

## CONSOLIDATION TREATMENT WITH INTRAPERITONEAL CISPLATIN IN EPITHELIAL OVARIAN CANCER FOLLOWING NEGATIVE SURGICAL ASSESSMENT

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### ABSTRACT

**Objective:** The goal of this study is to evaluate the efficacy of intraperitoneal (IP) cisplatin as consolidation treatment, in epithelial ovarian cancer patients with pathologically negative surgical reassessment, following first-line platinum-based chemotherapy.

**Methods:** This study included 22 patients with FIGO stage (IIc- IV) epithelial ovarian cancer (EOC) which had no evidence of disease and were assessed by second-look surgery. They were given 3 cycles of intraperitoneal (IP) cisplatin (100 mg/m<sup>2</sup>) with 3 weekly intervals as consolidation therapy. Survival was compared to that of a group of contemporaneous patients undergoing observation only, after completion of standard therapy.

**Results:** Median age of these 22 patients was 56 years (30-70 years). Stage distribution was II (3), III (16), and IV (3). Histologic grade was I(1), II (11), III (9), and residual disease at completion of initial surgery was none/microscopic in 4/22 (17%) patients. Median age of 43 patients who did not receive consolidation therapy was 52 years (28-74years). Stage distribution was II (7), III (32), and IV (4). Histologic grade was I (8), II (17), III (15), and not recorded (3). Median follow-up for both groups has been 46 months. Median disease-free survival (DFS) for the observed patients is 28 months and 44 months in the consolidation group. DFS distribution between groups was compared using the log-rank test and found to be significant ( $p= 0.03$ )

**Conclusion:** Multivariate analysis revealed that the only significant predictor of improved DFS was protocol treatment ( $p< 0.01$ ). This study indicates that consolidation IP cisplatin following negative second-look surgery is feasible, severe toxicity was not frequent and may provide a favorable outcome in terms of DFS compared to non-protocol patients who underwent observation alone. Further trials will be required to

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evaluate the role of consolidation treatment and improve its options in ovarian cancer.

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## INTRODUCTION

The management of advanced epithelial ovarian cancer consists of initial tumor debulking and staging laparotomy followed by platinum-based chemotherapy. Although high response rates (up to 80%) are attained, only about 50% of patients who are clinically free of disease will be found to have no evidence of disease at second-look laparotomy. Nevertheless 30 to 50% of cancers ultimately recur within 2 years. The peritoneal cavity is the most common site of recurrence (60%).<sup>1,2</sup> Thus consolidation with IP chemotherapy is reasonable treatment to delay or prevent recurrence. IP administration has the advantage of attaining high concentrations and long exposure to drugs, while preventing some of the toxicities associated with intravenous (IV) treatment. Therefore it can effectively treat both local and systemic tumor deposits.<sup>3</sup> Cisplatin is one of the most active drugs against ovarian cancer. Although following IP injection, the ratio of exposure for the peritoneal cavity compared to plasma is 12-fold, it does not cause clinical chemical peritonitis.<sup>4</sup> The effective role of IP cisplatin in the primary treatment has been established,<sup>5,6</sup> but the role of IP chemotherapy in the consolidative setting is not clearly established yet. In this study we undertook this prospective trial of consolidation therapy with 3 cycles of IP cisplatin following negative second-look surgery in an attempt to decrease recurrence and improve outcome in patients with surgically documented complete responses.

## PATIENTS AND METHODS

From March 1996 to April 2000, 26 patients with stage IIc-IV epithelial ovarian cancer were enrolled into the study to evaluate the efficacy of IP cisplatin as consolidation therapy. All patients had undergone a negative second-look surgical assessment, (8 laparotomy, 14 laparoscopy) and provided signed informed consent.

Patients were excluded for any of the following:

Histologic, cytologic, or clinical evidence of persistent ovarian cancer; concomitant malignancy; more than 60 days elapsed from the date for completion of systemic chemotherapy; presence of cardiac, liver, renal and neurologic impairment or insulin-dependent diabetes mellitus.

Inclusion criteria were histologically confirmed epithelial ovarian cancer (FIGO stage IIc-IV); performance status <2, age less than 75 years; adequate bone marrow reserve.

Pretreatment laboratory eligibility requirements included: leukocyte count >3000/mm<sup>3</sup>, platelet count <100000/mm<sup>3</sup>, granulocyte count >1500 /mm<sup>3</sup>, serum creatinine <2mg%, bilirubin <1.5×, SGOT and alkaline phosphatase <3× upper limit of institution normal. All 26 eligible patients had undergone initial debulking surgery followed by six-cycles of I.V. cisplatin-based combination chemotherapy.

Before IP therapy, patients received IV hydration fluids to achieve a urine output of >100mL/h. Cisplatin (100mg/m<sup>2</sup>) was diluted in a volume of 1000 mL 0.9% saline solution 37°C and administered via a laparoscopic Verres needle. Following infusion of 1 lit of medication, 1 lit of additional DW5% was given to distend the abdomen to ensure adequate distribution. All patients received antiemetics such as serotonin antagonists, metoclopramide, and dexamethasone, 15-30 minutes before treatment, and analgesics as required depending on the severity of abdominal pain. They were given 3 cycles of IP at 3 week intervals. Cisplatin dose was reduced for renal and hematologic toxicity. A 50% reduction for nephrotoxicity was based on serum creatinine (>1.5 mg/dL) or creatinine clearance (<50 mL/min) on the day of treatment. It was discontinued permanently if serum creatinine was greater than 2 mg/dL. Cisplatin dose was reduced by 50% in patients with WBC < 3000 or platelet < 100000 on the day of therapy. All patients in both groups were followed by physical and pelvic examination, complete blood counts, blood chemistries, and CA 125 every 3 months. Normal CA-125 was defined as <35/mL. Patients with any significant elevations in CA125 concentration of >100 U/ mL or who experienced a doubling of two consecutive measurements, was considered to have recurrent disease.

CT scan of the pelvis and abdomen was performed to determine the extent of disease or for evaluation in symptomatic patients with normal tumor markers.

Survival and recurrence data for these patients were compared to the control group of 43 patients who met protocol eligibility requirements but underwent observation alone. All patients in the untreated group received six-cycles of platinum-based combination chemotherapy following cytoreductive surgery and underwent second-look surgery (12 laparotomy, and 31 laparoscopy).

Survival was analyzed by the method of Kaplan and Meier,<sup>7</sup> and differences in survival distributions were tested using the log-rank test of Mantal.<sup>8</sup>

DFS was measured from the date of second-look reassessment until the first evidence of recurrence or last follow up.

## RESULTS

The characteristics of the two groups are summarized in Table I. 4 patients refused to complete the protocol after one or two courses of IP therapy. Twenty-two patients undergoing protocol treatment were eligible for efficacy and toxicity evaluation. Median age was 56 years (range 30-70 years). Advanced stages were prominent with high frequency of stage III, i.e. 16 (72%) patients. The majority of them had an optimal primary surgery (14 patients, 63%).

3 courses of IP chemotherapy were administered. The toxicity of treatment was substantial; 16 patients were able to complete 3 cycles of IP without dose modification. 6 patients required dose reduction for nephrotoxicity and neutropenia, including two with grade 3 leukopenia and urosepsis who required hospitalization and I.V. antibiotic therapy.

Nausea, vomiting and abdominal pain were commonly observed but did not lead to dose reduction. Grade 1 and 2 neuropathy was common, but no patient experienced grade 3 or 4 peripheral neuropathy. One patient developed peritonitis with fever, severe abdominal pain and tenderness. She was treated with ileostomy and antibiotic therapy. She had a prolonged hospitalization and second surgery for closing the ileostomy. At last follow-up (28 months) she had no evidence of disease and no long-term complication.

There were no treatment-related deaths. After a median follow-up of 46 months, 13(56%) patients are alive without evidence of recurrence, and in non-protocol patients, 16 (35%) of them are without disease. The median DFS for protocol and observation groups was 44 and 28 months respectively. When DFS in the observation group was compared (using the log-rank test) to the consolidative group, there was a significant improvement ( $p<0.03$ ) in DFS. The prognostic significance of IP chemotherapy was evaluated using a Cox proportional hazard regression analysis along with other known prognostic factors, stage, grade, and residual disease ( $p=0.17, 0.63$ , and  $0.67$ ), and only consolidation therapy was significant ( $p=0.01$ ).

## DISCUSSION

The majority of epithelial ovarian cancer patients have

disseminated peritoneal disease at diagnosis. For these patients, optimal initial treatment consists of cytoreductive surgery, but the risk of recurrence following primary therapy remains very high. Finally, almost half of these patients will relapse within 2 years, and the main site of recurrence is the peritoneum.<sup>2</sup> Obviously, new strategies are needed to improve DFS and overall survival for advanced stages. These include the introduction of new, active agents as first-line chemotherapy,<sup>9</sup> and another therapeutic strategy based on the evaluation of consolidation or maintenance treatment to increase DFS for patients with a pathological complete response at second-look reassessment following primary treatment.

In spite of the fact that the benefit of consolidation therapy has not been established, the Gynecology Oncology Group study provides evidence favoring this approach.<sup>10</sup>

In our study, we have shown that IP cisplatin is an effective and feasible approach, and can be administered safely with acceptable toxicity and result in an improvement in DFS compared to that of patients undergoing observation alone. Menzer et al. showed the efficacy of high-dose IP cisplatin ( $200 \text{ mg/m}^2$ ) + thiosulfate in 17 patients who received 3 cycles of IP consolidation following negative second-look laparotomy. The median DFS was reported as 41 months. They concluded that short-term IP cisplatin should be considered as consolidation therapy in patients with no residual disease after first-line chemotherapy.<sup>11</sup>

In 1992, Degramont et al.<sup>12</sup> reported 13 complete responders who received 3 courses of IP cisplatin ( $200 \text{ mg/m}^2$ ), and noted a median progression-free interval of 37 months. Tarraza et al<sup>13</sup> reported the role of IP cisplatin ( $80 \text{ mg/m}^2$ ) as consolidation therapy following negative second-look laparotomy. The median time to recurrence was determined as 18 months. Dufour et al<sup>14</sup> treated 50 patients with 6 courses of IP mitoxantrone ( $20 \text{ mg/m}^2$ ) as consolidation therapy. They noted a median DFS of 22 months. At 5 years, the estimated overall survival was 59.8 % and DFS 47.3%. Finally, Barakat et al.<sup>15</sup> noted a 39% recurrence rate in patients receiving IP consolidation (36 patients) compared to 54% (46 control patients) for a similar group of patients who did not receive consolidation. The median follow-up was 36 months.

In the present study, severe toxicity was not frequent and our patients did not experience severe neuropathy, which is comparable to those studies that had similar cisplatin doses.<sup>15</sup> Serious neuropathy has been reported by others with higher-dose regimens, such as  $200 \text{ mg/m}^2$ .<sup>11,16</sup>

Other trials<sup>17</sup> such as ours have shown that complications related to IP therapy are not considerable.

## Consolidation Treatment with Intraperitoneal Cisplatin

The recurrences following negative second-look reassessment in advanced epithelial ovarian cancer, are mostly mild insignificant. The prognostic factor of relapse, including residual disease after primary debulking, tumor grade and stage has been identified. Consolidation treatments play a role in the therapeutic direction.

However IP chemotherapy has demonstrated its safety and reports indicate a favorable outcome; nevertheless further randomized trials are required, and new drugs and new concepts should be evaluated.

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