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Cytoreductive surgery and Hyperthermic intraperitoneal chemotherapy (HIPEC) for recurrent advanced ovarian carcinoma: initial experience in Mexico

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Abstract: Background: Ovarian cancer is a lethal tumor, 70% of which occurs in locally advanced stages. Despite its high initial response rate to chemotherapy, recurrence takes place in up to 90%. Prognosis of recurrent disease remains poor. In recent years, a new approach has been developed, combining a maximal cytoreductive effort with Hyperthermic intraperitoneal chemotherapy (HIPEC).Methods: We conducted a pilot study of 14 patients with recurrent ovarian cancer who were treated with Cytoreductive surgery (CRS) and HIPEC at the Mexico City-based National Cancer Institute of México (INCan) between January 2007 and January 2012.Results: There were 14 patients with recurrent ovarian cancer, including 13 with clinical stage IIIC and one with clinical stage CEIV due to retroperitoneal tumor with recurrence. Average age was 52 years (range, 20–72 years). Mortality and morbidity rates were 0 and 40%, respectively. Average surgical operative time was 7.5 h (range, 4.7–11 h). Average bleeding amounted to 1,171 mL (range, 100–3,700 mL).Overall median survival (OMS) was 14 months (range, 2–37 months). Peritoneal carcinomatosis index (PCI) showed eight patients with <20 and six with >20 points. Bleeding correlates with the PCI of >20 points. Performance status was a significant prognostic factor in patients with extensive peritoneal carcinomatosis (PCI, >20).Conclusions: Therapy combining CRS and HIPEC is feasible in selected patients with recurrent ovarian carcinoma with high morbidity. With ovarian cancer, novel therapies should be explored, one of which could be HIPEC.

Keywords: Cytoreductive Surgery, HIPEC, Recurrent Ovarian Cancer, Cisplatin

1. Introduction

Epithelial ovarian cancer (EOC) affects >200,000 women annually throughout the world and is the cause of 125,000 deaths per year worldwide[1].

Ovarian cancer is a lethal tumor, and 70% occur in locally advanced stages. Despite a high initial response rate to chemotherapy, recurrence takes place in up to 90%[2]. Prognosis of recurrent disease remains poor; 5-year Overall survival (OS) is <50%[3,4].EOC is a peritoneal surface malignancy that remains confined to the peritoneal cavity and retroperitoneal lymph nodes for much of its natural history[5]; in the U.S., EOC affects 22,280 women annually and is responsible for 15,500 deaths [6]. The disease causes few symptoms initially and in the majority of cases has already spread outside the pelvis, with 50%found in International Federation of Gynecology and Obstetrics (FIGO) stage III (with peritoneal cavity or evolving para-aortic, pelvic, or inguinal lymph node involvement) and 13% in FIGO stage IV (beyond the peritoneal cavity, including lung and liver parenchyma) [7]. With optimal debulking followed by the two-drug combination of carboplatin plus paclitaxel, responses are generally short-lived and the clinical outcome continues to be unsatisfactory, with median Progression-free survival (PFS) rates between 16 and 21 months. With the recent European registration of bevacizumab for upfront treatment of advanced ovarian cancer stages IIIb/IIIc and IV, median PFS rates have increased up to 24 months. In general, no curative

treatment is available for recurrent disease. Based on their response to previous platinum therapy after first-line treatment, patients are categorized into the following groups: platinum-sensitive, with a Progression-free interval (PFI) of >12 months; intermediate platinum-sensitive (PFI between 6 and 12 months), or resistant groups (PFI <6 months). There is a pressing need to identify more efficient therapies. In addition to the promising results of bevacizumab, it is the first antiangiogenic agent to demonstrate a PFS benefit in addition to standard treatments in both primary and recurrent ovarian cancer; no real improvements in treatment results have occurred the past decennium [8,9].Witkamp et al.[10]hypothesized that intraperitoneal (i.p.) placement of certain chemotherapeutic agents could lead to significantly greater peritoneal-cavity drug exposure than placement in the systemic vascular compartment. Because EOC remains confined to the peritoneal cavity for much of its natural history and is relatively sensitive to chemotherapy, it should be a good target for i.p. treatment. For drugs that are most active in EOC, the ratio of their i.p. to plasma concentrations varies from 18–20 times for carboplatin and cisplatin to 120–1,000 times for the taxanes, docetaxel, and paclitaxel [11]. In recent years, a new approach has been developed that combines maximal cytoreductive effort with Hyperthermic intraperitoneal chemotherapy (HIPEC).

2. Materials and Methods

We conducted apilot study of patients with recurrent ovarian cancer who were treated with CRS and HIPEC at the National Cancer Institute of México (INCan) between January 2007 and January 2012, and based on data from medical records.

3. Patient Selection

Inclusion criteria were:1. Recurrent ovarian cancer; 2. World Health Organization (WHO) status performance <2; 3. Age 18 to <75 years; 4. No concomitant liver, respiratory, heart, or kidney diseases; 5. Clinical, radiological, or pathological diagnosis of peritoneal carcinomatosis, and 6. Absence of hepatic or extra-abdominal metastatic disease.

4. Cytoreductive Surgery

Evaluation was carried out during surgical exploration, cavidity was reviewed to determine the extent of the disease and the feasibility of cytoreduction, and the goal was to remove all of the visible disease, according to the technique described by Sugarbaker[12]. The Peritoneal Cancer Index (PCI) was integrated and employed to determine the extent of the tumor [13]; all patients who underwent complete cytoreduction or who were optimally cytoreducted, hemodynamically stable, and who did not experiencemajor complications underwent HIPEC. The chemotherapy agents employed were cisplatin 25 mg/m^2/L) and mitomycin C (3.3 mg/m^2/L) for 90 min[14]. HIPEC was performed with the closed technique in all patients, and the perfusion solution was maintained at an average of 41°C (temperature range, 40–43°C). The total chemotherapy dose was fractionated into the following three portions: 50; 25, and 25%, and each dose was perfused for 30 min. Statistical analysis was performed with descriptive measures.

5. Results

From January 2007 to January 2012, a total of 14 patients with recurrent ovarian cancer underwent HIPEC. The patients' characteristics are summarized in Table 1.

Table1. *Patients' demographic and clinical characteristics (14 patients)*

Variable	*N* %
Age (years)	52 (range, 20–72 years)
Recurrent disease	14 (100%)
Histology	
Papillary serous	14 (100%)
Previous chemotherapy	14 (100%)
Neoadjuvant	14 (100%)
Adjuvant	14 (100%)
Performance status (WHO)	
0	6 (43%)
1	5 (36%)
2	3 (21%)
Clinical stages	
IIIC	13 (93%)
IV	1 (7%)
PCI (points)12.8(range, 2–33)	
<20	8 (57%)
>20	6 (43%)

PCI = Peritoneal cavity index; WHO = World Health Organization.

Patients were found to be in the following stages: 13 in clinical stage III C, and one in clinical stage CE IV due to retroperitoneal tumor with recurrence. Average age was 52 years (range, 20–72 years).

6. Operative Outcomes

Average operative time was 7.5 h (range, 4.7–11 h), average blood-loss volume was 1,171 mL (range, 100–3,700 mL), and the average number of transfusion packages per patient was 2.3.

The following intraoperative complications occurred: diaphragm opening (n=4), and bleeding (n = 1)

Eleven of the 14 patients (79%) included in the study required postoperative admission to the Intensive Care Unit (ICU); average stay in the ICU was 1.9 days (range, 1–4 days).

The major postoperative complications (Table 2) were as follows: bleeding (*n*= 1); acute renal failure (*n*= 1), and fistula (*n*= 1). Return to the operating room for control of postoperative bleeding was needed in one patient, and no operative deaths occurred. Mortality and morbidity rates were 0 and 40%, respectively.

Table2. *Surgical outcome*

Procedures	***N* (range) (%)**
Duration of procedure	7.5 h (4.75–11 h)
Blood loss (mL)	1,171 (100–3,700 mL)
Blood transfusion units	2.3
Yes	12 (86%)
No	2 (14%)
ICU stay (days)	2.2
Yes	11 (79%)
No	3 (21%)
Complications	
Yes	7 (50%)
No	7 (50%)
Complication types	
Four diaphragm openings	(29%)
One acute kidney failure	(7%)
One bleeding	(7%)
One fistula	(7%)
Mortality	

ICU = Intensive care unit.

Overall median survival (OMS) was 14 months (range, 2–37 months) (Table 3). The Peritoneal CarcinomatosisIndex showed eight patients with <20 points and six patients with >20 points.

Table3. *Follow-up and PCI*

Variable	**No %**
Follow-up	
>12 months	8 (57%)
<12 months	6 (43%)
Current status	
Alive without disease	6 (43%)
Alive with disease	5 (36%)
Dead with disease	3 (21%)
PCI	
<20	8 (57%)
>20	6 (43%)

PCI = Peritoneal cancer index.

7. Discussion

Ovarian cancer is a problem because despite a high initial response rate to chemotherapy, the recurrence rate is very high, and prognosis of recurrent disease is poor. Hyperthermic intraperitoneal chemotherapy (HIPEC) in peritoneal metastases from epithelial ovarian cancer is a controversial treatment.The first report on EOC was in 1994 [15];since that time, the published reports are mainly case series and early phase II studies. Spiliotis et al. [16], in a small phase III prospective trial, evaluated the role of Cytoreductive surgery (CRS) and HIPEC plus systemic chemotherapy vs. CRS plus systemic chemotherapy in women with recurrent EOC after initial debulking surgery and systemic chemotherapy. The median survival rate was 19.5 vs. 11.2 months (p<0.05), and 3-year survival was 50 vs. 18% in favor of the HIPEC group. Our findings from this review of 14 patients with recurrent ovarian cancer with diffuse peritoneal carcinomatosis are good. To date, this procedure is sought only for patients undergoing secondary cytoreduction because this is considered as salvage treatment. However, we think that completed cytoreduction remains a main prognostic factor; it is the main factor of the target prior to cytoreduction and HIPEC.

The use of HIPEC as frontline treatment is presented in several studies with small numbers of patients. The data suggest that with HIPEC, 2-year OS and PFS were not significantly different from those of CRS and systemic chemotherapy. Deraco et al. [17] reported, after a median follow-up of 25 months, that 5-year OS was 60.7% and 5-year PFS was 15.2% (median, 30 months).

We think that the results found in our initial experience are consistent with others reported in the literature [18,19], and we suggest that cytoreduction plus HIPEC in patients with ovarian carcinomatosis, if it strictly complies with the selection criteria, such as age, platinum sensitive sensitivity, without comorbidities, and functional status, should be the treatment-of-choice for this select patient group because, as already reported, patients with compromised performance status are not eligible to undergo peritonectomy plus HIPEC [20–22].

In this series, we did not use diagnostic laparoscopy to assess the extent of the disease, because we think it to be of no help and that it may even change the decision due to inadequate exploration. We think that diagnostic laparoscopy may be useful in selected, and in less problematic, cases. The majority of our cases include extensive ovarian carcinomatosis with a mean Peritoneal Cavity Index (PCI)of 13 points.

Considering the extent of cytoreduction, operating time (7.5 h), that 14 (100%) patients had been previously operated on, and that the number of cases falls within the surgical team's learning curve, morbidity (50%) and mortality (0%) are similar to those reported in the literature. A critical factor for reducing morbidity and mortality in CRS and HIPEC is the importance of the learning curve. The performance of at least 130 procedures is necessary for the physician to be an expert in cytoreduction using the Sugarbaker technique[15,23,24]. A question arises when discussing morbidity and mortality in this treatment. It is unclear whether increased morbidity and mortality is

related to CRS or to HIPEC. Assessment of morbidity and mortality related with HIPEC delivery is complicated by the fact that the major surgery with visceral resections and peritonectomy procedure is itself associated with high morbidity. In a recent study by Fagotti et al. [25]on recurrent ovarian cancer with CRS and HIPEC, the morbidity rate was 34.8% with no mortality. Ileus, anastomotic leakage, bleeding, wound infection, fistula formation, pleural effusion, and thrombocytopenia represented the most common complications.

Results from different studies published [7,18,20,26–29]suggest that HIPEC is an interesting and promising treatment in recurrent EOC when combined with complete cytoreduction. The numbers are small but interesting, in that 3- and 5-year survival was significantly better in the HIPEC group than inthat of patients administered the conventional treatment. Prognostic factors, which can predict the survival outcome, also define the criteria for "optimal" HIPEC in recurrent ovarian cancer. These factors are age, performance status, interval from initial treatment to recurrence, PCI, completeness of cytoreduction, presence of lymph nodes, and initial platinum response.

In this pilot study with 14 patients with recurrent and platinum-sensitive ovarian cancer treated by CRS and HIPEC, OMSwas 14 months (range, 2–37 months) (Table 3). The PCI was high in 43% of patients (eight, <20, and six, >20). In addition, we found that bleeding correlates with the PCI at >20 points.

8. Conclusions

Therapy combining CRS and HIPEC is feasible in selected patients with recurrent ovarian carcinoma, with high morbidity in ovarian cancer.

Peritoneal metastases in patients with EOC are a poor prognostic factor for survival. Thus, conducting mandatory innovative clinical studies with the sufficient data needed to compare conventional treatment with and without HIPEC is required.

The chemotherapy regimen, the new agents, and the chemotherapy dose need to be explored.

In the future, we think that understanding both the genome structure variation and functional deregulation in cancer may predict which patients with EOC are candidates for developing peritoneal metastases and which patients will be benefitted by CRS and HIPEC, with selected chemotherapy agents. Patient selection and complete cytoreduction of the disease comprise the most important issues.

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