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ORIGINAL ARTICLE

The role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of recurrent advanced ovarian cancer: a prospective study

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Summary

Purpose: *Ovarian cancer is the leading cause of death from gynecological cancer. The current treatment of this type of cancer consists of cytoreductive surgery (CRS) and systemic chemotherapy. The aim of this study was to examine if the hyperthermic intraoperative chemotherapy (HIPEC) is an alternative modality to treat this category of patients along with a second attempt of surgical resection and second or third line systemic chemotherapy.*

Methods: *Forty-eight patients suffering from advanced ovarian cancer (FIGO stages III and IV) who recurred after initial treatment with conservative or debulking surgery and systemic chemotherapy were included in this study. Twenty-four patients (group A) were treated with CRS followed by HIPEC and then systemic chemotherapy. Due to various reasons the remaining 24 patients (group B) were treated with CRS and systemic chemotherapy alone.*

Results: *The median survival for group A was 19.4 months vs. 11.2 months in group B ($p < 0.05$). One-year survival was 85% in group A vs. 35% in group B ($p < 0.05$). The 3-year survival rate was 50% in group A vs. 18%. in group B ($p < 0.01$). The resection status was found to be a significant predictor of overall survival ($p < 0.05$). Patients with peritoneal cancer index (PCI) score < 15 appeared also to have longer survival.*

Conclusion: *The use of HIPEC along with the extent of the disease and the extent of cytoreduction play an important role in the survival of patients with a recurrence in an initially advanced ovarian cancer.*

Key words: cytoreduction, HIPEC, ovarian cancer

Introduction

Ovarian cancer is the most common cause of death from gynecological cancer in the Western world (4.4% among all female malignancies) with over 200,000 new cases and over 100,000 deaths annually worldwide [1,2]. The high mortality rate is due to the tumor spread in extraovarian sites and the lack of satisfactory screening methods [1], so that the 2/3 of patients suffer from metastatic disease at the time of diagnosis.

Current standard treatment of advanced ovarian cancer is CRS in order to remove the primary tumor and debulk any metastatic disease, in combination with systemic chemotherapy with paclitaxel and platinum-based agents (carboplatin or cisplatin) [3,4]. The disease often recurs and the pattern of dissemination or recurrence of ovarian cancer is mostly locoregional, involving only the peritoneum and adjacent intra-abdominal organs. This makes it ideally suited for locoregional therapy [5]. One of the new treatments that have been proposed is HIPEC in combination with CRS.

HIPEC is an attractive modality to treat these patients. This therapy combines major CRS with peritonectomy procedures and the instillation of chemotherapeutic drugs into the peritoneal cavity at 42° C [4]. Therefore, the procedure includes the following modalities: hyperthermia, intraperitoneal (i.p.) chemotherapy and CRS.

The rationale of intra-operative i.p. chemotherapy is based on high drug concentration exposure in the peritoneal cavity controlled by the surgeon who stirs the

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chemotherapeutic agent-containing solution by hand. The i.p. administration permits the high concentration of drugs without the toxic effects of intravenous (i.v.) administration due to the peritoneal plasma barrier. However, despite the advantage of a high concentration of anticancer drugs, the results obtained by HIPEC are still controversial.

The drugs that were used in our study were cisplatin 50 mg/m^2 and doxorubicin 15 mg/m^2 according to the Washinghton Cancer Institute Protocols.

Cisplatin is the most widely used systemic anticancer agent in ovarian cancer. It is also indicated for i.p. application with comparable antiblastic results. Cisplatin has a high AUCpe/AUCpl ratio, a deep tumor penetration ability and a partial response rate of up to 65% in normothermic conditions when applied intraperitoneally [1].

Doxorubicin has a high AUCpe/AUCpl ratio (around 80). A 30% response rate has been reported with i.p. chemoperfusion with this agent. Unfortunately the toxicity of the drug and the occurrence of chemically induced peritonitis sets limitations to the applicable dosage [1].

Hyperthermia alone is tumoricidal and increases the cytotoxicity of many anticancer agents in both human cell lines and animal models. Hyperthermic i.p. chemotherapy increases the permeability of drugs into the tumor cells from 2-3 mm to 5-6 mm compared to conventional i.p. chemotherapy, thus increasing the therapeutic potential. However, despite the sedulous research, the precise underlying molecular mechanisms of these effects are still unknown [2].

Methods

This was a prospective study carried out in one center from January 2003 to April 2009 which included 48 patients with recurrent ovarian cancer classified as stage IIIC-IV according to FIGO staging system.

Inclusion criteria

The inclusion criteria were: 1) age < 80 years; 2) diagnosis of recurrent ovarian cancer confirmed by abdominal and pelvic CT scan and elevated tumor marker CA-125; 3) satisfactory cardiorespiratory and renal status; 4) American Society of Anesthesiologists (ASA) physical status score P1-P2; 5) PCI score < 20 in the previous laparotomy; and 6) written informed consent.

Exclusion criteria

The exclusion criteria were: 1) age > 80 years; 2) PCI >21 in the previous laparotomy; 3) ASA physical status score ≥P3; 4) cardiac or renal failure; 5) patients with metastases outside the peritoneal surfaces (extra-abdominal, parenchymal or bulky retroperitoneal disease) [6].

ASA physical status score includes the following categories: P1: a normal patient; P2: a patient with mild systemic disease; P3: a patient with severe systemic disease; P4: a patient with severe systemic disease that is a constant threat to life; P5: a moribund patient who is not expected to survive without the operation; P6: a declared brain-dead patient whose organs are being removed for donor purposes.

Previous therapeutic manipulations

All of the patients had been treated with surgical debulking and systemic chemotherapy prior to tumor recurrence. Seventy per cent of the patients had completed 6 cycles of first-line systemic chemotherapy and the remaining 30% stopped treatment due to drug toxicity or other reasons.

The patients were divided in 2 groups according to the treatment that was applied.

The diagnosis of recurrence was confirmed by abdominal and pelvic CT scan and elevated tumor markers (CA-125) as mentioned above. The peritoneal cavity was the main site of recurrence and ascites was observed in 50% of the cases.

Group A consisted of 24 patients treated with cytoreductive surgery plus HIPEC and systemic chemotherapy after the 3rd postoperative week.

Group B consisted of 24 patients treated with cytoreductive surgery alone and systemic chemotherapy after the 3rd postoperative week.

After having been informed by medical oncologists, all patients agreed to have a second attempt of cytoreductive surgery and a consensus statement about the HIPEC protocol was signed by the group A patients.

The median time from initial surgery and first line chemotherapy to recurrence was 39 months (range 19-52) for both groups.

All resected tumors were reviewed by the department of Pathology and were characterized as either epithelial cancers or as a mixed carcinoma of ovarian origin.

Tumor load measurements were done using the PCI as described by Sugarbaker et al [7]. The completeness of cytoreduction was scored as proposed by Sugarbaker [7]: CC-0: no residual disease; CC-1: residual nodules < 2.5 mm; CC-2: residual nodules 2.5 mm-2.5 cm; and CC-3 residual nodules > 2.5 cm.

PCI integrates both peritoneal implant size and distribution of peritoneal surface malignancy. The ab-

domen is divided into 13 areas (9 abdominopelvic regions plus upper jejunum, lower jejunum, upper ileum and lower ileum) and –depending on the size of the tumor– each area is rated on a scale of 0-3 (LS-0: no tumor seen; LS-1: tumor up to 0.5 cm; LS-2: tumor up to 5 cm; LS-3: tumor >5 cm or confluence). The summation of the lesion size score in each of the 13 abdominopelvic regions is the PCI. A maximal score is 39 (13 x 3) [7].

Cytoreductive operation

Cytoreduction consisted of peritonectomy procedures according to Sugarbaker's recommendations with a few modifications [8]. Complete resection of tumor nodules, including gastrointestinal (GI) tract resection if necessary, and peritonectomy were performed whenever possible to maximally reduce tumor volume.

Morbidity and mortality were classified according to the criteria outlined in Table 1.

HIPEC technique

The open abdomen (Coliseum technique) was used for group A patients. The abdominal catheters were connected to an extracorporeal perfusion circuit. The i.p. temperature was maintained at 42.5° C for 90 min. The drugs that were used was cisplatin 50 mg/m^2 diluted in 1L of 1.5% dextrose peritoneal dialysis solution and doxorubicin 15 mg/m^2 diluted in 2 L of 1.5% dextrose peritoneal dialysis solution. In 25% of the cases the drugs dosage administered was decreased by 33% due to prior heavy chemotherapy, marginal renal function, age > 65 years, extensive intraoperative trauma of small bowel surfaces or prior radiotherapy. The solution was perfused at a rate of 0.8-1.2 L/min for 90 min. After HIPEC, intestinal reconstruction was performed as indicated.

Statistical analysis

Continuous variables were presented as median (range). All demographic data, laboratory values and pathology data were analyzed with univariate analysis for their ability to significantly predict survival. P-values were calculated using chi-square test. A p-value <0.05 was considered statistically significant. Survival was also analyzed using the method of Kaplan-Meier and the curves were compared using the Cox-Mantel log-rank test.

Table 1. Criteria for morbidity and mortality grading

Grade	*Complications*
I	No complications
II	Minor complications
III	Major complications requiring reoperations or ICU admission
IV	In-hospital mortality

Results

The clinical outcomes of both groups in relation to the PCI score, the completeness of cytoreduction and overall survival are demonstrated in Tables 2 and 3.

The median follow-up time was 24 months (range 12-60). The mean patient age was 56.6 years (range 24-74) for group A, and 59.5 years (range 39-78) for group B.

The median survival for group A was 19.4 months vs. 11.2 months for group B (p <0.05). The one- and 3-year survival rates were 85 and 50% for group A vs. 35 and 18% for group B, respectively (p <0.05).

The median PCI score was 21.2 for group A vs. 19.8 for group B (p nonsignificant). The PCI score could not predict the survival rate in our study. However, there was a statistically significant difference for better survival in patients with PCI score <16 vs. >16 (p <0.03) in the same group of patients (Figures 1, 2). This differ-

Table 2. Patient characteristics in Group A

	Age (years)	*Months from initial treatment to recurrence*	*PCI*	*CCS*	*Survival after second line treatment (months)*
1	68	19	35	CC2	5
2	74	28	15	CC1	12
3	72	40	31	CC2	6
4	70	52	12	CC1	16*
5	36	40	27	CC1	12
6	59	28	18	CC0	18
7	56	50	6	CC0	28*
8	24	36	10	CC0	30*
9	70	29	26	CC0	18*
10	68	34	32	CC0	38
11	72	22	16	CC0	26*
12	36	31	20	CC0	28*
13	43	26	26	CC0	19*
14	58	44	31	CC1	24
15	67	52	10	CC0	22*
16	33	24	14	CC1	22*
17	57	18	18	CC1	14
18	64	27	24	CC2	12
19	71	31	15	CC0	26*
20	48	10	22	CC1	8
21	47	17	21	CC0	30*
22	42	12	30	CC2	10
23	48	18	24	CC1	22*
24	54	16	26	CC1	21*

*Still alive, PCI: peritoneal cancer index, CCS: completeness of cytoreduction score

Table 3. Patient characteristics in Group B

	Age (years)	*Months from initial treatment to recurrence*	*PCI*	*CCS*	*Survival after second line treatment (months)*
1	48	27	30	CC1	8
2	46	19	18	CC1	8
3	72	34	30	CC2	4
4	71	38	16	CC2	7
5	78	27	25	CC2	5
6	67	27	18	CC1	12
7	48	44	8	CC0	14
8	42	46	16	CC0	16*
9	39	52	20	CC1	8
10	47	36	36	CC2	6
11	70	29	18	CC1	14
12	43	34	6	CC0	12*
13	41	27	22	CC2	4
14	59	31	19	CC1	9*
15	76	21	27	CC2	9
16	63	26	16	CC1	14*
17	52	22	14	CC1	14*
18	67	18	8	CC0	16
19	51	16	24	CC2	14
20	69	22	26	CC2	10
21	71	27	14	CC0	6*
22	76	21	12	CC0	18
23	64	12	27	CC1	21*
24	67	17	26	CC1	20*

For abbreviations see footnote of Table 2

ence existed during the first 12 months after which the survival curves of the two groups were superimposed.

In group A complete cytoreduction (CC0 + CC1) was achieved in 20/24 patients (83%) vs. 16/24 (66%) patients in group B ($p < 0.01$). In group A, patients with complete cytoreduction (CC0+CC1) had a median survival of 21.7 vs. 8.2 months of patients with CC2 ($p<0.05$). Therefore, the resection status was a significant predictor of overall survival.

The same results were achieved in group B between the patients with complete (CC0+CC1) vs. incomplete cytoreduction (CC2) (median survival 13.1 vs. 7.3 months, respectively; $p < 0.05$).

Regarding morbidity, 40% of the group A patients had a grade II or III adverse event, while in group B only 20% of the patients had a complication of that grade ($p<0.04$). The morbidity grades are listed in Table 1. The postoperative complications were divided into surgical and medical and are listed in Table 4. The most frequent surgical complications in group A were wound

Table 4. Postoperative complications observed in Group A and Group B

Complication	*Group A*	*Group B*
Surgical		
Wound infection	4	3
Pleural effusion requiring drainage	4	1
Intestinal fistula	1	3
Abdominal abscess	1	2
Urinary fistula	1	0
Prolonged ileus	6	3
Pulmonary embolism	2	0
MOF (death)	0	0
Medical		
Grade 2 hematological toxicity	3	1
Acute renal failure	1	2
Arrhythmias	7	3
Cutaneous rash	3	1

MOF: multiple organ failure

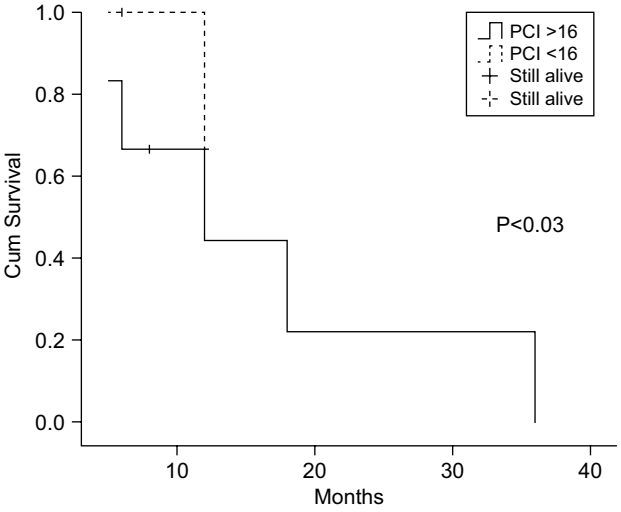

Figure 1. Survival of patients with peritoneal cancer index score below and above 16 in Group A.

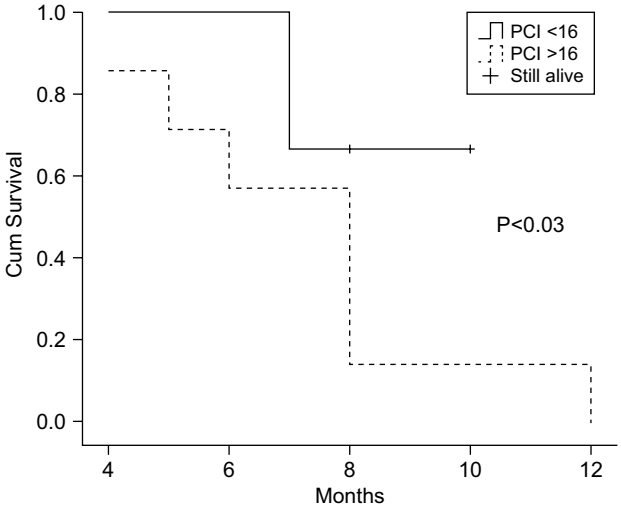

Figure 2. Survival of patients with peritoneal cancer index score below and above 16 in Group B.

infection (4 cases), pleural effusion requiring drainage (4 cases) and prolonged ileus (6 cases). Regarding the most common medical complications in group A, there were 7 cases of cardiac arrhythmias, 3 cases of grade 2 hematological toxicity and 3 cases of cutaneous rash.

Discussion

The peritoneal cavity is the principal site of metastatic disease in ovarian cancer [9-11]. The intensity of i.v. chemotherapy is limited mainly by its myelotoxicity. However, several active drugs can be administered directly into the peritoneal cavity. Intraperitoneal administration of anticancer drugs has many pharmacokinetic advantages and provides high response rates because the "peritoneal plasma barrier" ensures sustained exposure to high concentrations of chemotherapeutic drugs, while systemic organs, such as kidneys, heart and bone marrow, are relatively spared [3].

The conventional clinical approach for advanced ovarian cancer is based on cytoreduction or debulking procedures followed by systemic chemotherapy. The critical role of optimal CRS in the treatment of ovarian cancer was supported by Bristow et al. in a meta-analysis of 6885 patients which indicated that on an institutional basis for each 10% increase in the percentage of patients undergoing maximal CRS there was a 5.5% increase in median survival duration [12]. The reason CRS is thought to be effective when combined with chemotherapy is that it removes bulky disease containing poorly oxygenated, non-proliferating cells which are either resistant or potentially resistant to chemotherapy and leaves small-volume tumors with a higher proportion of proliferating cells [2]. Unfortunately, most patients relapse within 5 years and the disease-free survival does not generally exceed 18 months [13].

There is a group of patients with advanced ovarian tumors who present with metastatic disease limited in the peritoneal cavity. These patients have a life expectancy of 6-12 months. CRS followed by systemic chemotherapy can not control sufficiently the disease in this group of patients as demonstrated in our study, as well as in previous reports [14-16].

I.p. chemotherapy appears to be a promising method to reduce peritoneal recurrence of the disease and to improve survival. Postoperative i.p. chemotherapy in combination with systemic chemotherapy as an adjuvant treatment has been used with controversial results [17,18]. Armstrong and GOG (Gynecologic Oncology Group) showed that CRS, chemotherapy using i.v. paclitaxel plus i.p. administration of cisplatin and paclitaxel significantly improved median and overall survival in patients with FIGO III disease [9]. The main criticism of this method was focused in the inadequate agent distribution due to adhesion formation and because of the tumor cell entrapment phenomenon [7,8].

There is an increasing number of published studies concerning the treatment of the various stages of ovarian cancer with HIPEC. Our study refers specifically to patients with recurrent ovarian disease comparing two groups of patients with similar clinical, morphological and histological characteristics who had been treated with CRS and systemic chemotherapy with/without HIPEC.

The first paper to report the use of HIPEC in recurrent ovarian cancer was that of Van der Vange et al. in 2000. Helm et al. in a recent review of the related literature found that the overall median survival ranged from 28.1 [19] to 57 months [2]. There are 4 recent reports with relatively big samples concerning patients with recurrent/persistent ovarian cancer treated with HIPEC, that are analyzed below.

Zanon et al. in a sample of 32 patients with recurrent ovarian cancer treated with HIPEC and CRS achieved a 39.0-month overall median survival rate for CCR-0/1 [20].

Raspagliesi et al. applied HIPEC plus CRS in 40 women with recurrent/persistent ovarian cancer and achieved a 41.4-month overall median survival [16].

Rufian et al. reported 28.1-month median overall survival in 33 patients. Three-year overall survival was 51%. Interestingly, there was a 75% rate in 2- and 5-year overall survival for patients with recurrent disease aged <55 years [19].

The largest study so far was that of Cotte et al. (81 patients) who reported a disease-free survival of 19.2 months and overall survival of 28.4 months in patients with recurrent disease treated with HIPEC and CRS [3]. Our study showed an overall survival of 19.4 months in a relatively big sample (24 patients) compared to 11.2 months in the group that did not receive HIPEC. This indicates a significant correlation ($p < 0.05$) between the application of the HIPEC protocol and median survival, in concordance with the findings from the most recent trials.

One more recent study by Ceelen et al. reported an overall survival of 37 months and a median progression-free survival of 13 months in 42 patients with recurrent ovarian cancer treated with CRS and HIPEC. Tumor grade and completeness of cytoreduction were found to be independent predictors of overall survival [21].

On the other hand there are several reports concerning patients with recurrent ovarian cancer treated with secondary CRS without HIPEC. A recent review indicates an overall median survival between 19.0 to 34.4 months in most studies [3].

Analyzing the factors that could predict survival in our patient population, we found that HIPEC, the extent of the disease (indicated by the PCI index) and the extent of cytoreduction appeared to play a significant role in the treatment of patients with ovarian cancer, prolonging their survival. Reported prognostic factors for survival in recurrent disease mentioned in the relative literature are the interval from diagnosis to HIPEC, PCI, extent of residual disease prior to HIPEC, patient age, WHO performance status and the presence of lymph node metastasis [2]. However, the principal factor appears to be the completeness of cytoreduction [3].

A recent review of perioperative morbidity rates in patients with recurrent ovarian cancer treated with CRS and HIPEC incorporated data from previous studies. In a total of 236 cases, the most frequent serious medical complications were grade III or IV hematologic toxicity (4.7%) and renal impairment due to the chemotherapeutic agents (3.4%). Concerning surgical complications wound infection occurred in 4.7% of the cases, anastomotic leaks in 1.7% and gastrointestinal perforations in 2.5% [2]. In our study there was also a high rate of hematologic toxicity (3/25) and wound infection (4/25), possibly attributable to the toxicity of chemotherapy [2].

As indicated by our study and other recent reviews, HIPEC appears to be a promising modality in combination with CRS and systemic chemotherapy in the treatment of recurrent ovarian cancer. The contribution is even more important in patients with disease limited in the peritoneal cavity, where optimal cytoreduction is achieved. In order to confirm these apparently encouraging results a prospective multicentric international study is needed. In this way the effectiveness of CRS combined with HIPEC and systemic chemotherapy can be compared to CRS and systemic chemotherapy alone. The primary endpoint is to maximize the benefit of the patients.

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