The efficacy of combination chemotherapy including intraperitoneal cisplatinum and mitoxantrone with intravenous ifosfamide in patients with FIGO stage I C ovarian carcinoma

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Summary

Objective: Patients with stage I ovarian cancer show a high incidence of recurrent disease ranging from 30% to 50%, which may be associated with a shortened survival. Therefore, a subset of early-stage patients with poor prognostic factors who are most likely to present with recurrent disease in the next few years may benefit from adjuvant treatment.

Patients and method: In this pilot study, we evaluated the efficacy of combination chemotherapy including intraperitoneal mitoxantrone (12 mg/m^2) and cisplatinum (75 mg/m^2) on day 1, in addition to intravenous ifosfamide (4000 mg/m^2) given on day 15 with mesna protection. Thirteen patients with a median age of 44 years were included in the study.

Results: Following a median of 5 cycles of chemotherapy, 12 patients had a complete response (92.3%), while one patient had progressive disease. At the latest follow-up, ten patients were alive with no evidence of disease, two patients had died and one patient was lost to follow-up. Overall and progression-free survival rates at eight years were 82.5±11.3% and 83.9±10.5%, respectively. Excluding grade 3 and 4 abdominal pain in three (23.1%) patients, there were no serious complications associated with this combination. Dose delay not longer than one week was observed in 3 cycles (5.6%). Port-related complications observed in three patients were colonic perforation, hematoma and leakage.

Conclusion: This combination has moderate efficacy and tolerable toxicity. However, further studies are required to make definite conclusions regarding the efficacy of this combination in the adjuvant setting in patients with high-risk early stage ovarian carcinoma.

Key words: Ovarian cancer; Early stage; Intraperitoneal; Chemotherapy.

Introduction

Approximately 33% of patients with ovarian cancer present with localized disease confined to the pelvis. Survival rates of patients with stage 1 disease are reported to range between 70% to 100% [1]. This high variance in survival may be related to the unexpectedly increased relapse rate, reaching almost 30% to 50% [2]. Therefore, it has become mandatory to define this subset of patients with poor prognostic factors who are most likely to benefit from adjuvant treatment. Some large scale trials have refuted the use of postoperative cytotoxic therapy over observation alone in patients with favorable prognostic factors, not only due to a lack of survival advantage, but also due to increased toxicity [3]. However, patients with FIGO IA, IB stage, poorly differentiated tumors or clear cell histology and those with more extensive disease (FIGO IC-IIC) with microscopic residual disease have been shown to require some type of adjuvant treatment [3]. Earlier adjuvant studies have investigated the role of radiotherapy, alkylating agents like melphalan or intraperitoneal P^{32} treatment strategies without a definite benefit [4-6]. Besides problems associated with the intraperitoneal administration of P^{32}, favorable results attained by platinum analogues in advanced and recurrent ovarian cancer, have led to studies evaluating the significant role of cytotoxic chemotherapy in this subset of patients with high risk of relapse [7]. Nevertheless limited data exists on the role of intraperitoneal chemotherapy combined with systemic agents in patients with early stage ovarian carcinoma.

Mitoxantrone has been shown to demonstrate strong activity against ovarian cancer [8]. Phase I studies have revealed approximately 1,000-fold increased peritoneal exposure compared to circulation with intraperitoneal (IP) administration [9]. In a phase II study, Markmann *et al.* [10] reported a 33% response rate with IP mitoxantrone and observed that chemical peritonitis rather than systemic toxicity was the dose limiting toxicity. Intraperitoneal therapy with cisplatinum yielded more encouraging response rates, reaching 70% in patients with minimal residual disease [11]. Combinations including these agents have been used successfully in a phase I trial [12]. Intraperitoneal cisplatinum and mitoxantrone combination has been previously evaluated by our group in two phase II studies involving patients with advanced ovarian cancer as an adjunct to primary surgery and as salvage therapy in relapsed patients [13, 14]. In the adjuvant setting similar to the present study, in which intravenous ifosfamide was employed in addition to intraperitoneal cisplatinum and mitoxantrone, we achieved 45% pathologic complete response rates with tolerable toxicity [14]. Significant results have also been reported with

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systemic ifosfamide in previous studies with response rates ranging between 33% and 79% [15, 16].

The aim of this study was to evaluate the efficacy and toxicity profile of combination chemotherapy including intraperitoneal cisplatinum and mitoxantrone and intravenous ifosphamide in patients with FIGO IC ovarian carcinoma.

Patients and Method

Thirteen chemotherapy-naive patients younger than 70 years, with histologically documented epithelial ovarian cancer were included in this phase II study. Initial surgical staging included a thorough exploration of the whole abdominal cavity, with peritoneal washings and swabs from subdiaphragmatic areas and paracolic gutters. Besides lymphadenectomy, numerous biopsies from the mesentery and omentum and from any suspected nodular lesion or mass were obtained during the operation. All patients had been shown to have disease limited to one or both ovaries, with either capsular involvement or positive peritoneal washing cytology (stage Ic disease) with microscopic residual disease. Patients with inadequate renal, hepatic or myeloid function were excluded from the study.

Intraperitoneal chemotherapy was administered through a temporary peritoneal catheter in two patients and the remaining were treated via an indwelling port system catheter placed at the time of the cytoreductive surgery before treatment. All patients received cisplatinum 75 mg/m^2 and mitoxantrone 12 mg/m^2 administered intraperitoneally on day 1 and ifosfamide 4000 mg/m^2 intravenously with mesna protection on day 15. Cycles were repeated with four weekly intervals. Patients were required to have adequate white blood cell (3 x10^9/L), neutrophil (1.5 x10^9/L) and platelet (>100 x10^9/L) counts before each cycle. Doses on subsequent cycles were modified for a delay of more than seven days for neutropenia and thrombocytopenia. Doses were permanently reduced by 25% in case of febrile neutropenia and grade 4 hematologic toxicity, regardless of the nadir of neutrophil counts. If the serum creatinine level was 1.5 mg/dl or higher, treatment was withheld and adequate hydration was applied until serum creatinine levels were restored. In case of persistent nephrotoxicity after two weeks delay, cisplatinum dose was reduced by 25% if the calculated GFR was between 50-75 mlt/min and discontinued permanently if GFR was 50 mlt/min or lower. Patients with any unacceptable toxicity relating to intraperitoneal administration were excluded from the study. All patients underwent clinical and radiologic reassessment after 3 cycles and following the completion of 6 cycles of chemotherapy by serum CA 125 levels and abdominopelvic CT scans obtained at 10 mm. intervals. In case of any clinical suspicion regarding disease status, a second-look laparotomy was performed. Patients with progressive disease were administered second-line combination chemotherapy, while those without any clinical evidence of progression as assessed by CA 125 levels and radiologic findings were followed-up regularly with three monthly intervals for the first two years, six monthly intervals for the next three years and annually thereafter.

Statistical analyses were performed by the statistical programming package SPSS for Windows Release 7.5.1. Data on survival were estimated by the Kaplan-Meier method.

Results

The median age of the 13 patients enrolled in this study was 44 years (24-68). Patient characteristics are listed in Table 1.

Table 1. — *Patient characteristics.*

		n	%
Menopausal status	Pre-	11	84.6
	Peri-	0	
	Post-	2	15.4
Menarche	>13 years	13	100
Parity	Nulliparous	1	7.7
	Multiparous	10	76.9
	Unknown	2	15.4
Pathology	Serous	5	38.5
	Mucinous	3	23.1
	Endometrioid	4	30.8
	Clear cell	1	7.7
Grade	I	5	38.5
	II	3	23.1
	Unassessed	5	38.5

Serous papillary adenocarcinoma was the most frequent histologic subtype (38.5%). Other subtypes included endometrioid (30.8%), mucinous (23.1%), and clear cell (7.7%) histologies. All patients had microscopic residual disease left after primary cytoreductive surgery. Mean and median serum CA 125 levels before chemotherapy were 99.5 and 40.6 mU/ml, respectively.

Each patient received a median of 5 cycles of cytotoxic therapy. Following the completion of chemotherapy, 12 patients (92.3%) had a continuous complete response, while one patient (7.7%) had progressive disease. Mean and median serum CA 125 levels after the completion of chemotherapy were determined as 11.3 and 10.1 mU/ml, respectively. During follow-up after a complete response, one patient had a local relapse, while one had a rising CA 125 level in the absence of a documented tumoral mass. The median duration of response was estimated as 18.5 months for the whole group (95% confidence interval: 12.2; 24.8). At the final evaluation, ten patients (76.9%) were alive with no evidence of disease, two patients had died of progressive disease and one patient was lost to follow-up. Overall and progression-free survival rates at eight years were 82.5±11.3% and 83.9±10.5%, respectively.

Thirteen patients received 54 courses of chemotherapy. There were neither treatment-related deaths nor serious hematologic or non-hematologic toxicity encountered throughout the treatment period. There were no dose reductions required. Dose delay not longer than one week was observed in 3 cycles (5.6%). The reason for the delay was hematologic toxicity in one patient and noncompliance in two others. Seven patients (53.8%) completed the planned schedule. Three patients (23.1%) refused chemotherapy while treatment was discontinued in two patients due to complications related to intraperitoneal chemotherapy. In one patient treatment was stopped due to unresponsiveness to treatment. Intraperitoneal chemotherapy caused grade 3 and 4 abdominal pain in three (23.1%) patients. Colonic perforation was observed in one patient who received chemotherapy with a temporary catheter while one patient suffered from hematoma and another had leakage around the port catheter. Two patients had problems with administration due to peritoneal adhesions and kinking of the catheter.

Discussion

The high rate of recurrence warrants the use of adjuvant chemotherapy in patients with high-risk early stage ovarian cancer. Besides the presence of residual tumors after primary cytoreductive surgery, higher grade or clear cell histology are predictive factors for a greater likelihood of relapse [17]. A randomized trial by the GOG, in which early stage ovarian cancer patients with poor prognostic factors were randomized to intermittant oral melphalan, pelvic radiotherapy or to observation alone, was the earliest study to demonstrate a benefit in terms of decreased recurrence [4]. In that study, patients on the melphalan arm had a significantly lower frequency of relapse (6%) compared to the others (30% and 17%, respectively). However, groups were not equally matched to make a definite conclusion. The role of adjuvant therapy was confirmed in two subsequent trials by the same group. In the first trial early stage (FIGO IA, IB) patients with well- or moderately well-differentiated tumors were given melphalan or no treatment. Overall survival (OS) (98% vs 94%) and disease-free survival (DFS) rates (98% vs 91%) at six years were not significantly different between the two arms. Based on this data, the investigators concluded that patients with early stage disease and favorable histology may not require additional treatment. In the second trial, the efficacy of melphalan or intraperitoneal P^{32} was compared in patients with poorly differentiated stage 1 or stage II disease with microscopic residual tumor. Progression-free survival (80% for both groups) and overall survival (81% vs 78%) at five years were similar, confirming the relevant role of adjuvant treatment except for patients with FIGO IA disease, well-differentiated tumors [3]. Therefore, intraperitoneal P^{32} treatment, requiring a single administration and causing no late hematologic toxicity, was accepted as the safest adjuvant treatment method for this group of patients [2]. A subsequent study including a similar group of patients as the latter study has demonstrated equivalent activity and lower toxicity with adjuvant intravenous cisplatinum compared to intraperitoneal P^{32}. The 5-year crude OS and DFS rates were estimated as 81% vs 83% and 75% vs 81%, respectively. Due to the increased frequency of late bowel complications, the authors favored the cisplatinum arm as the standard approach for subsequent studies [7].

Intraperitoneal chemotherapy offers a logical alternative treatment strategy for patients with early stage cancer and minimal residual disease. Several phase II studies have given encouraging results with intraperitoneal chemotherapy [18, 19]. A small randomized study by Kirmani *et al.* [20] has revealed similar response rates (48% vs 52%) and survival at 46 months with intraperitoneal cisplatinum and intraperitoneal etoposide compared to intravenous cisplatinum and cyclophosphamide in patients with FIGO IIC-IV ovarian carcinoma. The role of intraperitoneal chemotherapy in advanced disease has been confirmed in a randomized study comparing intraperitoneal cisplatinum to intravenous (IV) cisplatinum in conjunction with IV cyclophosphamide where intraperitoneal treatment offered a survival advantage of eight months with significantly lower systemic toxicity [21]. Unfortunately, limited data exists on the role of intraperitoneal chemotherapy in early stage ovarian cancer. Malmström *et al.* [22] investigated the efficacy of intraperitoneal carboplatinum in a group of patients with localized disease. In that study, 23% of patients were found to relapse after a median DF period of 11.5 months with a significantly higher rate of relapse among patients receiving less than 3 cycles of chemotherapy.

In our study we investigated the efficacy of intraperitoneal mitoxantrone and cisplatinum used in conjunction with IV ifosfamide in patients with high-risk early stage disease. To strengthen the anti-tumoral efficacy and achieve a more pronounced systemic effect, our patients were additionally given IV ifosphamide with mesna protection. With the combined regimen, we observed a similar relapse rate when compared to the previous study with single-agent carboplatinum which reported 23% of patients experiencing recurrence in two years [22]. Furthermore, the overall survival rate was similar to earlier data mentioned previously in the text [3]. One patient who progressed despite ongoing therapy had clear cell histology. The remaining two patients who experienced relapse within two years, had mucinous and endometrioid tumors. Abdominal pain was the most frequent complaint and was easily controlled with analgesic medications. Excluding one patient with colonic perforation due to a misplaced percutaneous catheter, complications due to IP chemotherapy like chemical peritonitis and major port-related side-effects were comparable to previous observations [20, 22]. In our study, hematologic toxicity was not of particular concern. There were neither dose modification requirements, nor any serious events due to myelosuppression.

Intraperitoneal treatment with mitoxantrone and cisplatinum combined with IV ifosfamide is a regimen with moderate efficacy and tolerable toxicity. However, the limited sample size and short follow-up period precludes us from making definite conclusions regarding the efficacy of this combination in the adjuvant setting in patients with high-risk early stage ovarian carcinoma.

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