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Ovarian Cancer

NIPEC with Single-Dose Intraperitoneal Cisplatin and Paclitaxel in Stage III Epithelial Ovarian Cancer

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Abstract

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Objectives Epithelial ovarian cancer (EOC) is a heterogeneous, essentially peritoneal disease. Standard treatment consists of staging, cytoreductive surgery (CRS), and adjuvant chemotherapy. In this study, we intended to assess the effectiveness of single-dose intraperitoneal (IP) chemotherapy in optimally debulked advanced EOC patients.

Materials and Methods A prospective randomized study of 87 patients with advanced EOC was done from January 2017 to May 2021 in a tertiary care center. Patients who underwent primary and interval cytoreduction received a single dose of IP chemotherapy for 24 hours after being divided into four groups: group A, IP cisplatin; group B, IP paclitaxel; group C, IP paclitaxel and cisplatin; and group D, saline. Pre- and postperitoneal IP cytology was assessed along with possible complications.

Statistical Analysis Logistic regression analysis was used to assess for intergroup significance in cytology and complications. Kaplan–Meir analysis was done to assess disease-free survival (DFS).

Results Of 87 patients, 17.2% of patients had FIGO stage IIIA, 47.2% had IIIB, and 35.6% had IIIC. Also, 22 (25.3%) patients were in group A (cisplatin), 22 (25.3%) patients in group B (paclitaxel), 23 (26.4%) in group C (cisplatin and paclitaxel), and 20 (23%) in group D (saline). Cytology samples taken during staging laparotomy were positive, and 48 hours post-IP chemotherapy, 2 (9%) of 22 samples in cisplatin group and 14 (70%) of 20 samples in saline group were positive; all of the post-IP samples in groups B and C were negative. No major morbidity was noted. In our study, DFS in saline group was 15 months, while in IP chemotherapy group it was 28 months and was statistically significant based log-rank test. However, there was no significant difference in DFS between different IP chemotherapy groups.

Conclusion Complete or optimal CRS in advanced EOC does have a possibility of microscopic peritoneal residue. Adjuvant locoregional strategies should be considered to prolong DFS. Single-dose normothermic IP chemotherapy can be offered to the patients with minimal morbidity, and its prognostic benefits are comparable to hyperthermic IP chemotherapy. Future clinical trials are required to validate these protocols.

- epithelial ovarian cancers
- cytoreduction
- intraperitoneal chemotherapy
- cisplatin
- paclitaxel
- disease-free survival

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Introduction

Epithelial ovarian cancer (EOC) is a heterogeneous disease and is the second most common gynecological cancer, with an increasing incidence of approximately 205,000 new cases and 125,000 deaths worldwide annually.[1,2] Advance EOC is a molecularly distinct disease represented by histology, routes of metastasis, response to surgery, chemotherapy, patterns of relapse, and prognosis.[3] EOC is essentially a peritoneal disease, and depending on the stage, standard treatment consists of staging, maximal cytoreductive surgery (CRS), and taxane/platinum-based adjuvant chemotherapy. In spite of a good response to conventional first-line chemotherapy, the 5-year overall survival (OS) remains unacceptably low.[4,5] The extent of CRS determines the prognosis in advanced EOC.[6] However, the probability of microscopic residual disease after complete CRS is around 98.14% in high-grade serous ovarian cancer and the 2-year peritoneal recurrence rate for early EOC is 20%, while it is 62.1% in advanced EOC, which strongly suggest that adjuvant locoregional therapies should be considered to prevent early recurrence and prolong disease-free survival (DFS).[7] Hence, the rationale of intraperitoneal (IP) chemotherapy in EOC is to provide sustained exposure to high concentrations of cytotoxic agents to the peritoneum, while the rest of the normal tissues are spared.[8] A randomised phase III Gynecological Oncology Group (GOG) trail (GOG 172) compared intravenous (IV) chemotherapy with IP chemotherapy arms in advanced EOC and found the median duration of progression-free survival (PFS) to be 18.3 and 23.8 months and the OS to be 4.7 and 65.6 months respectively, in the IV chemotherapy and IP chemotherapy using cisplatin and paclitaxel agents, proving prognostic advantage of IP route. A subset analysis of GOG 172 and the MSKCC studies revealed that the patients receiving one to two courses of IP chemotherapy also had significant OS advantages compared with IV arm.[2] Thus, in this study, we intended to assess the effectiveness of single-dose IP chemotherapy in optimally debulked patients (<1-cm residual disease) in advanced EOC and DFS.

Methods

This is a prospective randomized study of 87 patients with advanced EOC (FIGO stage IIIA–IVA) conducted at the Department of Surgical Oncology at Sri Aurobindo Institute of Medical Sciences, Indore, from January 2017 to May 2021 after obtaining approval from the Institutional Ethics Committee and tumor board. A total of 261 cases underwent CRSs for high-grade advanced EOC during the study period. Complete cytoreduction was achieved in 102 (39%) cases, optimal cytoreduction (residual disease < 1 cm) in 93 (35.6%) cases, and suboptimal cytoreduction (residual disease > 1 cm) in 66 (25.4%) cases. In total, 87 (44.6%) complete and optimal cytoreduction cases consented for the study. Inclusion criteria for selecting patients to primary debulking surgery are based on patient's good performance status Eastern Cooperative Oncology Group (ECOG) (0–1), optimal resectability on computed tomography (CT) scan study, clinical examination, and serum albumin > 3 g/dL. Patients with poor performance status (ECOG > 2), serum albumin < 3 g/dL, malignant pleural effusion, liver parenchymal metastasis, optimally nonresectable disease on CT scan, and age > 80 years would receive three courses of neoadjuvant chemotherapy (NACT) followed by interval cytoreduction (IDS) followed by reimaging with CT scan. Surgical staging was performed and ascitic fluid cytology was taken immediately before any intervention, peritoneal lavage was performed with 100 mL of physiologic saline solution (37°C) in those patients without ascites, peritoneal cancer index (PCI) was calculated, and surgical procedure was performed to attain cytoreduction including total hysterectomy with bilateral salpingo-oophorectomy, total omentectomy, and tumor debulking, i.e., removal of peritoneal deposits, diaphragmatic stripping/resection, bowel resection, splenectomy, and peritonectomy, as required for optimal debulking. Pelvic and paraaortic lymphadenectomy was done if there was evidence of enlarged node (>1 cm) on imaging and/or surgical exploration. The patients with nonconsenting, poor ECOG score and suboptimal cytoreduction (residual disease > 1 cm) were excluded from the study. Patients consenting for the study were randomized into four groups.

1. Group A: receiving IP cisplatin dose of 100 mg/m^2 (diluted in 1,000 mL Normal Saline (NS)).
2. Group B: receiving IP paclitaxel dose of 60 mg/m^2 (diluted in 1,000 mL NS).
3. Group C: receiving IP paclitaxel and cisplatin in the dose as mentioned above.
4. Group D: control group of saline instillation.

The IP chemotherapy agent was administered intraabdominally after the optimal Primary Debulking Surgery (PDS)/ Interval Debulking Surgery (IDS). All these patients received prechemotherapy medication IV prednisolone 100 mg and pheniramine maleate 25 mg. The IP chemotherapeutic agent was thoroughly circulated in the whole abdomen and left intraperitoneally for absorption, and the abdomen was closed with a sealed drain and was released after 24 hours. Patients were observed for any hemodynamic instability throughout the in-patient treatment period, and complete blood count (CBC) and renal and liver function tests were repeated every alternate day. After 48 hours of surgery, the drain was clamped for 6 to 8 hours and then upon releasing the clamp, the drain fluid thus collected was sent for cytology and named as postoperative cytology sample. Patients were scheduled to receive the next cycle of IV chemotherapy after 21 days. CBC and renal and liver function tests were done before initiating the next cycle of IV chemotherapy. All patients received six courses of IV chemotherapy and one intraoperative IP chemotherapy. The adjuvant chemotherapy would be modified or postponed in case of delayed wound healing or any morbidity. Patients were followed up for 36 months to assess the response and DFS.

Results

A total of 87 patients (mean age, 52 years [range, 30–79 years]) with 15 (17.2%) patients having FIGO stage IIIA, 41

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(47.2%) having FIGO stage IIIB, and 31 (35.6%) having FIGO stage IIIC received IP chemotherapy. Of these, 62 (71.3%) patients had high-grade serous histology, while 18 (20.7%) and 7 (8%) had low-grade serous and endometrioid variety with a mean CA-125 level of 487 units/mL. All the consenting and eligible patients underwent CRS, with primary debulking surgery in 15 (17.3%) patients and interval debulking surgeries in 72 (82.7%) patients (►Table 1). Also, 22 (25.3%) patients were in group A (cisplatin), 22 (25.3%) patients in group B (paclitaxel), 23 (26.4%) patients in group C (cisplatin and paclitaxel), and 20 (23%) patients in group D (saline). All the cytology samples taken during staging laparotomy were positive, and post-IP chemotherapy, 2 (9%) of 22 samples in cisplatin group and 14 (70%) of 20 samples in saline group were positive after 48 hours; all of the post-IP chemotherapy samples from groups B and C were negative. When compared based on logistic regression analysis, these were statistically significant (►Table 2). All patients were able to tolerate IP chemotherapy for 24 hours. Two patients in group A, one in group B, and three in group C had episodes of vomiting during the 24-hour waiting period but were managed with continuous nasogastric aspiration and antiemetics. However, in our study, complications such as nephrotoxicity, neurotoxicity, and wound complications (e.g., burst abdomen) were not present. However, complications such as prolonged ileus for more than 5 days, neutropenia, and lymphorrhea were noted and were not statistically significant (►Table 3). Patients with prolonged ileus 5 (6%) were managed conservatively with parenteral nutrition and nasogastric aspiration. None of our patients received prophylactic granulocyte-stimulating factor. We repeated CBC and renal and liver function tests every alternate day. Of the 87 patients, 3 (3%) required granulocyte-stimulating factor injections. Also, 5 (6%) had lymphorrhea, which continued for more than 14 days. These patients were managed conservatively. Thus, none of the patient's quality of life was affected, and patients were able to tolerate the procedure well. There was no mortality recorded in our study. DFS in the saline group was 15 months, while in IP chemotherapy group it was 28 months and was statistically significant based on log-rank test (►Fig. 2).

Table 1 Patient characteristics

Patient characteristics	
Mean age (y)	52
Age range (y)	30–79
Surgeries	
Primary debulking surgery	15 (17.3%)
Interval debulking surgery	72 (82.7%)
FIGO stage	
IIIA	15 (17.2%)
IIIB	41 (47.2%)
IIIC	31 (35.6%)
Histopathology	
High-grade serous	62 (71.3%)
Low-grade serous	18 (20.7%)
Endometrioid	7 (8%)
Mean CA-125	487 units/mL
Mean PCI	18

Abbreviation: PCI, peritoneal cancer index.

Discussion

The main objective in the surgical management of advanced EOC is achieving complete CRS. The OS ranges between 46.5 and 106 months for patients with complete CRS (no residual disease) and between 12 and 39 month for incomplete CRS (residual disease of more than 1 cm).[9] However, during the process of CRS, the surgical intervention itself increases the

Table 2 Pre- and post-IP fluid cytology

Group	IP chemotherapy agent	Number	Pre-IP cytology positive	Post-IP cytology positive	*p*-Value
Group A	Cisplatin	22	22	2	<0.001
Group B	Paclitaxel	22	22	0	0.996
Group C	Cisplatin + paclitaxel	23	23	0	0.996
Group D	Saline	20	20	14	<0.0003

Abbreviation: IP, intraperitoneal.

Table 3 Complications in IP chemotherapy groups

Group	IP chemotherapy agent	Number	Ileus	Neutropenia	Lymphorrhea
Group A	Cisplatin	22	2	1	2
Group B	Paclitaxel	22	1	0	1
Group C	Cisplatin + paclitaxel	23	2	2	2
Group D	Saline	20	0	0	0

Abbreviation: IP, intraperitoneal.

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probability of dissemination of disease through various pathways. In laparoscopic oncological surgeries, tumor cell dissemination occurs after resection and includes port-site recurrences probably due to extensive manipulation of the tumor. Not using retrieval bag or cold CO_2 insufflation induces damage to the peritoneum lining, leading to tumor cell implantation even in procedures with minimal invasive tumor characteristics.[10] Gross en masse tumor resection also can result in local dissemination of cells. Although surgeons have been trained to minimize the risk of tumor seeding, there are certain unavoidable negative effects of surgical procedures as they induce changes in the local tumor microenvironment, which has an impact on tumor cell gene expression and behavior. They exert both protumoral and antitumoral effects. Tumor cells often create an immunosuppressive microenvironment that favors tumor progression and metastatic spreading by avoiding immune surveillance.[11] Tumor resection can even further promote immunosuppressive infiltrates in the remaining tumor mass by secreting proinflammatory factors such as S100A8, COX2, CCL3, and CXCL2, inflammatory cytokines, chemokines, and growth factors followed by a significant increase in the number of myeloid-derived suppressor cells locally.[12] Surgical wound tissue potentiates neoangiogenesis and secretes mitogens; growth factors such as heparin-binding epidermal growth factor (HGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF-β), and basic fibroblast growth factor (FGF) present in the wound fluid support tumor growth rate.[13] Apart from these, tumor-associated macrophages can promote tumor cell migration and these growth factors, EGF, PDGF, TGF-β1, HGF, and FGF-2, stimulate tumor proliferation and survival.[14] Besides increased growth rate, surgical trauma can also enhance tumor cells migratory capacity and gets recolonized by forming tumor microtubes leading to tumor cell invasion, proliferation, usually gets entrapped within the adhesions facilitated by presence of protein-rich fluid environment.[12] Tumor cell dissemination to distant organs occurs by circulatory tumor cells (CTCs) into the lymphatic and blood vasculature. Underlying surgically induced hypothalamic–pituitary axis depression, imbalance of the innate and adaptive immune regulatory mechanisms, and impaired immune function increase CTCs' ability to survive and extravasate.[15,16] Surgical induced systemic effects such as inflammatory response mediated by the release of inflammatory cytokines like TNF-α and IL-1 stimulate tumor cell adhesion, invasion and neoangiogenesis and potentiate metastasis formation and in the peritoneal cavity, exposure of the extracellular matrix after mesothelial cell detachment in response to surgical trauma can facilitate tumor cell adhesion in non-traumatized areas of the peritoneal cavity as well.[12,17–19] Surgical interventions can lead to metastatic progression by altering inhibitory control exerted by the primary tumor by secreting antigrowth factors and antiangiogenic effects on distant micrometastases.[20] On tumor resection, these inhibitor levels drop and angiogenic switch takes place at distant tumor sites, leading to tumor expansion and premetastatic niche formation.[20,21] All these mechanisms, combined or singly, have a potential to affect tumor progression and spread (►Fig. 1). Since the prognostic benefit of CRS outweighs its negative effects, these procedures should not be discouraged; rather, to curtail locoregional spread, IP chemotherapy should be considered in the same setting in the same setting should be considered. Due to the presence of the peritoneal–plasma barrier, high doses of IP chemotherapy can be administered safely while minimizing systemic effects. On the other hand, systemic chemotherapy is ineffective for peritoneal implants due to this barrier.

As previously discussed, outcomes strongly depend on CRS. With optimal CRS, median OS ranging from 49 to 66 months has been reported.[22] Although some trials such as the GOG 252 trial may not have demonstrated any differences in PFS and OS between IV dose-dense paclitaxel and carboplatin plus bevacizumab versus IP cisplatin and carboplatin chemotherapy plus bevacizumab in patients with advanced ovarian cancer, in the iPocc trial there was an improvement in DFS when treated with IP carboplatin plus paclitaxel compared with IV chemotherapy; however, the benefit was not seen in OS. However, the inclusion of larger residual tumors and exclusion of bevacizumab in the iPocc trial may be another reason for the difference between these two trials.[23,24] A phase III randomized trial by GOG/Southwest Oncology Group (SWOG) compared systemic cisplatin and paclitaxel with systemic carboplatin, paclitaxel, and postoperative IP cisplatin after an optimal cytoreduction and concluded that the latter IP group had an improved PFS (28 vs 22 months) and OS (63 vs 52 months).[22] Similarly, Armstrong et al study a subset of patients who could not complete all the planned six courses. IP chemotherapy group had an improved OS and those who completed the trial had an improvement in PFS (23.8 vs 18.3 months) and OS (65.6 vs 49.7 months) in the systemic and IP chemotherapy group compared with the systemic chemotherapy.[8] Suidan et al conducted a study in MSKCC and concluded that patients with the least number of IP chemotherapy had significantly improved OS compared with pure IV chemotherapy arm.[2] The efficiency of IP chemotherapy depends on the depth of tissue penetration of IP chemotherapy drugs. As per the study by Goodman et al, various cytotoxic drugs have limited penetration, with some of them being 1 to 3 mm into tissue which necessitated a good CRS so that tumor deposits should be 2.5 mm or less for IP chemotherapy to demonstrate its effects.[25] Moreover, the physical properties of cytotoxic drugs should be such that there should be higher concentrations of drugs intraperitoneally so that it would passively diffuse into the tumor nodules and only the small amount of drug gets into the systemic circulation, so the drug should be large with high molecular weight, hydrophobic, ionized compound with high area under the curve (AUC).[25] Cisplatin has an exposure time of 30 minutes to 20 hours, AUC ratio of 7.8 to 21, and penetration depth of 1 to 5 mm, while paclitaxel's exposure time is 30 minutes to 23 hours, AUC ratio is 1,000, and penetration depth is >80 cell layers.[25] Since the molecular weight of paclitaxel is higher, certain studies have reported that its effect lasts as long as 8 days intraperitoneally.[8] Due to these properties, IP administration

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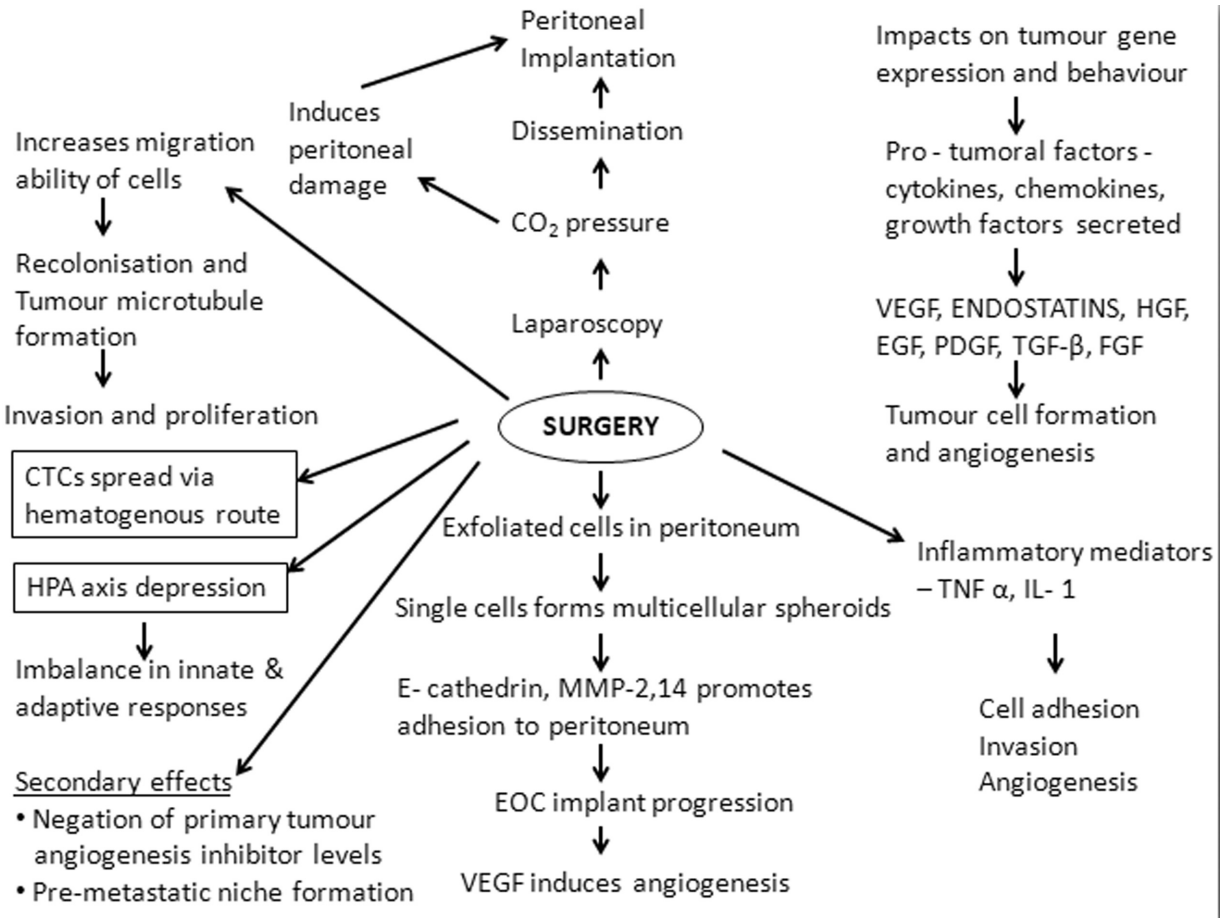

Fig. 1 Mechanisms leading to surgical dissemination.

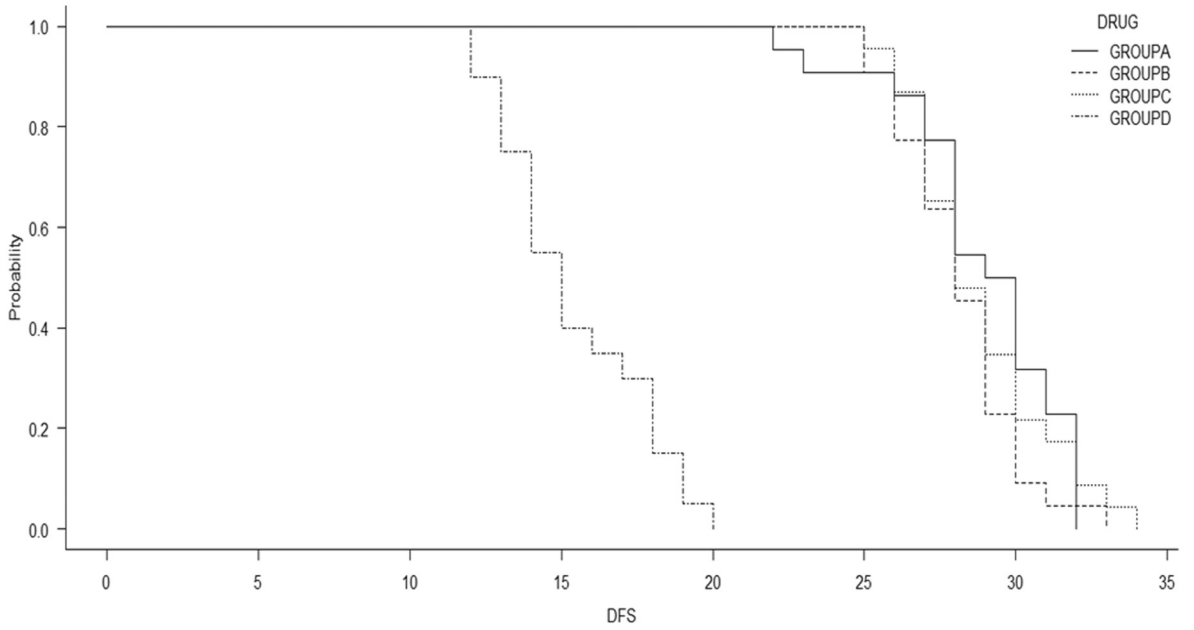

Fig. 2 Disease-free survival of intraperitoneal group A (cisplatin), group B (paclitaxel), group C (cisplatin and paclitaxel), and group D (saline).

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of cisplatin and paclitaxel can achieve 20- and 1,000-fold greater concentration, respectively, than its IV route.[26] Since paclitaxel is heat-labile molecule, its role in hyperthermic IP chemotherapy (HIPEC) is limited.[8] Thus, in our study we compared these two drugs individually and in combination with saline with pre-IP and 48 hours post-IP peritoneal fluid cytology as an indicator based on the study by Loggie et al.[27] Based on our findings, cytology was post-IP peritoneal cytology fluid positive in 70% (14/20) of cases in saline, 9% (2/22) in the case of cisplatin IP agent, and negative in paclitaxel and cisplatin/paclitaxel combination IP agent. Nor were the complications significant. Five patients had prolonged ileus and lymphorrhea, which recovered with a conservative approach, and three patients had neutropenia, which required granulocyte-stimulating factor injection. This could be due to smaller molecular weight and hydrophilic properties of cisplatin drug leading to its rapid absorption. There was no mortality in our study. These patients were later able to continue with an adjuvant chemotherapy schedule.

A retrospective multicenter study of advanced ovarian cancer by Di Giorgio et al analyzed 511 patients who underwent CRS plus HIPEC and found DFS of 53.8 months and OS of 54.2 months in the primary debulking group, while OS was 16.6 months in the recurrent malignancy group.[28] Another prospective multicenter study by Mercier et al analyzed the impact of CRS and HIPEC on survival of 210 patients with peritoneal metastasis EOC and concluded that median DFS and OS were 43.5 and 69.3 months, respectively.[28] A randomized control trial (RCT) comparing CRS with HIPEC and systemic chemotherapy versus CRS and IV chemotherapy in primary ovarian carcinoma by Lim et al reported 21% increase in the 5-year DFS and 51% increase in the 5-year OS in the former group.[29] Another multicenter phase III RCT done by van Driel and his colleagues on stage III ovarian cancer post NACT randomized patients into two groups after receiving three cycles of IV carboplatin and paclitaxel: one with CRS alone and other with CRS plus HIPEC. The authors reported DFS of 14.2 months and median OS of 45.7 months in the latter group.[30] All these studies support the role of CRS plus HIPEC in advanced EOC. IP chemotherapy studies conducted by Gynecologic Oncology Group where IV cisplatin and paclitaxel were compared with IV carboplatin/paclitaxel and IP cisplatin after an optimal cytoreduction reported that IP chemotherapy group DFS was 28 versus 22 months and OS was 63 versus 52 months.[22] A similar study by Armstrong et al reported DFS of 23.8 versus 18.3 months and OS of 65.6 versus 49.7 months in the IV and IP chemotherapy group compared with the IV chemotherapy group.[8] In our study, DFS in saline group was 15 months, while in IP chemotherapy group it was 28 months and was statistically significant based log-rank test(►Fig 2). However, there was no significant difference in DFS between different IP chemotherapy groups. Although CRS and HIPEC have proven its efficacy in ovarian cancers, it has got a learning curve and is not easily available, affordable, and associated with significant morbidity and mortality.[28] Single-dose IP chemotherapy after optimal CRS can be practiced in centers without HIPEC facility and has got acceptable morbidity, mortality, and comparable DFS with HIPEC.[31–33] A French multicenter study by Bakrin et al assessed early and long-term survival in 566 patients treated with CRS and HIPEC and found that median DFS was 11.8 months and OS was 35.4 and 45.7 months for advanced and recurrent EOC, respectively.[31] Pavlov et al reviewed their 12-year results with CRS and HIPEC with intraoperative doxorubicin and cisplatin on postoperative days 1 to 5 in patients with advanced primary and recurrent ovarian cancer with an average PCI of 13.4 and mean follow-up of 56 months. They observed that median DFS was 26.2 months and median OS was 34.1 months for primary and 40.1 months for recurrent ovarian cancer.[32] A phase II multi-institutional trial by Deraco et al assessed OS after CRS and HIPEC with cisplatin and doxorubicin in upfront advanced EOC and reported a 5-year DFS of 15.2% (median, 30 months) and 5-year OS of 60.7%.[33] Based on the findings of the present study, we suggest that normothermic IP chemotherapy (NIPEC) in advanced EOC does play an important role in controlling disease progression and further randomized multicenter trials can generate effective protocols for single or a combination of chemotherapy agents.

Conclusion

Complete or optimal CRS in advanced EOC does have a possibility of microscopic peritoneal residue. Adjuvant locoregional strategies should be considered to prolong DFS. Single-dose NIPEC can be offered to patients with minimal morbidity and prognostic benefits comparable to HIPEC. Future clinical trials are required to validate these protocols.

Conflict of Interest

The authors declare no conflicts of interest and no external funding was received for the study.

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