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A PROSPECTIVE STUDY ON THE ROLE OF CYTOREDUCTIVE SURGERY WITH HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY IN PERITONEAL CARCINOMATOSIS

Oncology

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ABSTRACT

Introduction Peritoneal carcinomatosis is associated with significant morbidity and mortality. 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 between June 2018 and May 2020 and included 33 patients who underwent cytoreductive surgery and HIPEC for peritoneal carcinomatosis. Post CRS, HIPEC was done with chemotherapy based on primary tumour. **Results** 24 (72.72%) patients had carcinoma ovary. 5 (15.15%) had colorectum as primary, 3 (9.09%) were pseudomyxoma peritonei from appendix, and 1(3.03%) was primary peritoneal carcinoma. Median age was 52.7yrs. 19 (57.57%) had performance status ECOG 0 and 14 (42.42%) had ECOG 1. Mean PCI index was 11.6 (range from 4-24). HIPEC was done by closed method with or without bidirectional technique. Postoperative morbidity developed in 22 (66.6%). 6 (18%) developed grade 3-4 toxicities. There was no 30-day mortality. Median follow up was 6.71 months (range, 2-15 months). 7 (21.2%) patients developed recurrence but no mortality. Out of these 4 (12.1%) had intra peritoneal recurrence and 3 (9.1%) had systemic recurrence. 4 out of 7 recurrences had PCI > 15. **Conclusion** CRS and HIPEC improves oncological outcomes in patients with PSM without adding much to morbidity or mortality and is feasible option but needs dedicated team efforts.

KEYWORDS

HIPEC, CRS, Peritoneal carcinomatosis

INTRODUCTION

Peritoneal carcinomatosis (PC), a disease with unfavourable prognosis, has evolved as a terminal condition of various abdominopelvic cancer. Occurring either as primary or secondary peritoneal involvement, disease has two spectrum i.e. Primary peritoneal surface malignancy like Diffuse Malignant Peritoneal Mesothelioma (DMPM) and secondary peritoneal surface malignancy which occur secondary to various malignancy like colorectal cancer, ovarian cancer, gastric cancer etc. Malignancies with progressive involvement of the peritoneal surfaces have resulted in increased morbidity and mortality. It not only results in early death but also a very miserable quality of life in those suffering from this disease.

Cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as major advancement to achieve loco regional control for tumors with intraperitoneal dissemination without evidence of systemic metastases.

The present study was done with aim to study the role of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis, and to assess the feasibility of this procedure with acceptable morbidity in our set up.

MATERIALS AND METHODS

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

Study area: Indraprastha Apollo hospital, New Delhi.

Study population:

A total of 33 patients 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 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 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: 33 patients were taken for the study purpose.

Tumors were categorized according to the primary site of origin.
Origin and histology of peritoneal carcinomatosis, its 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. HIPEC protocol was unidirectional or bidirectional depending on the primary etiology. We used oxaliplatin based regimen with 5-FU/ leucovorin and 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 stay 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 (as appropriate) at each follow-up visit and when clinically indicated.

RESULTS

Total cases	33
Median Age	52.7years
Male: female	4:29

ECOG performance status	0 -57.57% 1 -42.42%
Median PCI score	11.65

Primary site of Origin	Ca Ovary -72.72% Colorectal Carcinoma -15.15% Pseudomyxoma Peritonei -9.09% Primary Peritoneal Carcinoma - 3.03%
Previous surgery	Done -84.84% Not done - 15.15%
Extend of Cytoreduction	Cytoreduction Alone - 54.54% With bowel resection -39.39% Multi visceral resection - 6.06%
Completeness of Cytoreduction	CC 0 - 93.93% CC 1- 6.06%

Mean Duration of Surgery	7.24 hrs
Mean Blood Loss	689.39 ml
HIPEC Protocol	Bidirectional - 27.27% Unidirectional - 72.72%
Mean Duration of ICU Stay	1.68 days
Median duration of Hospital Stay	11.32 days

Adverse Events

Hypokalemia	36.36%
Hypocalcemia	33.33%
Hypoalbuminaemia	36.36%
Fall in Hb	18.18%
Anastomotic leak	9.09%
SAIO	18.18%
Lymphocele	24.24%
Transaminase level elevation	9.09%
Acute Renal failure	6.06%

DISCUSSION: -

Peritoneal carcinomatosis (PC) has been regarded as a lethal condition. Complete cytoreduction focusing at removal of all gross macroscopic disease coupled with intra peritoneal chemotherapy at a temperature of 41 to 43 °C increases the cellular uptake of drug, with pharmacokinetic advantages of the intraperitoneal route. It also enhances the cytotoxicity of anticancer drugs.

Our study included 33 cases of peritoneal carcinomatosis who were medically fit to undergo cytoreductive surgery and HIPEC. Out of 33 cases in our study 24 (72.72%) cases of PSM was from ovarian cancer. 5 cases (15.15%) had colorectum as primary, 3 cases (9.09%) were pseudomyxoma peritonei from appendix, and 1(3.03%) case was primary peritoneal carcinoma. Among patients with ovarian carcinoma, 24 were FIGO stage IIIC (recurrent 22, 66.66%and primary 2, 6.06%).

All colorectal patients were stage IVB. Among 3 pseudomyxoma peritonei patients, 2 patients (6.06%) had disseminated peritoneal adenomucinosis (DPAM) and 1 (3.03%) had peritoneal mucinous carcinomatosis (PMCA). We included 4 platinum-resistant carcimona ovary patients in our study. All twenty-four patients (interval and secondary CRS) received platinum-based chemotherapy prior to HIPEC.

Patient Factors

In our study, undertaken 33 patients belong to age group of 38yrs to 70 yrs. Median age of patients undergoing CRS and HIPEC in our study 52.7yrs.

Most of the cases (23, 69.69%) were in 5th and 6th decade. Considering the age related comorbidities, which might hamper the outcome and preclude long hour surgery, none of the cases were above 70 yrs. But advance age alone is not a contraindication for CRS and HIPEC, performance status and medical fitness is also necessary before planning for surgery.

In present study 29 (87.87%) patients were female and rest 4 (12.12%) were male. This was due to predominance of carcinoma ovary as primary site for peritoneal carcinomatosis in our study.

Performance status

Performance status of each case was assessed as per ECOG (Eastern Cooperative Oncology Group) performance score. 19 (57.57%) patients had performance status ECOG 0 and 14 (42.42%) had ECOG 1 performance status. Poor preoperative performance status is an important predictor of morbidity and mortality following CRS and HIPEC.

PCI score

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. 28 (85%) patients had PCI of less than or equal to 15 and rest 5 patients (15%) had PCI of >15. 1 patient had PCI of > 20. Mean PCI index was 11.6 (range from 4-24). In many studies done previously high PCI is a poor predictor for disease free survival. In our study also we found recurrence among patients with higher PCI (p-value is .000482). 7 patients who showed recurrence during follow up, 4 of them had PCI> 15.

Extend and completeness of cytoreduction: -

Completeness of cytoreduction score measures the amount of macroscopically visible tumor that is seen after CRS. We achieved a score of CC 0 in 94% of our cases, meaning no residual disease seen after cytoreduction. While in 2 patients completeness of cytoreduction score was CC-1 indicating <2.5 mm tumor nodules persisting after cytoreduction. This forms another important pillar in determining the success of HIPEC. The extent of residual disease left after cytoreduction directly impacts the long-term survival. Dedrick (1978) studied the depth of tissue penetration by different drugs and identified a group of cytotoxic drugs that can penetrate 1-3 mm into tissue. So, tumor deposits needed to be 2.5 mm or less for intraperitoneal chemotherapy to be effective[59,60].

In our study cytoreduction alone was done in 18 (54.54%) patients, in 13(39.39%) patients it was done with bowel resection. 2 (6.06%) patients had multi visceral resection. Multivisceral resection include splenectomy in 1 cases and non-anatomical liver resection in 1 case.

Fig.1 Intraoperative peritonectomy

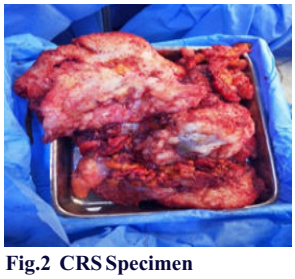

Fig.2 CRS Specimen

Other intra operative parameters: -

Mean duration of operative time in our study was 7.24 hrs. Total duration included surgery plus HIPEC. Mean blood loss during procedure was 689.39ml. 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 protocol

HIPEC was done by closed method with or without the bidirectional technique. In ovarian carcinoma for platinum sensitive cases we used cisplatin 100 mg/m2 and for platinum refractory cases cisplatin 75 mg/m2 with doxorubicin 15 mg/m2. For colorectal PSM, the bidirectional method was used with leucovorin 20 mg/m2 i.v. push followed by 5 fluorouracil 400 mg/m2 in 500 ml of normal saline over 60 minutes and then oxaliplatin 460 mg/m2 in dextrose (50 mg/ml) containing perfusate for 30 minutes. Our protocol was 30 minutes for oxaliplatin using the bidirectional method and 60-90 minutes for other chemotherapeutic agents at 42 °C. We used perfusate temperature of 42 °C, which our patients tolerated well with an acceptable change in core body temperature.

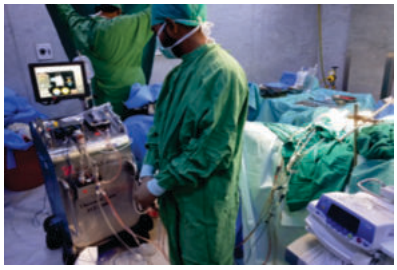

Fig.3 HIPEC machine

Fig.4 Intraoperative CRS

ICU and hospital stay: -

Post operatively we kept all patients in ICU for 24 hrs. Mean duration of ICU stay was 1.68 days. 3 patients (9.09%) had ICU stay for more than 3 days. Commonest reason for prolonged ICU stay was electrolyte imbalance. Median duration of hospital stay was 11.32 days (range 8-20 days). Prolonged hospital stay beyond 15 days was seen due to post operative anastomotic leak and re exploration in 3 patients.

Complications

Postoperative morbidity developed in 22 (66.6%) patients after CRS and HIPEC. All complications were noted and graded as per Clavien Dindo classification. In our study 6 (18%) patients developed grade 3-4 toxicities. There was no 30-day mortality noted in our patients. Most common infectious complication noted was wound infection in 8 (24.24%) patients, others were UTI, seen in 4 patients (12.12%). and gram-negative septicemia seen in 1 patient (3.03%). All these complications were grade 1 and were managed conservatively.

3 (9.1%, grade 3) of our patients had anastomotic leak for which re exploration with diversion stoma was done. They recovered well after it. Other grade 1 complications were electrolyte imbalance, hypoalbuminaemia. Most common electrolyte imbalance was hypokalemia seen in 12 (36.36%) cases followed by hypocalcemia in 11 cases (33.3%). Hypoalbuminaemia was seen in 12 cases (36.3%), fall in hemoglobin and platelet counts were seen in 6 cases (18.1%). Post operative Ileus was seen in 6 cases (18.18%), was managed conservatively. Lymphocele occurred in 8 (24.24%) 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 8 patients had 8-12 months of follow up. 14 patients had total follow up for 4-8 months and rest 7 had follow up for less than 4 months. All the patients were evaluated as per our protocol during follow up. 7 (21.2%) patients developed recurrence. Out of these 4 (12.1%) patients had intra peritoneal recurrence including liver parenchymal secondaries and rest 3 (9.1%) had systemic recurrence. These patients were considered for palliative chemotherapy. 4 out of 7 recurrences had PCI > 15. There was no mortality noted till conclusion of the study. Rest 26 patients (78.8%) till now had no recurrence are on regular follow up.

We analyzed the data of our study and found that median time of recurrence in 7 (21.21%) patients in our study was 310 days (range107 to 392 days). Earliest recurrence was observed in patients after 107 days, who had PCI of 24. Rest of the 6 recurrences occurred between 266 to 392 days. 7 patients who showed recurrence during follow up, 4 of them had PCI> 15. Median disease-free survival in our study was 6.875months (range 48days to 456days). Post-operatively patients received systemic adjuvant chemotherapy.

CONCLUSION

Peritoneal carcinomatosis either primary or secondary to gynaecological or GI malignancy can be effectively treated by CRS and HIPEC. 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 do not add significantly to morbidity and mortality. Patient selection for the procedure is very important for favorable outcome. Good performance status as determined by ECOG performance score of 0 or 1 has positive impact on the outcome of the procedure. PCI can be used as a tool to select patients and it can also be used as a prognostic marker. PCI of >15 is poor prognostic factor and may points towards early recurrence. Effectiveness of entire procedure depends on complete cytoreduction. 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. For ovarian cancer currently, there is insufficient evidence to recommend its routine use as part of first line therapy outside the setting of a clinical trial but the procedure can be used in interval setting after neoadjuvant chemotherapy and recent NCCN guidelines also support this. However, there is sufficient evidence demonstrating its benefit as second line therapy, where it can be used in both platinum resistant and platinum sensitive cases. We also used this as first line therapy in 2 patients of ovarian cancer and both are currently disease free. We may need to wait for the result of various ongoing trial to establish its role as first line therapy. In patients with PSM, 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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