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EJSO
the Journal of Cancer Surgery
ELSEVIER
EJSO xx (2006) 1–5
www.ejso.com

Cytoreduction combined with intraperitoneal hyperthermic perfusion chemotherapy in advanced/recurrent ovarian cancer patients: The experience of National Cancer Institute of Milan

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Accepted 2 March 2006

Abstract

Aims: We report the effects of cytoreductive surgery (CRS) and intraperitoneal hyperthermic perfusion (IPHP) in the treatment of advanced/recurrent epithelial ovarian cancer (EOC) on survival, morbidity and mortality.
Patients: Forty EOC patients were studied. Median age was 52.5 years (range: 30–68) and median follow-up 26.1 months (range: 0.3–117.6). Most patients presented advanced disease (stage III/IV). Previous systemic chemotherapy included cisplatin-based, taxol-based or taxol/platinum containing regimens.
Results: After the CRS, 33 patients presented no macroscopic residual disease. Five-year overall survival was 15%; the mean overall and progression-free survivals were 41.4 and 23.9 months, respectively. The morbidity, toxicity and mortality rates were 5%, 15% and 0%, respectively.
Conclusion: Our results suggest that CRS + IPHP merits further evaluation by a formal prospective trial.

Keywords: Advanced ovarian cancer; Locoregional therapy

Introduction

Primary surgery followed by systemic platinum-based chemotherapy is the cornerstone in the management of ovarian cancer patients. However, many patients present persistent disease after the first-line chemotherapy and/or relapse after complete clinical response.[1] There is no standard second-line treatment. Several drugs can be used with response rates varying from 14% to 34%.[2] Progressive disease almost always develops and survival is poor. The combination of secondary cytoreductive surgery and intraperitoneal hyperthermic perfusion (locoregional therapy; LRT) represents a feasible and potential option for this subset of patients. In this paper we report the experience of the National Cancer Institute (NCI) of Milan in treating patients with advanced/recurrent ovarian cancer with cytoreductive surgery (CRS) and intraperitoneal hyperthermic perfusion (IPHP), with special emphasis on survival and morbidity and mortality.

Patients and methods

Patients

The study was conducted on 40 patients with epithelial ovarian cancer (EOC) who were treated with CRS and IPHP at the NCI of Milan. With respect to our previously

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doi:10.1016/j.ejso.2006.03.011

published series,[3] we restricted the study group to cases treated in our Institute.

Median patient age was 52.5 years (range: 30–68) and median follow-up 26.1 months (range: 0.3–117.6). Disease staging was carried out according to the FIGO criteria, with 34 as stage III, and 3 as stage IV. In 3 patients this information was not available as they were inadequately staged elsewhere before being referred to our Institute. Serous tumours were the most frequent type and were observed in 35 patients; 3 patients had mucinous tumours and 1 patient had an endometrioid lesion.

Thirteen patients presented partial response to first-line chemotherapy and were treated in a second-look setting. Twenty-seven patients had advanced relapsing disease and had received a median of two lines (range: 1–5) of systemic chemotherapy, which consisted of cisplatin-based, taxol-based or taxol/platinum-containing regimens.

Patients were classified as platinum sensitive in the case of a recurrence at least 6 months after the end of first-line therapy, after a documented initial response to platinum-based treatment. Patients were classified as platinum resistant in the case of an initial partial response to platinum-based treatment or in the case of a recurrence within 6 months following the completion of treatment after a complete documented initial response to platinum-based treatment.

Cytoreductive surgery

Description of the surgical technique can be found elsewhere in this issue, and is based on the Sugarbaker principles of peritonectomy with a few modifications.[4] Peritoneal carcinomatosis was classified as follows: dissemination into pelvic peritoneum; slight dissemination into remote peritoneum; and marked dissemination into remote peritoneum.[5] Cytoreduction was classified into three levels according to the number of procedures performed: level I, 1 or 2 procedures; level II, 3 or 4 procedures; level III, 5 or more procedures.

IPHP technique

The closed abdomen technique was used for all our patients. The abdominal catheters are connected to an extracorporeal perfusion circuit (Performer LRT®, RAND, Medolla (MO), Italy). The intraperitoneal temperature is maintained at 42.5 °C during the perfusion. The following drugs were used: cisplatin (CDDP; 25 mg/m^2/l) and mitomycin C (MMC; 3.3 mg/m^2/l), and cisplatin (CDDP; 43 mg/l of perfusate) and doxorubicin (DX; 15.25 mg/l of perfusate). The perfusate is then instilled into the peritoneal cavity at a mean flow of 600 ml/min.

Immediate postoperative surveillance and follow-up

Analysis of chemotherapy-related toxicity was performed according to the World Health Organization criteria. Morbidity and mortality was classified according to the criteria outlined in Table 1. The patients were visited every 6 months up to the 5th year. Survival was calculated from the date of surgery to date of death or time of last follow-up, whichever occurred first. Estimated survival curve distribution was calculated by the Kaplan–Meier method. The log-rank test was used to assess the significance of survival distributions.

Results

Clinical outcome

Eighteen patients underwent a level I procedure, 19 patients underwent a level II procedure and 3 patients a level III procedure. The mean duration of CRS + IPHP procedures was 410 min (range: 240–660). The mean number of blood transfusions during the procedure was 1.6 units (range: 1–5). After the CRS 33 patients presented no macroscopic residual disease (RD) = 0; and 7 patients, minimal RD > 0.5 mm and <2.5 mm. The mean length of stay was 21 days (range: 8–59).

With regard to recurrences, 4 patients presented distant metastases (liver $n = 2$, lung $n = 1$, brain $n = 1$), 12 patients showed locoregional relapse, and 5 patients had both locoregional and distant metastases (distant lymph node $n = 1$, liver $n = 3$, lung $n = 1$).

Five-year overall survival (OS) was 15% and the mean overall and progression free survivals were 41.4 months (CI 95%: 28.3–54.6) (Fig. 1) and 23.9 months (CI 95%: 13.9–33.8), respectively. Mean overall and progression free survivals were 31.5 months (95% CI: 21.8–41.2) and 10.5 months (95% CI: 8.4–12.6), respectively. Factors influencing the outcome were completeness of cytoreduction, WHO performance status, and carcinomatosis extent. Other tested variables such as age, number of previous systemic chemotherapy lines, procedure extension, histological subtype, grading and sensibility to platinum did not present a prognostic significance.

Toxicity, morbidity, and mortality

In the immediate postoperative period, one patient presented an ileo-colic anastomotic fistula and an additional

Table 1
Criteria for morbidity and mortality grading[28]

Grade	Complications
I	No complications
II	Minor complications
III	Major complications (requiring re-operation or ICU admission or interventional radiology)
IV	In-hospital mortality

We considered only those unfavourable events occurring within the 28th day after the procedure. ICU, intensive care unit.

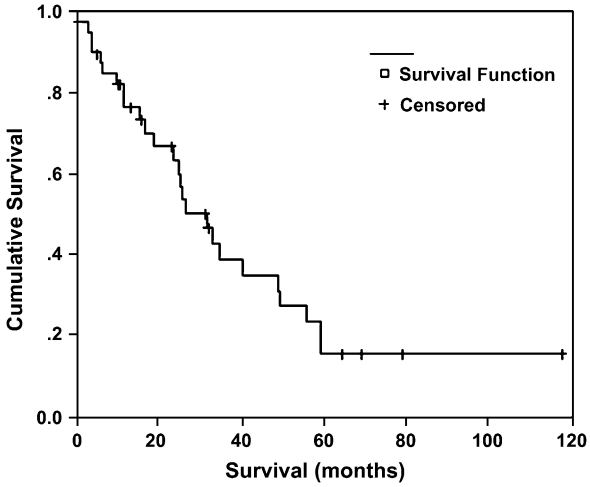

Figure 1. Overall survival in ovarian cancer patients treated with CRS + IPHP.

patient presented a lymphocele together with bowel obstruction secondary to adhesions. Both cases were treated conservatively. The resultant treatment-related morbidity was 5%. Six out of 40 (15%) patients presented acute toxicity: 3 cases of G2 haematological toxicity, 2 cases of renal toxicity grade II and 1 case of G2 gastrointestinal toxicity. There were no treatment-related deaths.

Discussion

The conventional clinical approach for advanced EOC is based on CRS followed by systemic chemotherapy. Clinical studies have shown that cisplatin and/or taxol-based first-line chemotherapy yields response rates of 70–80%, with a considerable proportion of complete responses.[1] However, about half of patients with negative second-look relapse within 5 years and disease-free survival does not generally exceed 18 months.[6,7] No standard treatment strategy for patients with relapsing or persistent EOC after completion of upfront chemotherapy has been defined. When previous effective drug combinations fail, there is virtually no chance of inducing a significant response with second-line treatment.

The real effectiveness of CRS in the treatment of EOC has not been clearly defined. When performed at the completion of the first line chemotherapy, the majority of studies, which are not randomized,[8–16] demonstrate some survival advantage for patients who can be cytoreduced to microscopic or small macroscopic RD. When the second-look operation is performed and residual tumour is detected, it seems advisable to remove all macroscopic disease if technically feasible. The level of evidence supporting the use of secondary CRS in relapsing EOC cases is also supported by no randomized data. Recently a retrospective review of the English literature was done looking at studies addressing the role of secondary CRS in recurrent EOC. Optimal cytoreduction was achievable in 38–87% of the study populations reviewed with acceptable perioperative complications and mortality. All the studies suggest that patients left with no gross RD after secondary CRS seem to benefit from prolonged survival in the range of 44–60 months.

During the last 10 years, several new drugs have been shown to be active in second line therapy. Paclitaxel, pegylated liposomal doxorubicin, topotecan, docetaxel, gemcitabine, oxaliplatin, vinorelbine, and ET-743 have been added to more ‘‘classical’’ drugs like carboplatin, cisplatin, epirubicin, ifosfamide, altretamine, or oral etoposide. However, no randomized trials have shown any drug to be the best second-line alternative. The available data show overall response rates ranging from 3.3% to 16% with median OS of 35–41 weeks in the subset of patients with platinum refractory EOC.[17,18]

CRS and IPHP was initially described to treat peritoneal carcinomatosis of various sites of origin.[19] The rationale pertaining to the synergistic effect between chemotherapies and heat was outlined elsewhere as well as the pharmacokinetics advantage of locoregional instillation of antiblastic drugs after macroscopic removal of tumour by an aggressive surgical procedure.[20] The LRT has yielded very encouraging results according to many phase II studies in selected patients affected by pseudomyxoma peritonei, peritoneal mesothelioma and carcinomatosis from colorectal cancer. In addition, a clear survival advantage was demonstrated in the only phase III randomized trial addressing colorectal cancer carcinomatosis. These favourable results have prompted many centres worldwide to initiate peritoneal surface malignancy programmes for various malignancies including carcinomatosis secondary to EOC (Table 2).[21–26]

In 2001 Hager et al. conducted a prospective clinical trial on 36 patients with ovarian cancer treated by CRS + IPHP. Median OS from the first IPHP chemotherapy treatment was 19 ± 4 months.[21] The 5-year OS of all patients from the start of the first IPHP was $16 \pm 7\%$. The adverse effects were mild especially compared to systemic chemotherapy.

Piso et al. published a series of 19 patients; of those, 11 patients had recurrent and 8 primary EOC. After CRS patients received IPHP with either cisplatin or mitoxantrone.[23] A 5-year OS of 15% was reported despite a total of 9 patients with concomitant liver metastases.

Ryu et al. published the biggest retrospective series on 117 patients with ovarian cancer patients (mainly recurrent disease) treated by CRS with or without IPHP consisting of carboplatin and interferon-α.[24] In the subgroup of stage III patients, the median survival was 60.9 months for the 35 patients receiving both CRS and IPHP compared with only 22.3 months for patients in the CRS only group ($p = .0015$). Five-year OS was 53.8% for the former and 33.3% for the latter. The use of IPHP was shown to be a positive independent prognostic factor along with RD < 1 cm.

Table 2
Phase II studies on cytoreductive surgery and intraperitoneal hyperthermic perfusion in ovarian cancer

Ref.	*N*	Disease setting	Study design	Drug schedule	OS (%)	Median OS (months)	Median PFS (months)
Present series	40	Recurrence or partially responsive to 1st line CHT	Retrospective not controlled	CDDP (25 mg/m^2/l) + MMC (3.3 mg/m^2/l) or CDDP (43.0 mg/l) + Dx (15.25 mg/l)	5 yr = 15%	41.4 (mean) 31.5; 95% CI: 21.8–41.2	23.9 (mean) 10.5; 95% CI: 8.4–12.6
[21]	36	Recurrence that have received at least 2 lines of CHT	Retrospective not controlled	CDDP 100 mg/CBDCA 450 mg	5 yr = 16 ± 7%	19 ± 4	–
[22]	20	Recurrent	Prospective not controlled, phase II	CDDP 50 mg/l		29 (mean)	
[23]	19	Primary/recurrent	Prospective not controlled	CDDP 75 mg or Mitoxantrone 15 mg/m^2	5 yr = 15%	33 ± 6	18
[24]	57	Mainly recurrent disease	Retrospective controlled	CBDCA 350 mg/m^2 + INFα 5000000 UI/m^2	5 yr = 63.4%	–	–
[25]	30	Completion of at least a 1st line CDDP-based CHT	Prospective not controlled	CDDP 100–150 mg/m^2	2 yr = 60%	28.1; 95% CI: 21.4–34.7	–
[26]	29	Consolidation therapy	Prospective controlled not randomized	CDDP 100 mg/m^2	–	64.4 (27.7 SD, 15–108)	–

Ref., reference; *N*, number of patients; CHT, systemic chemotherapy; CDDP, cisplatin; MMC, mitomycin-C; CBDCA, carboplatin; SD, standard deviation; INFα, interferon-α; OS, overall survival; PFS, progression-free survival.

The results of the present study did not differ substantially from those of our previous experience after a longer follow-up period and recruitment of more patients.[3] Moreover, they seem to be in line with the published data both in terms of survival and morbidity and mortality. However, it is difficult to ascertain to which extent this survival advantage, with respect the other systemic treatment options, reported by uncontrolled clinical studies, resulted from individual physicians selection bias. In addition, most of the studies, including the present series, were retrospective and some authors have reported on heterogeneous study populations with the inclusion of histological subtypes other than the epithelial one, different stage distribution, use of different IPHP techniques and IPHP drug schedules.

In order to confirm these apparently encouraging results, the SITILO (Italian Society of Integrated Locoregional Therapy) is conducting a prospective multicentric randomized study to test the effectiveness of secondary CRS and IPHP in patients with cisplatin-resistant advanced EOC, as second-line therapy. Patients will be randomly allocated to secondary CRS + IPHP + second-line chemotherapy or only second-line chemotherapy. The primary endpoint is overall and progression-free survival.[27]

Acknowledgements

This work was partially supported by AIRC and CNR-miur.

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