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HIPEC in recurrent ovarian cancer patients: Morbidity-related treatment and long-term analysis of clinical outcome

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ABSTRACT

Objective. To evaluate morbidity and mortality rates associated with the use of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) after optimal cytoreduction (CRS) in a large single-institutional series of platinum-sensitive recurrent ovarian cancer patients. Moreover, disease free (DFS) and overall survival (OS) of previously studied patients have been assessed after a longer follow-up period.

Method. From May 2005 to October 2010, recurrent ovarian cancer patients with a platinum-free interval of at least 6 months have been prospectively enrolled in a protocol of CRS plus HIPEC with oxaplatinum (460 mg/m^2) heated to 41.5 °C for 30 min, followed by 6 cycles of systemic chemotherapy with taxotere 75 mg/m^2 and oxaliplatin 100 mg/m^2.

Results. Forty-one patients experienced 43 procedures (CRS + HIPEC). An optimal cytoreduction was achieved in all cases (CC-0 95.3%; CC-1 4.7%). A complication rate of 34.8% was registered, with no case of intraoperative death or within 30 days after surgery. Survival curves have been calculated in a group of 25 patients with a minimum follow-up of 18 months, obtaining a median DFS and OS of 24 (range 6–60) and 38 months (range 18–60), respectively.

Conclusion. In recurrent platinum-sensitive ovarian cancer patients, the use of CRS plus HIPEC represents a safe treatment, able to significantly influence the survival rates compared to chemotherapy alone or surgery plus standard chemotherapy.

Introduction

In the last decade, only a slight improvement has been achieved in survival rates of advanced ovarian cancer (AOC) [1], and even after optimal cytoreduction followed by platinum-taxol based chemothera py about 60% to 70% of stage III patients develop a recurrence [2,3].

The standard treatment for recurrence is still debated. Recently, the role of cytoreductive surgery (CRS) in platinum-sensitive recurrent ovarian cancer patients has been enhanced, supported by a meta-analysis [4] proving residual tumor as the most powerful determinant of survival also in relapsed disease.

Adding hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) to the current treatment modalities for recurrent ovarian cancer seems to improve survival rates in some series at the cost of acceptable mortality, but significant morbidity rates [5–7]. However, most of the studies testing the combined approach are observational and have been conducted in inhomogeneous series. Thus, the evidence supporting the performance of CRS + HIPEC is still poor, as well as it is unclear which patient will benefit most from this treatment.

In a previous pilot study we carried on between 2005 and 2008, we obtained encouraging data in 25 recurrent platinum-sensitive ovarian cancer patients [8] submitted to CRS + HIPEC, but the low number of cases and the short follow-up did not allow us to draw any definitive conclusion. Based on these considerations, we kept on treating this subset of patients according to this schedule.

Primary objectives of the present study were the following: i) to re-assess morbidity and mortality rates associated to oxaliplatin (OXA)-based HIPEC after optimal cytoreduction in a larger single-institutional series of recurrent ovarian cancer patients, and ii) to re-calculate disease free (DFS) and overall survival (OS) of the previously studied patients after a longer follow-up period.

Patients and methods

This is a single-institutional study planned to evaluate the role of the oxaliplatin-based HIPEC associated with optimal CRS and followed by systemic administration of docetaxel (DTX) and OXA in recurrent platinum-sensitive ovarian cancer patients. The approval of the local ethic committee was obtained before starting the trial.

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Eligibility

The study included patients with histologically documented ovarian cancer (OC), who have relapsed after at least 6 months after the completion of primary chemotherapy with platinum. Further inclusion criteria were: age between 18 and 65 years, patients with first recurrence of OC, life expectancy of at least 3 months, ECOG Eastern Cooperative Group Performance Status (PS) ≤2, OC confined to the peritoneal cavity, with or without resectable extraperitoneal disease, previous carboplatin-paclitaxel based chemotherapy, normal cardiac, hepatic, respiratory and bone marrow functions (creatinine clearance>60 ml/min according to Cockroft formula, absolute neutrophil count>1500/ll, a platelet count>150,000/ll, bilirubin levels and creatinine <1.5 times upper the range), compliant patients able to follow the study procedures.

Exclusion criteria were: pregnancy or lactation, patients suffering from major depressive disorder or minor mood disorders, severely impaired respiratory, hepatic or renal functions, presence of pharmacologically uncontrolled cardiovascular, neurological or metabolic disease, inadequate bone marrow function, no obvious peritoneal disease at surgical exploration, prior or concurrent malignancies in different sites (with the exception of basal or squamous cell carcinomas skin and cervical carcinoma in situ), symptomatic metastases of the central nervous system, uncontrolled sever infections.

Treatment plan

All patients gave an informed consent to participate to the protocol, which included complete blood work (blood count, tests blood chemistry, urine analysis and Ca125 serum levels) and FDG-PET/CT scan and staging-laparoscopy (S-LPS) to exclude extra-abdominal disease and to assess the chances of optimal cytoreduction [9].

A preoperative anesthesiological and psychological evaluation was also performed once the decision of trying a successful cytoreduction and HIPEC was set up.

Surgical procedures and HIPEC Technique

Surgery and HIPEC were performed as previously described [8,10].

The HIPEC was always preceded by an optimal cytoreduction, which was defined as the removal of all macroscopically detectable disease or residual intraperitoneal lesions each less than 0.25 cm [11]. The completeness of cytoreduction (CC) was assessed using a score ranging from 0 to 3 (CC-0 indicates no residual tumor, CC-1 indicates nodules <0.25 mm, CC-2 for nodules between 0.25 and 2.5 cm in diameter; CC-3 for nodules>2.5 cm) [11].

Table 1
Patients' characteristics at recurrence.

Characteristics	N°
All patients	41
Procedures	43[a]
Stage (at diagnosis)	
I	2
II	5
IIIa	0
IIIb	5
IIIc	29
IV	2
Median BMI (range)	23.7 (18–43.1)
Median age (years) (range)	52.6 (43–67)
Median ECOG PS (range)	0 (0–1)
Median Ca125 (UI/ml) (range)	68.9 (9–434)
Presence of ascites	0
Median primary DFS[b] (months) (range)	19 (6–72)

[a] 2 patients repeated HIPEC on the secondary recurrence.
[b] Primary DFS: disease free survival from primary surgery to first recurrence.

Table 2
Intraoperative parameters.

Parameter	N° (%)
Type of recurrence	
Single	8 (18.6)
Multiple	18 (41.9)
Diffuse carcinosis	17 (39.5)
Site of recurrence	
Exclusively Intraperitoneal	19 (42.8)
Mixed with	
➢ Lymphnodes	11 (25.6)
➢ Intraparenchimal disease (liver/spleen)	11 (25.6)
➢ Lymphnodes and intraparenchimal	2 (4.6)
Number of surgical procedures performed	
Abdominal/pelvic peritonectomy	29 (67.4)
Bowel resection	20 (46.5)
Diaphragmatic stripping and/or resection	15 (34.9)
Splenectomy	10 (23.2)
Aortic/pelvic lymphadenectomy	13 (30.2)
Cholecystectomy	3 (7.0)
Distal pancreatectomy	2 (4.6)
Upper vaginectomy	6 (13.9)
Liver resection	2 (4.6)
Median operating time (min) (range)	300 (138–619)
Median Peritoneal Cancer Index (PCI) (range)	6 (2–21)
Completeness of cytoreduction (CC)	
CC-0	41 (95.3)
CC-1	2 (4.7)

CC-0: no residual disease; CC-1: residual nodules measuring less than 2.5 mm; CC-2: residual nodules measuring between 2.5 mm and 2.5 cm; and CC-3: residual nodules greater than 2.5 cm. [11].

Oxaliplatin (OXA) 460 mg/m2 at the temperature of 41.5 °C was administered intraperitoneally for 30 min and after HIPEC completion the abdomen was carefully re-explored with particular attention to haemostasis and bowel anastomoses.

Patients' demographics, surgical and post-operative data were collected. Operative time was calculated starting from the skin incision to the end of all surgical procedures.

The anesthesiologist's estimated blood loss (EBL) was used. The decision of performing an autologous blood transfusion was made intra- and/or post-operatively according to the hemodynamic conditions. Post-operative recovery was calculated starting from the first post-operative day to the day of hospital discharge.

Any adverse event occurring within 30 days from surgery was defined as early post-operative complication and was considered severe [12] if it resulted in an unplanned admission or in a secondary surgical procedure.

Statistical analysis

Primary DFS was defined as the time elapsed between primary surgery and first recurrence. Second DFS was defined as the time elapsed between HIPEC and second recurrence of disease or date of last follow-up. Overall Survival (OS) was defined as the time elapsed between HIPEC and the date of death or the date of last follow-up.

Kaplan–-Meyer method and log-rank test were used to estimate and compare the median survival time survival between groups ($p<0.05$ was considered statistically significant) [13]. The comparison of proportions was carried out using the chi-square test (χ^2).

The Crunch Interactive Statistical Package (CRISP 3.0, San Francisco, CA) was used.

Results

From May 2005 to October 2010, a total of 41 patients with platinum-sensitive recurrent ovarian cancer underwent 43 procedures of CRS + HIPEC at the Division of Gynecologic Oncology of the Catholic University of Sacred Heart of Rome and Campobasso.

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These patients include the first 25 women, enrolled between May 2005 and September 2008 and previously published in a pilot study [8], and 2 women who experienced a second platinum-sensitive recurrence and were treated with the same schedule.

The clinical characteristics of the patients are shown in Table 1. The median DFS was 19 months (6–72). In all patients except one an optimal residual tumor (RT) (<1 cm) was achieved during primary cytoreduction or interval debulking surgery (IDS). The performance status (PS), according to the ECOG criteria was 0 in 34 patients (82.9%) and 1 in the remaining cases (17.1%). Ca125 median levels at the time of recurrence were 68.9 IU/ml (9–434) and none patient presented ascites.

Type of recurrence was registered according to our previously published criteria [14] as following: i) single in 8 patients (18.6%), ii) multiple (up to 3 nodules) in 18 cases (41.9%), iii) diffuse carcinosis in 17 patients (39.5%). The recurrence was only intraperitoneal in 19 cases (44.2%), whereas it was associated with lymph nodal or intraparenchymal disease (spleen/liver) in 24 women (55.8%).

Table 2 shows surgical procedures and intra/post-operative parameters in the study population. The median Peritoneal Cancer Index (PCI) [11] was 6 (range 2–21) and optimal cytoreduction was achieved in all cases (CC-0 95.3%; CC-1 4.7%). Median operative time was 300 min (range 138–619 min). Median 'Intensive Care Unit' (ICU) and hospital stay were 1 day (range 0–6) and 10 days (range 5–30), respectively.

Overall, the incidence of major complications was 34.8% (15 out of 43 procedures) and re-operation rate was 14.0% (6 out of 43 procedures) (Table 3). The most frequent complication was bleeding, observed in 7 patients (16.3%) within 36 h after surgery. In particular, five women experienced hemoperitoneum and 3 patients had copious rectal bleeding after bowel resection, with one patient having both complications. Two of these women needed a re-laparotomy, while an endoscopic treatment was performed in 3 cases. One patient underwent both treatments. Furthermore, blood and plasma transfusions were provided in 19 (44.2%) and 6 (13.9%) cases, respectively. Other major complications included 1 sub-phrenic abscess following pancreatic fistula that required open-drainage; 2 wound large abscesses requiring re-hospitalization, curettage and i.v. antibiotic therapy; 1 portal vein thrombosis and 1 sepsis. In addition, eight (19.5%) pleural effusions were observed, but only two cases needed drainage.

Table 3
Post-operative parameters.

Parameter	N° (%)
Number of patients transfused	
Blood	19 (43.9)
Plasma	6 (9.8)
30-day mortality	0
Post-operative major morbidity	15 (34.8)
Haemorrhage	7 (16.3)
Pleural effusion requiring drainage	2 (4.6)
Fistula	1 (2.3)
Pneumonia	0
Heart arrhythmia	0
Small bowel obstruction	0
Heart failure	0
Tissue necrosis	0
Central vein thrombosis	1 (2.3)
Femoral neuropathy	0
Pulmonary embolus	0
Septicemia	1 (2.3)
Line sepsis	0
Abdominal abscess	3 (7)
Wound seroma	0
Urinary infection	0
Re-operation rate	6 (14.0)
Open	3 (7.0)
Endoscopic	3 (7.0)

Table 4
Recurrence pattern in total population.

Variables	Nr (%)
All patients	41 pts
Median follow-up (range)	29 (4–60)
Death	2
Secondary recurrence	18 (43.9%)
Site of secondary recurrence	
Intraperitoneal	11 (61.1%)
Exclusively	5 (27.8%)
Mixed with	
➢ Lymphnodes	1 (5.55%)
➢ Intraparenchimal disease (Liver/Spleen)	2 (11.1%)
➢ Lymphnodes and intraparenchimal	1 (5.55%)
➢ Extra-abdominal disease[a]	2 (11.1%)
Extraperitoneal	7 (38.9%)
Parenchimal (liver/spleen)	4 (22.2%)
Extra-abdominal disease[a]	3 (16.7%)

[a] Lung, supra-clavear nodes, crural nodes, mediastin nodules.

Dividing the study population by the year of treatment, 11 (73.3%) major complications occurred in the period between May 2005 and September 2008 and 4 (26.7%) occurred after September 2008 ($p<0.01$).

Finally, no case of intraoperative death or within 30 days after surgery was observed.

Survival analysis

Overall, with a median follow-up of 29 months (range 4–60), 18 recurrences (43.9%) and 2 deaths of disease (4.9%) have been observed. In particular, relapse was exclusively intraperitoneal in only 5 cases (27.8%) and extraperitoneal or mixed in 13 patients (72.2%). Type of recurrence is shown in Table 4. Death of disease occurred 34 and 40 months after HIPEC, respectively.

Survival curves have been calculated in the first 25 patients, having a minimum follow-up of 18 months (median 38; range 18–60) and DFS of 25 months (range 7–67). In this group of patients, the three-year estimated DFS and OS were 44% (95% CI 0.72–0.98) and 92% (95% CI 0.25–0.64) respectively (Fig. 1). Median DFS after CRS + HIPEC was 24 months (range 6–60) and median OS was 38 months (range 18–60).

Discussion

Since its first appearance in 1980 [15], HIPEC associated to CRS has gone on to play an increasing role in the treatment of several malignancies with intraperitoneal spread of disease [16,17].

The rationale for such therapeutic approach is based on the achievement of higher drug concentrations within peritoneal surface with theoretically reduced toxicity due to lower systemic drug levels [18–20]. Moreover, hyperthermia has been shown to play a direct cytotoxic effect on cancer cells as well as a synergistic effect with some cytotoxic agents, including OXA [21,22].

However, despite the obvious biological and pharmacological bases of HIPEC and its application for more than 10 years in ovarian cancer, this treatment still receives heavy criticism due to the related morbidity and mortality rates, precluding it to many patients with peritoneal disease.

Moreover, the lack of randomized trials and the heterogeneity of several phase II studies conducted in patients with primary or recurrent ovarian cancer have been translated into a lack of levels I–II of scientific evidence, hence limiting its general acceptance.

Two recent reviews [6,23] on CRS + HIPEC in heterogeneous ovarian cancer populations have shown three-year overall survival (OS) ranging

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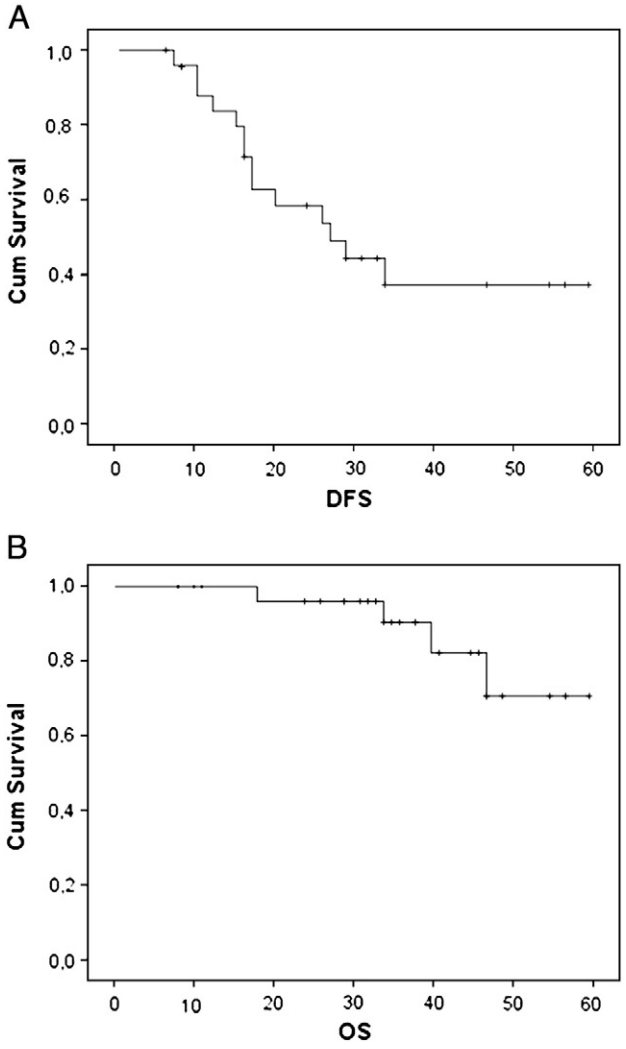

Fig. 1. DFS (A) and OS (B) in platinum-sensitive recurrent EOC patients submitted to CRS + HIPEC.

between 20 and 63%, at the price of morbidity and mortality rates ranging between 12 and 52% and 0.9 and 5.8%, respectively.

To our knowledge, this is the largest study on CRS followed by HIPEC performed in a homogeneous single-institutional series of recurrent platinum-sensitive ovarian cancer patients. Here, we show values of morbidity and mortality rates of about 35% and 0%, respectively, which well compare with 28% and 0% reported in the previous series [8]. Moreover, results are in the range of those reported in other studies and consistent with recent literature data on surgery alone [4]. However, in the light of the very high percentage of optimal cytoreduction obtained in the present population, these results appear even more encouraging, considering that the majority of complications are usually related to the extension of cytoreduction. Furthermore, in this series, comparing the first 25 procedures with the following ones, there is a significant reduction in the rate of complications occurred ($p<0.01$) in favor of the second group, probably related to an increased familiarity of the surgeons with the procedure. Finally, the replication of the procedure (tertiary cytoreduction + HIPEC), although performed in a small number of cases, does not seem to represent any additional risk factor for postoperative complication.

Regarding survival analysis, we report a median DFS and OS of 24 and 38 months respectively, with a 3-year estimated DFS and OS of 44% and 92%. As previously discussed, these data match up favorably with the 3-year OS reported by recent papers on HIPEC and CRS (20–63%) [6,23], probably due to the intrinsic heterogeneity of patients assembled in the reviews. Moreover, they also match up favorably with results from the meta-analysis by Bristow et al., [4] analyzing recurrent platinum-sensitive ovarian cancer patients submitted to secondary cytoreduction and standard chemotherapy (median post-recurrence survival time of 38 vs. 30.3 months). This result can be justified by both the higher percentage of complete cytoreduction in the present series (95.3% vs. 52.2%) and HIPEC. Finally, considering the recent results from the Cochrane database analysis [24], suggesting no evidence from RCTs to inform decisions about secondary cytoreduction plus chemotherapy instead of chemotherapy alone in recurrent ovarian cancer patients, we have also matched up these results to those obtained in an historical comparable group of patients treated with combination of oxaliplatin and docetaxel alone [25]. By using log-rank test, an improved survival in terms of DFS and OS has been observed in patients undergoing CRS + HIPEC vs. chemotherapy alone ($p=0.009$).

A further relevant data has emerged from this study, which is the long duration of DFS in primary recurrent platinum-sensitive ovarian cancer patients undergoing CRS + HIPEC. In fact, based on Markman's criteria [26], any second-line treatment achieving a DFS after recurrence close to or overlapping with the one after primary disease is considered effective. We tried to compare primary and second DFS in the previous study but the short follow-up did not allow us to draw any conclusion. At present, with a median follow-up of 38 months in the same original 25 patients, we can state that primary and second DFS are substantially super-imposable (25 and 24 months, $p=$ n.s.). According to these results, it would be possible to sustain that combined CRS + HIPEC in recurrent platinum-sensitive ovarian cancer patients is able to give these patients the same prognostic chances as at the time of primary treatment.

In conclusion, the present study confirms that the association of CRS + HIPEC is safe, in terms of morbidity and mortality rates, in selected recurrent ovarian cancer patients. Furthermore, it is associated with an improvement in terms of DFS and OS with respect to chemotherapy alone or surgery plus standard chemotherapy. Finally, it seems that platinum-sensitive recurrent ovarian cancer patients benefit most from this treatment with respect to other subset of patients. In order to better discriminate the role of HIPEC in this group of patients, a randomized prospective trial comparing this treatment with CRS alone is now ongoing in our Institution.

Conflict of interest statement

The authors report no conflict of interest.

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