrs. 18 (75%) had performance status ECOG 0 and 6 (25%) had ECOG 1. Mean PCI index was 11.2 (range from 4-22). We used closed method for HIPEC. Postoperative morbidity developed in 15 patients (62.5%). But grade 3 toxicities occurred in only 1(4.16%) patient. There was no 30-day mortality. Median follow up was 6.71 months (range, 2-15 months). 5 (20.83%) patients developed recurrence but no mortality. Out of these 4 (16.66%) had intra peritoneal recurrence and 1 (4.16%) had systemic recurrence. 4 out of 5 recurrences had PCI > 15. **Conclusion** CRS and HIPEC improves oncological outcomes in patients of ovarian cancer with peritoneal disease without much additional morbidity or mortality and is feasible option but needs dedicated team efforts.

KEYWORDS

HIPEC, CRS, Ovarian cancer, Peritoneal carcinomatosis.

INTRODUCTION

Epithelial ovarian cancer (EOC) has the highest mortality among gynecologic tumors in the western world. The 10-year survival rate of women with advanced disease is only 10% to 15%. 2\3rd of ovarian cancer patients are diagnosed in the advanced stage (III &IV) when the disease has spread in the peritoneal cavity. [1,2] Classically treatment includes of cytoreductive surgery (CRS) and with adjuvant chemotherapy. And if upfront CRS is not feasible because of the extent of the disease, interval CRS is performed after neoadjuvant chemotherapy.[3-5] Even after macroscopically complete CRS, many patients experience peritoneal disease relapse. Hyperthermic intraperitoneal chemotherapy (HIPEC) is a potentially more effective way to treat microscopic peritoneal tumor deposits. Hyperthermia has direct cytotoxic effects on tumor cells. It induces heat shock proteins that serve as receptors for natural killer cells which leads to apoptosis. Also, it enhances cytotoxicity of anticancer drugs, along with the pharmacokinetic advantages of the intraperitoneal route for chemotherapy[6]. Administration of chemotherapy into the peritoneal cavity not only ensures better exposure of tumour tissue to the drug, but also less systemic toxicity, because only a limited portion of the drug is absorbed from the peritoneal cavity into the systemic circulation [7,8]. Further, the vascular drainage from a large portion of the peritoneum occurs through the portal venous system, allowing for early metabolism and inactivation of the drug in the liver[7].

MATERIALS AND METHODS

This was a prospective observational study conducted in Indraprastha Apollo hospital, New Delhi and included patients who underwent cytoreductive surgery and HIPEC for ovarian cancer with peritoneal carcinomatosis. We assessed the feasibility and perioperative outcomes of HIPEC in our patients. We also analyzed the short-term oncological outcome of the HIPEC procedure.

Study area: Indraprastha Apollo hospital, New Delhi.

Study population:

A total of 24 patients of ovarian cancer with peritoneal surface malignancy, treated with cytoreductive surgery (CRS) and HIPEC between June 2018 and May 2020 at our institute were included as per inclusion and exclusion criteria.

Inclusion criteria:

1. Medically fit patient with ECOG performance status <2.
2. No extra-abdominal metastatic disease.

Exclusion criteria:

1. Age > 70 years
2. Serious medical histories (especially cardiorespiratory, neurological or renal),
3. Concomitant extra-abdominal metastasis
4. Liver metastases, more than 3 on the same lobe, or multiple, bilateral, unresectable
5. Massive retroperitoneal bulky disease or lymph node involvement.
6. Extensive involvement of small bowel mesentery, more than 1 segment of bowel stenosis, large tumour masses in the lesser omentum, extensive disease in the hepatoduodenal ligament, biliary or ureteric obstruction.
7. Allergy to chemotherapeutic agent

Sample size: 24 patients were taken for the study purpose.

Extent was assessed intraoperatively with Sugarbaker peritoneal carcinomatosis index (PCI).

Cytoreductive surgery was considered to be complete when a score of CC-0 or CC-1 was achieved.

HIPEC was done by closed method in all the cases after cytoreduction.

We used cisplatin-based regimen. And total duration of HIPEC ranged from 30 mins to 90 mins.

Post operative data included were postoperative morbidity, total duration of hospital stays and within 30 days mortality.

Post operative complications were graded as per Calvien Dindo classification.

Follow-Up

Follow up was done to look for recurrence, mortality and adjuvant therapy. The clinical follow-up for all the patient was at 1 month post procedure, and at least every 3 months thereafter. Follow up was done with history, physical examination, Chest x-ray or chest CT and abdominal/pelvic CT scans with oral and IV contrast along with tumor markers (CA 125, CEA) at each follow-up visit and when clinically indicated.

RESULTS

Total patients	24
Median Age	53.4years

ECOG performance status	0 -75% 1 -25%
Median PCI score	11.2

Extend of Cytoreduction	Cytoreduction Alone – 95.83% With bowel resection -4.16%
Completeness of Cytoreduction	CC 0 - 100%

Mean Duration of Surgery	7.36 hrs
Mean Blood Loss	638.41ml
HIPEC Protocol	Closed method, 60-90 mins at 42 °C
Mean Duration of ICU Stay	2.12days
Median duration of Hospital Stay	11 days

Adverse Events

Hypokalemia	33.33%
Hypocalcemia	29.16%
Hypoalbuminaemia	33.33%
Fall in Hb	37.5%
SAIO	12.5%
Lymphocele	16.66%

Grade of Complications (As per Clavien Dindo classification)	Grade 1 – 41.66% Grade 2 – 33.33% Grade 3 - 4.16% Grade 4 - 0
Outcome during Follow up	Within 30 days mortality - 0 Alive patient without disease – 79.16% Alive patient with disease – 20.83% Total mortality during follow up - 0

DISCUSSION

EOC is the most common cause of gynaecological cancer death worldwide, with a late onset diagnosis and poor overall prognosis.[9] Ovarian cancer cells have a particular pattern of dissemination and it selectively invades the mesothelium of the peritoneal surface, spreads within the peritoneal cavity, encasing various organ.[10] The addition of HIPEC to CRS is a potential therapeutic option for peritoneal surface malignancy management. HIPEC can be used at the time of primary CRS (upfront CRS and HIPEC), or at the time of interval CRS which is performed after neoadjuvant chemotherapy (Interval CRS and HIPEC) or as a consolidation therapy following completion of first line therapy along with second look surgery (Consolidation CRS and HIPEC). HIPEC can be used along with CRS performed as second line therapy, in patients who have had suboptimal surgery followed by chemotherapy and therefore have residual disease (secondary CRS and HIPEC) or in patients who have recurred after complete response to first line therapy (salvage CRS and HIPEC)[11]. A recent meta-analysis which included 9 comparative studies and 28 other studies examining CRS + HIPEC for primary and/or recurrent ovarian cancer, showed that the addition of HIPEC to CRS and systemic chemotherapy improves survival for both primary and recurrent ovarian cancer[12].

Our study included 24 patients of stage IIIC ovarian cancer who were medically fit to undergo cytoreductive surgery (CRS) and HIPEC. Among these, 22 patients had interval or secondary CRS and HIPEC in 2 patients primary CRS and HIPEC was done. We included 4 platinum-resistant patients in our study.

Patient Factors

Patients included in this study belong to age group of 41yrs to 68 yrs. Median age of patients undergoing CRS and HIPEC in our study was 53.4yrs. Most of the cases (19, 79.16%) were in 5th and 6th decade. No patients above 70 yrs were included as age related comorbidities might hamper the outcome and preclude long hour surgery. But advance age alone is not a contraindication for CRS and HIPEC, rather performance status and medical fitness is more important for planning surgery.

Performance status was assessed as per ECOG (Eastern Cooperative Oncology Group) performance score. 18 (75%) patients had performance status ECOG 0 and 6 (25%) had ECOG 1 performance status. Poor preoperative performance status is an important predictor of morbidity and mortality following CRS and HIPEC.

Disease Burden

Intraoperatively we calculated tumor burden as peritoneal carcinomatosis index (PCI) and PCI< 15 was considered as low tumor load and PCI> 15 as high tumor load. 20 (83.33%) patients had PCI of less than or equal to 15 and rest 4 patients (16.66%) had PCI of >15. 1 patient had PCI of > 20. Mean PCI index was 11.2 (range from 4-22). Studies done previously reported high PCI as a poor predictor for disease free survival. In our study also we found recurrence among patients with higher PCI (p-value is. 000482). 5 patients who showed recurrence during follow up, 4 of them had PCI> 15.

CRS comprises of peritonectomy procedures and visceral resections. The goal is to remove all macroscopic disease leaving no residual disease, atleast not greater than 2.5 mm in size. The reason being intraperitoneal chemotherapy is not effective in eradicating tumor nodules larger than 2.5 mm in size[13]. And this is reflected in completeness of cytoreduction score. Completeness of cytoreduction score measures the amount of macroscopically visible tumor that is seen after CRS. This forms a very important in predicting oncological outcomes. We achieved a score of CC 0 in all of our cases, meaning no residual disease seen after cytoreduction. In our study cytoreduction alone was done in 23 (95.83%) patients, and 1 (4.16%) patient also underwent bowel resection.

Other intra operative parameters: -

Mean duration of operative time in our study was 7.36 hrs. Total duration included surgery plus HIPEC. Mean blood loss during procedure was 638.41 ml. Blood loss and intra operative fluid loss was managed judiciously by our anesthetist with packed red cell, FFP transfusion and iv crystalloids and colloids.

HIPEC was done by closed method. For platinum sensitive cases we used cisplatin 100 mg/m2 and for platinum refractory cases cisplatin 75 mg/m2 with doxorubicin 15mg/m2. Our protocol was 60-90 minutes at 42 °C which our patients tolerated well with an acceptable change in core body temperature.

Post operative parameters: -

Post operatively we kept all patients in ICU. Mean duration of ICU stay was 2.12 days. Commonest reason for prolonged ICU stay was electrolyte imbalance. Median duration of hospital stay was 11 days (range 9-18 days).

Postoperative morbidity developed in 15 (62.5%) patients after CRS and HIPEC. All complications were noted and graded as per Clavien Dindo classification. In our study we did't encounter any grade 4 toxicities. There was no 30-day mortality noted in our patients. Most common infectious complication noted was wound infection in 12 (50.0%) patients, others were UTI, seen in 3 patients (12.5%). All these complications were grade 1 and were managed conservatively. Electrolyte imbalance, hypoalbuminaemia was also noted and managed accordingly. Most common electrolyte imbalance was hypokalemia seen in 8 (33.33%) patients followed by hypocalcemia in 7 patients (29.16%). Hypoalbuminaemia was seen in 12 patients (36.3%), fall in hemoglobin and platelet counts were seen in 9 patients (37.5%). Lymphocele occurred in 4 (16.66%) patients and 3 of them required image guided aspiration.

Follow up and outcomes: -

Median follow up in our study was 6.71 months (range, 2-15 months). 4 patients had more than 12 months and 6 patients had 8-12 months of follow up. 10 patients had total follow up for 4-8 months and rest 4 had follow up for less than 4 months. All the patients were evaluated as per our protocol during follow up. 5 (20.83%) patients developed recurrence. Out of these 4 (16.66%) patients had intra peritoneal recurrence including liver parenchymal secondaries and 1 (4.16%) had systemic recurrence. These patients were considered for palliative chemotherapy. 4 out of 5 recurrences had PCI > 15. There was no mortality noted till date. Median time of recurrence in our study was 310 days (range114 to 392 days). Earliest recurrence was observed in patients after 114 days, who had PCI of 22. Rest of the 4 recurrences occurred between 266 to 392 days.

CONCLUSION

Addition of HIPEC to CRS can effectively treat advance ovarian cancer with peritoneal surface disease. The procedure is long and time consuming. But a good and completely done cytoreduction followed by HIPEC improves not only survival but also quality of life of patients. HIPEC adds very little toxicity, and the recent National Comprehensive Cancer Network guidelines include the option to

consider HIPEC at the time of interval CRS in patients with stage III disease treated with neoadjuvant chemotherapy. Patient selection for the procedure is very important for favorable oncological outcome. Good performance status and PCI can be used as a tool to select and prognosticate patients. PCI of >15 is poor prognostic factor and may results in early recurrence. Every possible effort should be made to achieve a completeness of cytoreduction score of 0 or at least 1. Many large retrospective studies, case control studies, and recent meta-analysis have demonstrated and echoed similar findings. There is currently insufficient evidence to recommend its routine use as part of first line therapy in ovarian cancer but there is sufficient evidence demonstrating its benefit in interval and second line therapy. We also used this as first line therapy in 2 patients of ovarian cancer and both are currently doing well. We may need to wait for the result of various ongoing trial to establish its role as first line therapy. In patients with stage III ovarian cancer, surgical cytoreduction and HIPEC is feasible and potentially beneficial. It can be done with low mortality and acceptable morbidity. It requires a dedicated team of surgeons, anesthetists and ICU and proper infrastructure.

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