RESEARCH ARTICLE

# Intra-Peritoneal Cisplatin Combined with Intravenous Paclitaxel in Optimally Debulked Stage 3 Ovarian Cancer Patients: An Izmir Oncology Group Study

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## Abstract

**Background: The advantage of intra-peritoneal (IP) chemotherapy (CT) in the initial management of ovarian cancer after cytoreductive surgery is well known. The feasibility and toxicity of a treatment regimen with an IP + intravenous CT (IPIVCT) for optimally debulked stage III ovarian cancer were here evaluated retrospectively. Materials and Methods: A total of 30 patients were treated in our institution between October 2006 and February 2011. Patients received IV paclitaxel 175 mg/m$^2$ over 3 hours followed by IP cisplatin 75 mg/m$^2$ on day 1; they also received IP paclitaxel 60 mg/m$^2$ on day 8. They were also scheduled to receive 6 courses of CT every 21 days. Results: The median age of the patients was 55 years (35-77), and the majority had papillary serous ovarian cancer (63.3%). The patients completed a total of 146 cycles of IPIVCT. Twenty-eight were able to receive at least three cycles of IPIVCT and 18 (60%) completed the scheduled 6 cycles. Two patients discontinued the IPIVCT because of toxicity of chemotherapy agents and 6 had to stop treatment due to intolerable abdominal pain during IP drug administration, obstruction and impaired access. Grade 3/4 toxicities included neutropenia (6 patients; 20%), anemia (2 patients; 6.7%) and nausea-vomiting (2 patients; 6.7%). Doses were delayed in 12 cycles (8%) for neutropenia (n=6), thrombocytopenia (n=3) and elevated creatinine (n=3). Drug doses were not reduced. The median duration of progression-free survival (PFS) was 47.7 months (95%CI, 38.98-56.44) and overall survival (OS) was 51.7 months (95%CI, 44.13-59.29). Two and five-year overall survival rates were 75.6 % and 64.8%, respectively. Conclusions: IPIVCT is feasible and well-tolerated in this setting. Its clinically proven advantages should be taken into consideration and more efforts should be made to administer IPIVCT to suitable patients.**

**Keywords:** Ovarian cancer - intra-peritoneal chemotherapy - intra-venous chemotherapy

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## Introduction

Ovarian cancer is the fifth leading cause of death from a gynecologic malignancy in the United States (Seigal et al., 2012). There is no established screening method for ovarian cancer; thus, 60-70% patients are at stage III or IV at the time of initial diagnosis (Arun-Muthuvel and Jaya, 2014). Currently the standard-of-care therapy for ovarian cancer is debulking surgery to minimize residual disease, followed by intravenous chemotherapy (IV CT) with a combination of a platinum analogue and paclitaxel (Chumworathayi, 2013; Koo et al., 2014; Suprasert et al., 2014). With surgery and standard IV CT, most patients achieve complete clinical remission(Gaemmaghami et al., 2011). However, disease recurrence occurs in approximately 80% of patients and usually involves the peritoneal cavity (Sarkar et al., 2013; Suprasert and Chalapati, 2013; Liu et al., 2014; Kokanali et al., 2014).

Intraperitoneal chemotherapy (IP CT) was first administered in 1950 for intra-abdominal cancer with the use of nitrogen mustard (Weisberger et al., 1955). However, pharmacological principles of using IP CT in ovarian cancer were described the first time in 1978 (Dedrick et al., 1997). Since 1990, three large randomized, controlled trials have found better progression-free survival and overall survival with intra-peritoneal chemotherapy compared to intravenous chemotherapy (Alberts et al., 1996; Markman et al., 2001; Armstrong et al., 2006). All of these studies included only stage 3 ovarian cancer patients and employed a combination of IV and IP CT, and this was compared to IV-only CT control arms. Cisplatin was the most commonly employed IP CT

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agent which was used every 3 weeks over 6 cycles. Median disease-free survival (DFS) ranged from 24 to 28 months, and OS ranged from 49 to 66 months in the IP CT patients. Most recently, GOG 172 study was completed which was conducted by the Gynecologic Oncology Group (GOG). This study demonstrated the longest median OS ever reported in optimally debulked, stage III ovarian cancer patients at 66.9 months and median PFS for the IV and IP/IV arms was 18.3 and 23.8 months, respectively (Armstrong et al., 2006).

Currently, IPIVCT is recommended by the guidelines for stage III patients with optimally debulked (<1 cm residual) disease based on randomized controlled trials. Stage 2 patients may also receive IPCT but there is no published evidence for stage 2 from randomized trials. In women with stage 3 cancer, survival was prolonged by 16 months following IP therapy using cisplatin/paclitaxel compared to the standard IV therapy (Armstrong et al., 2006). Despite the evidence from randomized controlled trials demonstrating superior DFS and OS rates achieved by IPIVCT, one of the factors limiting its widespread acceptance is the associated toxicity, as demonstrated by the most recent study, GOG 172. In that study, only 42% of patients in the IP arm completed their planned 6 cycles of IPIVCT. The present study retrospectively assessed the feasibility and toxicity of an IPIVCT regimen when used for the treatment of patients with optimally debulked stage III epithelial ovarian cancer in our center.

## Materials and Methods

*Patients*

All patients who underwent surgery between October 2006 and February 2011 had histologically confirmed stage III ovarian carcinoma. Staging was accomplished according to the International Federation of Gynecology and Obstetrics (FIGO) classification for staging. To be included in the study, patients were required to be 18 years or older and have adequate bone marrow reserve and normal hepatic and renal function. This study included patients with Eastern Cooperative Oncology Group (ECOG) performance status of ≤2. Toxicity was determined according to the NCI (National Cancer Institute) Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

*Port placement*

All patients underwent primary cytoreductive surgery. A Bard IP port system was placed within the subcutaneous fat tissue before abdominal closure. Usually, the site preferred for port placement was the upper right abdomen.

*Treatment protocol*

Intra-peritoneal treatment consisted of 175 mg/m$^2$ of IV paclitaxel over three hours followed by 75 mg/m$^2$ of IP cisplatin on day 1 and 60 mg/m$^2$ of IP paclitaxel on day 8. Standard premedication with dexamethasone, famotidine and diphenydramine was given to prevent hypersensitivity reactions to paclitaxel. Two thousand milliliters of 0.9% NaCl IV was given over 4 h before and after cisplatin administration for sufficient hydration of patients. The standard antiemetic regimens consisted of intravenous granisetron and dexamethasone given before initiation of chemotherapy. Also, aprepitant 125 mg on Day 1 and 80 mg on the second and third days was given orally. The planned number of cycles was 6, to be administered every 21 days.

*Statistical analysis*

Disease-free survival was defined as the time from surgery to last visit, relapse or death. Overall survival was defined by the time from cytoreductive surgery to last visit or death. SPSS 15.0 for Windows software package was used for statistical analysis. Survival rates were calculated according to Kaplan-Meier Method.

## Results

A total of 30 patients with stage III ovarian cancer were analyzed. Most of the patients were ECOG performance status of 0 (96.7%). Median age of the patients was 55 years (range 35-77). Demographic characteristics of the patients are shown in Table 1. All patients had stage III disease at diagnosis. Papillary serous was the most common histologic type (19 patients, 63.3%). Three patients had family history of ovarian cancer. The median Ca 125 level before the ovarian surgery was 185 U/ml (range 3-1420). The median follow-up at the time of data analysis was 32.2 months (range, 7-62 months). All patients had prior optimal cytoreduction surgery (residual disease<1 cm).

The median time between surgery and chemotherapy was 53 days (range, 12-187 days). Thirty patients

**Table 1. Clinical and Histopathological Characteristics of Patients**

| | | N | % |
|---|---|---|---|
| Median age (min-max), years | | 55 (35-77) | |
| Median follow up, months (min-max) | | 32.2 (7-62) | |
| Stage | III | 30 | 100.0 |
| Histology | Papillary serous carcinoma | 19 | 63.3 |
| | Endometrioid carcinoma | 7 | 23.3 |
| | Clear cell carcinoma | 2 | 6.7 |
| | Other | 2 | 6.7 |
| Grade | Unknown | 13 | 43.3 |
| | Well | 6 | 20.0 |
| | Intermediate | 8 | 26.7 |
| | Poor | 3 | 10.0 |
| Family history | | 3 | 10.0 |
| ECOG (Eastern Cooperative Oncology Group) | | | |
| | 0 | 29 | 96.7 |
| | 1 | 1 | 3.3 |

**Table 2. Distrubituon IP Chemotherapy Cycles**

| Treatment cycles | Patients(n,%) |
|---|---|
| 1 | 1 (3.3%) |
| 2 | 1 (3.3%) |
| 3 | 6 (20%) |
| 4 | 3 (10%) |
| 5 | 1 (3.3%) |
| 6 | 18 (60%) |

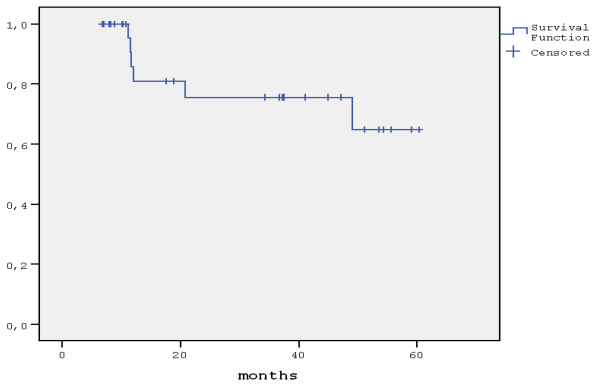


**Figure 1. Mean Progression free Survival Curve of the Patients**

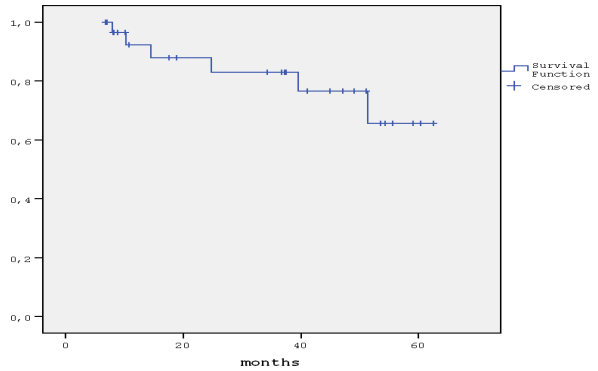


**Figure 2. Mean Survival Curve of the Patients**

completed 146 cycles of chemotherapy with IP cisplatin and IV paclitaxel. Eighteen (60%) patients completed six cycles. Dose delays were noted prior to 12 cycles for neutropenia (n=6), thrombocytopenia (n=3) and elevated creatinine (n=3). The dose of IP chemotherapy was not reduced. Nine patients were switched to IV chemotherapy (carboplatin AUC 5+ paclitaxel 175 mg/m$^2$ every 21 days). One of these nine patients refused further treatment after the first IP chemotherapy cycles, 2 patients had renal toxicity and 6 patients (20%) had catheter complications (1 patient with obstruction, 1 patient with impaired access and 4 patients with abdominal pain). IP chemotherapy cycles received by the patients are shown in Table 2. Nine patients had a total of 26 cycles of IV chemotherapy. Most of the adverse events were mild (Table 3).

Relapse of the disease occurred in 6 patients (20%) and 6 patients (20%) died during the follow up. The median duration of PFS was 47.7 months (95%CI, 38.98-56.44) and OS was 51.7 months (95%CI, 44.13-59.29) (Figure 1 and 2). Two and five-year overall survival rates were 75.6% and 64.8%, respectively.

## Discussion

Data of patients with ovarian cancer who were given IPCVT treatment as adjuvant therapy in a single center were reviewed in this retrospective study. The majority of the patients had serous carcinoma histology and their median age was 55 years. Also, similar demographic and pathological characteristics were observed compared with previous intraperitoneal chemotherapy studies (Yen et al., 2001; Armstrong et al., 2006; Walker et al., 2006). Intra-peritoneal CT has its own side effects and procedural difficulties.

IPCVT has its own side effects and procedural difficulties. For all IPCVT regimens, the percentage of patients completing scheduled chemotherapy cycles is low. For example, the percentage of patients completing all 6 cycles of IPCVT was 61% in Oaknin et al.'s study. In their study, Armstrong et al. found that 92% of patients in carboplatin group and 60% of cisplatin group successfully completed all 6 cycles (Armstrong et al., 2006; Gray et al., 2010; Oaknin et al, 2011). Nicoletto et al.'s study 53% of patients completed 6 cycles of IPCVT (Nicoletto et al., 2010). In the present study, 60% of patients had 6 cycles of chemotherapy, which was consistent with other studies in literature.

During IPCVT, catheter-related complications frequently occur such as infection, impaired access, catheter blockage and abdominal pain. These complications were reported at a rate between 10-18% in some previous studies (Alberts et al., 1996; Markman et al., 2001; Piccart et al., 2003; Armstrong et al., 2006; Skaznik-Wikiel et al., 2012). In our study, catheter complications occurred at a frequency of 20%, consistent with those reported in literature.

Also IPCVT has some well-known side effects. In our study, Grade 3 and 4 toxicity were observed at a frequency between 0-20%. Most of these grade 3-4 toxicity events were cases of neutropenia, which occurred at a rate of 20%. In prospective IPCVT studies, grade 3-4 neutropenia occurred at a frequency between 40-76% (Alberts et al., 1996; Markman et al., 2001; Armstrong et al., 2006). In another retrospective study, neutropenia was observed at a rate of 20% wit use of different therapeutic agents (Seamon et al., 2009).

In a first randomized controlled study conducted by South Western Oncology Group (SWOG) and GOG 104 published in 1996 (Alberts et al., 1996). In the 546 eligible patients, the estimated OS was significantly longer in the IP group (49 months, 95% confidence interval CI: 42-56). The second phase 3 IP study was also conducted by GOG and SWOG, and the results published in 2001 (Markman et al., 2001). Improved PFS and OS of 426 assessable patients were observed in favor of IP group. It was reported 28 and 63 months of PFS and OS in the IP group, respectively. The third study was conducted by GOG (Armstrong et al., 2006). In this study, 417 patients with optimally de-bulked stage 3 ovarian cancer were randomized IVCT or IVIPCT groups. The improvement in median OS was 15, 9 months with a treatment favoring the IP study arm. The median duration of OS for the IP arm of this trial (66 months) was 10 months longer than that for the current standard treatment schedule arm of the GOG 158 trial (57 months) (Ozols et al., 1999). Consistent with the literature, our study showed PFS of 47 months and OS of 51 months. Fujiwara et al.'s study evaluated at the first line IP carboplatin based CT patients with epithelial ovarian carcinoma (Fujiwara et al., 2003). In this retrospective analysis, the median OS of the patients with small (<2 cm) residual disease was 51 months. Although the median OS of patients in this population treated with

a dose of <400 mg/m$^2$ carboplatin was 24,5 months, the median OS was not reached until 84 months when the carboplatin was dosed >400 mg/m$^2$. Our study protocol was used an IP cisplatin according to Barlin's study (Barlin et al., 2012). This study is retrospective analysis, it is reasonable to argue that the data further support the prospective evaluation of IP carboplatin administration. After the GOG study demonstrated improved PFS and OS for patients with stage 3 optimally de-bulked ovarian and peritoneal carcinoma treated with IVIPCT compared with standard IVCT, Barlin et al.'s study was evaluated the modified outpatient IP regimen (Barlin et al., 2012). Eighty percent of patients completed 4 or more cycles, 55% of patients completed all 6 cycles. The median PFS and OS were 29 and 67 months in respectively in this study (Barlin et al., 2012). Barlin's study result is also consistent to ours.

In spite of an enormous effort in the past few decades, improvement of the prognosis of ovarian cancer has been limited. The IVIPCT has been extensively investigated both preclinically and clinically. Phase 3 trials showed PFS and OS advantage and also demonstrated by the meta-analysis. Several trials currently ongoing randomized phase 3 will provide extremely important information about whether a less toxic IP regimen using carboplatin will be beneficial for patients with advanced ovarian cancer. We are aware of the limitations and biases of our study resulting from its retrospective nature and, this study was not comparative and controlled. Due to the small number of patients assessed, toxicity was observed at the low rate. One of the strengths of our study follow-up period is long and other the percentage of completion of IVIPCT cycles is high. In conclusion, IVIPCT is an important alternative for the treatment of ovarian cancer and currently, it is associated with improved survival, as shown by clinical trials. It should be administered in experienced centers and complications associated with use of IP port should be monitored more attentively.

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