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## Utilization of an alternative docetaxel-based intraperitoneal chemotherapy regimen in patients with ovarian, fallopian tube or primary peritoneal carcinoma: A continued need for ovarian cancer patients<sup>†</sup>

David A. Becker, MD<sup>1</sup>, Charles A. Leath III, MD, MSPH<sup>2,\*</sup>, Christen L. Walters-Haygood, MD<sup>2</sup>, Brentley Q. Smith, MD, MSPH<sup>1</sup>, and Kerri S. Bevis, MD, MSPH<sup>2</sup>

<sup>1</sup>Department of Obstetrics & Gynecology, University of Alabama at Birmingham

<sup>2</sup>Division of Gynecologic Oncology, University of Alabama at Birmingham

### Abstract

**Objective**—The objective of this study was to report the tolerability and toxicity of a regimen consisting of intravenous (IV) docetaxel and intraperitoneal (IP) cisplatin and paclitaxel with granulocyte colony-stimulating factor support.

**Methods**—We conducted a retrospective cohort study of patients with surgical stage II-IV epithelial ovarian, fallopian tube or primary peritoneal carcinoma treated with an outpatient IP chemotherapy regimen consisting of docetaxel 75mg/m<sup>2</sup> IV and cisplatin 75mg/m<sup>2</sup> IP day 1 followed by paclitaxel 60mg/m<sup>2</sup> IP day 8 every 21 days. Grade 3 and 4 toxicity, dose delays and reductions, port complications, and tolerability are reported. Outcomes, including response rate, progression-free survival (PFS), overall survival (OS) are also reported.

**Results**—60 patients received this IP regimen. Most common toxicities included neutropenia (47%), gastrointestinal (28%) and anemia (25%). Most patients (85%) experienced no IP port complications. Dose delay or reduction was required in 30% of patients. Two-thirds completed all prescribed cycles, with 80% of total planned cycles completed. Complete response was achieved for 88%, and 43% are currently without evidence of disease. Median PFS for all patients was 25.5 months (95% CI 20.4-30.5) while OS for all patients was 56.8 months (95% CI 47.7-65.9 months). For the 44 patients with stage III disease, median PFS was 22.1 months (95% CI 16.3-28.0 months), while median OS was 56.8 months (95% CI 47.3-66.3 months).

**Conclusions**—This docetaxel-based IP chemotherapy regimen demonstrates an improved tolerability profile compared to GOG172. Additional evaluations on alternative IP regimens remain warranted. Short follow-up time limits survival assessment, but results are encouraging.

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\*Corresponding Author: cleath@uabmc.edu, University of Alabama at Birmingham, Division of Gynecologic Oncology, 1700 6<sup>th</sup> Avenue South, Room 10250, Birmingham, AL 35233, Phone: +1 205 934 4986, Fax: +1 205 975 6174.

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## Keywords

Docetaxel; intraperitoneal chemotherapy; ovarian cancer

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## Introduction

The American Cancer Society's annual projections for ovarian cancer include 22,440 new cases with 14,080 women expected to die from ovarian cancer within the United States [1]. Traditionally, advanced stage disease has been treated with primary cytoreductive surgery followed by intravenous (IV) platinum and taxane-based chemotherapy [2]. Alternative treatment regimens have included the use of both dose dense paclitaxel and platinum [3-5] as well as the use of a combination of both IV and intraperitoneal (IP) therapy [6-8].

Attention has been focused on IP administration of anti-neoplastic agents because of the intra-abdominal dissemination pattern of ovarian cancer, and has been evaluated in a series of trials by the Gynecologic Oncology Group (GOG) [6-8]. While the first two trials, GOG104 and 114, were considered positive trials, the improvement in overall survival was somewhat modest at the expense of added toxicity [6, 8]. However, GOG172 demonstrated the clear superiority of an IP and IV chemotherapy regimen when compared to an IV regimen alone in the primary treatment of stage III optimally-cytoreduced epithelial ovarian or primary peritoneal carcinoma [7]. GOG172 reported a 23.8 month progression-free survival (PFS) and 65.6 month overall survival (OS) for patients receiving IP chemotherapy as compared to 18.3 month PFS and 49.7 month OS for patients in the IV treatment group. These trial results prompted a US National Cancer Institute (NCI) Clinical Announcement in 2006 encouraging IP chemotherapy as the preferred method of treatment for these women [9]. Importantly, the rates of both grade 3 and 4 leukopenia (76% vs. 64 %,  $p < 0.001$ ) and neurologic events (19% vs. 9%,  $p = 0.001$ ) were more common in the patients receiving the IV/IP regimen.

Despite this endorsement and the subsequent support from numerous other multidisciplinary professional societies, adoption of IP chemotherapy use has been slow. Notable barriers include the need for coordinated multidisciplinary care, high toxicity, catheter related issues, inpatient administration, and limited access to facilities with experience providing such therapy [9]. Catheter-related complications and patient unwillingness to continue therapy are also potential obstacles. Secondary to side effects, only 42% of the patients receiving the IP arm in GOG172 were able to complete all assigned cycles [7]. Other studies have demonstrated similar findings [11].

Most recently, the GOG reported preliminary findings from GOG252 (NCT01167712), a phase III trial evaluating a modification of the GOG172 regimen with a lower dose of IP cisplatin versus two dose dense, or weekly paclitaxel regimens, one with IV carboplatin, and the second with IP carboplatin, all in combination with bevacizumab induction and maintenance [12]. Preliminary data demonstrated no survival benefit for either of the IP therapy arms with median PFS survival ranging from 26.8 to 28.7 months for the three arms. Moreover, Wright and colleagues utilized the MarketScan database and noted that IP therapy was used in only 15% of patients and that in the absence of a confirmatory trial in the US,

dose dense paclitaxel appears to be increasing. However, two reports from ASCO 2016 note continued utility of IP regimens in ovarian cancer patients traditionally excluded from IP trials, namely those having a suboptimal cytoreduction as well as following an interval cytoreduction [13, 14].

In an effort to reduce toxicity and increase rates of therapy completion, modifications of the GOG172 regimen have been reported [10, 11]. We adopted a modified outpatient regimen consisting of IV docetaxel 75mg/m<sup>2</sup>, IP cisplatin with a fixed dose of 75mg/m<sup>2</sup> and IP paclitaxel 60mg/m<sup>2</sup> as our primary IP therapy regimen. Compared to paclitaxel, docetaxel has been shown to have a different side effect profile with less neuropathy at the expense of more neutropenia and without a detriment in quality of life for patients, all without sacrificing PFS or OS [15]. The objectives for this study are to report: 1) our docetaxel-based IP regimen protocol; 2) toxicity and tolerability of this regimen; 3) early outcomes including response rate and PFS.

## Materials and Methods

After institutional review board (IRB) approval was obtained, a retrospective cohort study was performed on 98 patients who received IP chemotherapy between January 1, 2008 and April 30, 2014 at a single institution. Patients were included if they received at least one cycle of the defined regimen. Patients enrolled on a clinical trial for either primary therapy (N=20) or recurrent disease (N=13) were excluded. Alternative IP-based regimens were also excluded (N=5).

Eligible patients included those with stages II-IV epithelial ovarian, fallopian tube, and peritoneal carcinoma. Patients who received this regimen as primary adjuvant therapy (N=52) or following interval debulking surgery (N=8) were included. All patients had GOG performance status of 0-1 and adequate renal, hepatic, and bone marrow function prior to initiation of therapy.

Abstracted data included patient demographics, medical co-morbidities, and oncologic history including histology, grade, stage, and surgical details. Data was collected regarding the timing of IP port placement and related complications. Charts were reviewed for chemotherapy cycles planned and received, adverse events, and any treatment delays, dose reductions, or hospitalizations. Toxicity data regarding hematologic, gastrointestinal, metabolic, renal, neurological, infectious and embolic events was collected. Grading of toxicity was based on the National Cancer Institute Common Toxicity Criteria Version 2. Response to the treatment regimen was noted to be complete, partial, or progression as documented by the treating physician. Patients without a response were considered to have no progression free survival time. PFS and OS were calculated from the date of surgery. Recurrence was based on one of the following: Gynecologic Cancer Intergroup Criteria for Ca-125 from the nadir [16], radiographic imaging, or physical exam. Patients without evidence of progression were censored at the time of their last clinic visit. Disease status at time of last clinic visit was recorded. Patients known to be deceased were considered to have died from their cancer. When date of death was not documented in the patient's chart, public death records were utilized.

The modified regimen in this study is based on a proposed 21-day cycle with therapy on D1 and D8 for a total of 6 cycles. The details of the regimen are outlined in Table 1. The primary modifications include substitution of D1 docetaxel for paclitaxel as well as administration of IP cisplatin on D1 in an ambulatory setting. The dose of cisplatin was reduced to 75 mg/m<sup>2</sup> from the 100 mg/m<sup>2</sup> used in GOG172. All patients were given GCSF with pegfilgrastim 6mg subcutaneously on D8. Pre-treatment labs were routinely checked prior to D1 and D8 of treatment. Additional IV fluids were not routinely administered following cisplatin administration although they were added to the regimen if patients experienced significant renal dysfunction or dehydration.

The treating physician, prior to the initiation of IP therapy, determined the number of planned cycles of IP therapy. Dose reductions, delays and alterations were also made at the discretion of the treating physician. Dose alterations included omission of D8 treatment or failure to complete D1 therapy for any reason. IP cycles were considered completed once the patient received D1 of the cycle. If IP chemotherapy was stopped prior to completion of the planned number of cycles, the patient continued with IV therapy alone on a standard 21-day cycle to complete therapy as tolerated. Descriptive and summary statistics were determined and Kaplan-Meier estimates of survival were compared with the Log Rank test (SPSS version 22, IBM Corporation, Armonk, NY).

## Results

### Patient characteristics

Sixty patients received at least one cycle of IP therapy, and were included. Patients were predominantly white (78%) with a median age of 63 (range 29-77). Most patients, 38 (63%), had stage IIIC disease at the time of initial cytoreductive surgery. Nearly all patients were at least optimally debulked (97%) and 33% had no residual disease. Bowel resection was performed in 40% of patients. Papillary serous (69%) was the most common histology. A majority (60%) of patients had delayed placement of their IP catheter. Eight patients (13%) received at least one cycle of neoadjuvant IV chemotherapy. Complete patient and disease characteristics are depicted in Table 2.

### Toxicity and tolerability

Table 3 lists the incidences of grade 3 or 4 toxicity. 18% of patients received therapy without experiencing significant toxicity. Neutropenia (47%), gastrointestinal (28%) and anemia (25%) were most frequently encountered. Other commonly observed toxicities included neurological (17%) and renal (10%). Thrombocytopenia, metabolic derangements, thromboembolic events and infection were all less frequent. Four patients (7%) experienced neutropenic fever. Twenty-three hospitalizations were documented among 18 patients during IP therapy. One patient was hospitalized for an IP port infection following cessation of IP therapy. No patients suffered death as a result of toxicity.

Complications related to the IP port were relatively uncommon with most patients (85%) experiencing no IP port-related complications. Infection (8%) was the most common port reported toxicity, although only one patient required removal. The remaining infections were

treated with oral antibiotics. Other complications included two port fractures (3%), one port that failed to function (2%) and one port occluded with a thrombus (2%). One patient suffered a bowel injury during laparoscopic placement and required laparotomy to repair.

## Efficacy

Table 4 demonstrates the tolerability of therapy. Of 328 total IP cycles prescribed, patients were able to complete 80%. Two-thirds of patients were able to complete all prescribed IP cycles. Six IP cycles were prescribed for 45 patients (75%). 56% of those patients completed all six, and median number of IP cycles received was four. For the patients unable to complete all prescribed IP cycles, only two were unable to complete at least six cycles of IV chemotherapy.

Delay in therapy greater than one week was required in 12 patients (20%), with one patient requiring two separate delays. Six patients (10%) required dose-reduction due to toxicity, most commonly from renal dysfunction. Thirty-eight dose alterations were made in 25 patients (42%), most frequently due to neutropenia (18 total alterations). Less commonly observed indications for alteration included renal (7 alterations) and gastrointestinal (5 alterations). IP therapy was stopped due to toxicity in 33% of patients. No patients stopped due to progression; however one stopped due to a plateau in response as measured by her Ca-125 level. Nearly all patients (88%) demonstrated a complete response to therapy, and only three patients (5%) had progressive disease during therapy. At the time of data analysis, 43% of patients were without evidence of disease, 23% were alive with disease, 27% were deceased and the status of 7% was unknown. Median PFS was 25.5 months (95% CI 20.4-30.5), while OS was 56.8 months (95% CI 47.7-65.9 months) (Data Not Shown). When considering the 44 patients with stage III disease, median PFS was 22.1 months (95% CI 16.3-28.0 months) and is depicted in Figure 1, while median OS was 56.8 months (95% CI 47.3-66.3 months) and is depicted in Figure 2.

## Discussion

Following the publication of GOG172, which demonstrated an improvement in OS of 16 months for patients that received any IP chemotherapy compared to IV therapy alone, the utilization of IP chemotherapy received increased attention; however, patients receiving IP therapy experienced greater toxicity. In an attempt to limit potential toxicity, we adopted a docetaxel-based regimen of IP chemotherapy designed to improve tolerability and transition the regimen to an ambulatory setting, while still preserving the survival benefit.

We previously described our early experiences in a multi-institutional study with this regimen, although patients previously may have received cisplatin 100mg/m<sup>2</sup> IP and amifostine administration was omitted [10]. This is based on published data, demonstrating similar efficacy but improved neurotoxicity and quality of life scores in women with advanced epithelial ovarian cancer [15, 17]. However, docetaxel was also associated with higher rates of neutropenia and neutropenic complications [15, 17]. Recognizing the high rate of neutropenia in GOG172, the substitution of an agent with higher bone marrow suppression justified the addition of primary prophylactic GCSF. This limited neuropathic toxicity to 17% while also minimizing neutropenic complications. Per institutional protocol,

these patients received their pegfilgrastim injections on D8 following their paclitaxel infusions, a practice demonstrated to be safe in gynecologic cancer patients [18].

Since the start of 2008, 60 of our patients with advanced ovarian, fallopian tube or primary peritoneal carcinoma have received at least one cycle of this outpatient docetaxel-based IP chemotherapy regimen. We demonstrated excellent tolerability of this regimen among a broad population of patients including those with stage 2, 3, and 4 disease, suboptimally debulked patients, and those treated with neoadjuvant chemotherapy. As part of the treatment protocol, we also checked hematologic parameters prior to the day 8 infusion, although this approach was not utilized in GOG172. Neutropenia was responsible for half the instances where patients missed D8 treatment, and was the most common reason for dose alteration. This conservative approach of utilizing results from D8 labs prior to treatment may have contributed to the improvements in safety and tolerability of therapy compared to GOG172; however, it may have resulted in unnecessary treatment modifications, as an abnormal lab value was primarily responsible for two-thirds of the instances where D8 treatment was missed. Based on the data presented here, we have further modified our protocol to eliminate routine hematologic monitoring prior to D8 paclitaxel. The incidence of neutropenia appears reasonable when considering just 14% of neutropenic patients experienced the comorbidity of fever.

Major side effects of platinum-based chemotherapy include renal, metabolic and gastrointestinal symptoms [19]. The IP therapy arm in GOG172 experienced a significant increase in gastrointestinal (46% vs. 24%) and metabolic toxicities (27% vs. 7%), in addition to an increase in renal toxicity (7% vs. 2%) [7]. We addressed these potential toxicities by reducing the IP cisplatin dose from 100mg/m<sup>2</sup> to 75mg/m<sup>2</sup>, and using an aggressive anti-emetic regimen of daily dexamethasone on D0 and D2-5 in addition to dexamethasone, diphenhydramine, fosaprepitant, palonosetron, and ranitidine on D1 and D8. The combination of anti-emetics used was aimed at preventing both acute and delayed emesis. Severe gastrointestinal and metabolic toxicities were observed in just 28% and 5% of patients, respectively, rates comparable to those observed in the IV therapy arm of GOG172 [7].

Overall, toxicity appeared to be favorable with thrombocytopenia, thromboembolic events and infection observed in 7% or fewer patients. Other infrequent toxicities included hearing loss and fatigue or weakness. Ten percent suffered severe renal toxicity. No patients experienced death as a result of complications from treatment. Hospitalizations were infrequent, occurring just 23 times total. Half of those occurred during or after cycle 1, and intractable nausea and emesis was the most common cause. Low rates of complications early in IP therapy may prevent conversion to less demanding IV therapy. Likewise, dose delays (13 total occurrences) and reductions (10% of patients) were infrequent, and are felt to be a direct result of the changes made to our regimen. Comparable statistics are not available from GOG172.

Treatment with IP chemotherapy carries a unique set of complications due to the presence of an intraperitoneal catheter. Comparable to GOG172, the IP port was placed during the debulking surgery in 40% of patients. During the initial adoption, delayed placement was

preferred. This pattern has changed with time, and placement during the primary debulking surgery is now the preferred method at our institution. IP port complications were rare, and led to just 3 patients (5%) discontinuing IP therapy. This compares favorably to GOG172, which found that 34% of patients discontinued IP therapy mainly due to catheter-related complications [20]. As seen in multiple other studies, infection was the most frequently observed complication [21].

IP therapy was tolerated remarkably well by our patients. The completion rate of IP cycles prescribed was 80%, and 65% of patients were able to complete all prescribed IP cycles. A smaller joint institutional study, including our institution, performed in 2009 examined outcomes from a similar outpatient regimen and reported that 71% of patients had to discontinue therapy prior to completion [10]. Here, toxicity was short lived and did not typically prevent patients from completing IP therapy. This led to excellent response rates, with 88% of patients having complete response and just 5% experiencing progression. GOG172 utilized second-look laparotomy as an option to determine pathologic response, and found that 57% of patients experienced a complete response within eight weeks. Whereas GOG172 was a large multicenter phase 3 randomized control trial, our current study is limited to a single institutional experience. Other potential biases include its retrospective design, small patient population, relatively short follow-up and potential confounding, which may all impact our results. Moreover, physician bias may help explain decisions to enroll in patients on a clinical trial versus the use of the outpatient docetaxel regimen. Nonetheless, during the study period the described outpatient docetaxel regimen was the preferred regimen for patients not treated on a clinical trial and for the 44 patients with stage III disease, was associated with a median PFS of 22.1 months (95% CI 16.3-28.0 months) with median OS 56.8 months (95% CI 47.3-66.3 months).

In conclusion, this modified IP chemotherapy regimen is safe and well tolerated, which resulted in reduced rates of severe toxicity compared to GOG172, no treatment-related patient deaths, and promising preliminary survival data. As noted by more recent publications, data still supports the use of IP chemotherapy in patients with advanced ovarian cancer. By moving treatment to an outpatient setting and improving the toxicity profile, we anticipate our ability to treat patients will improve, as will our institutional survival rates. Further investigation into this docetaxel-based regimen is warranted.

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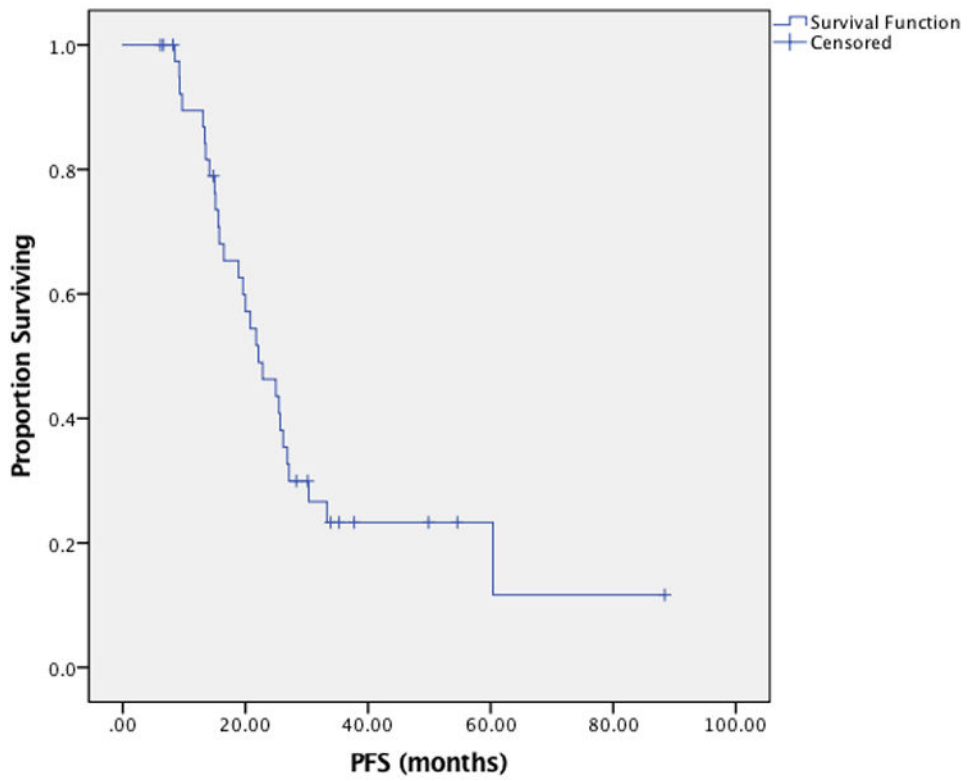
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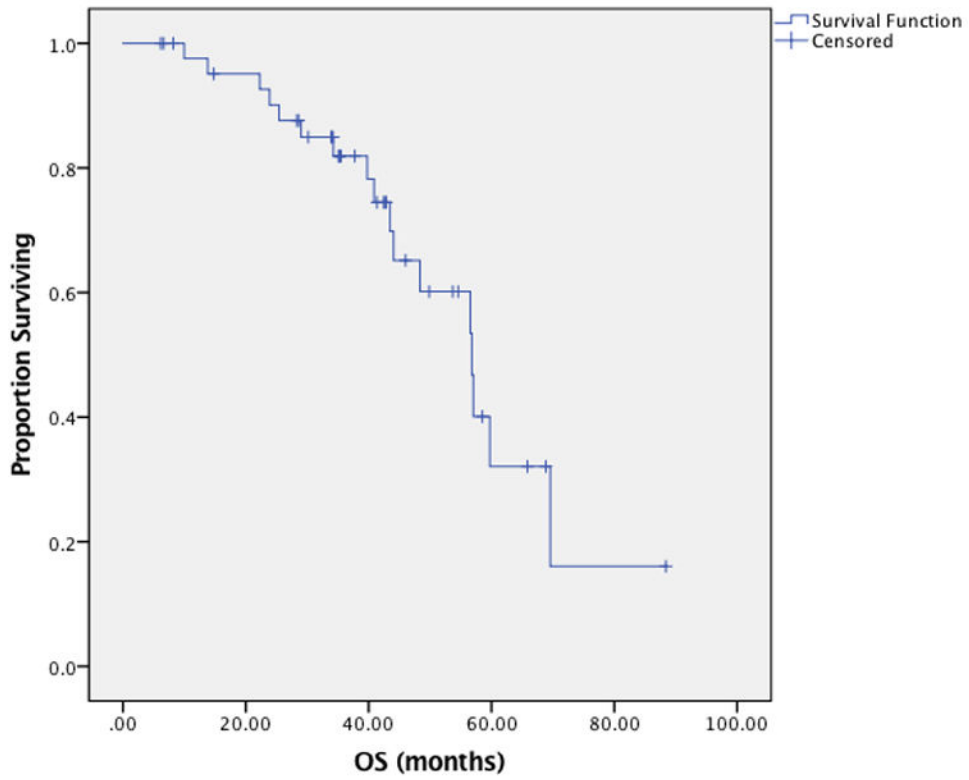
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**Figure 1.** Progression-free survival among patients with stage III ovarian cancer treated with docetaxel based intraperitoneal regimen.



**Figure 2.** Overall survival among patients with Stage III ovarian cancer treated with docetaxel based intraperitoneal regimen.

**Table 1**  
**Outpatient docetaxel-based IP chemotherapy protocol**

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<b>Day 0</b>
<ul style="list-style-type: none"><li>• Dexamethasone 8mg p.o.</li></ul>
<b>Day 1</b>
<ul style="list-style-type: none"><li>• Intravenous pre-hydration of 1Liter (L) 0.9% Saline</li><li>• Pre-chemotherapy IV medications: dexamethasone 10mg, diphenhydramine 50mg, fosaprepitant 150mg, palonosetron 0.25mg, and ranitidine 50mg</li><li>• Intravenous Docetaxel 75mg/m<sup>2</sup>, administered over 1hour (h)</li><li>• Intraperitoneal Cisplatin 75mg/m<sup>2</sup>, to gravity in 1L 0.9% Saline flushed with 500mL 0.9% Saline and administered over 1h</li></ul>
<b>Day 2-5</b>
<ul style="list-style-type: none"><li>• Dexamethasone 8mg p.o.</li></ul>
<b>Day 8</b>
<ul style="list-style-type: none"><li>• Pre-chemotherapy IV medications: dexamethasone, diphenhydramine, fosaprepitant, palonosetron, and ranitidine</li><li>• Intraperitoneal Paclitaxel 60mg/m<sup>2</sup>, to gravity in 1L 0.9% Saline flushed with 500mL 0.9% Saline and administered over 1h</li><li>• Pegfilgrastim 6mg subcutaneously</li></ul>

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**Table 2****Patient demographics (N=60)**

<b>Characteristic</b>	<b>Number (%)</b>
<i>Median age (range)</i>	63 (29-77)
<i>Race</i>	
White	47 (78)
Black	9 (15)
Other	4 (7)
<i>Median BMI (range)</i>	26.6 (16-44)
<i>FIGO stage</i>	
II	13 (22)
IIIA	4 (7)
IIIB	2 (3)
IIIC	38 (63)
IV	3 (5)
<i>Disease site</i>	
Ovary	53 (88)
Fallopian tube	2 (3)
Peritoneal	5 (8)
<i>Histology</i>	
Papillary serous	42 (69)
Endometrioid	5 (8)
Clear cell	1 (2)
Mixed	12 (20)
<i>Debulking status</i>	
No residual disease	20 (33)
Optimal	38 (64)
Suboptimal	2 (3)
<i>IP catheter placement</i>	
Primary	25 (40)
Delayed	35 (60)

**Table 3****Toxicity**

<b>Toxicity</b>	<b>Number (%)</b>
<i>Anemia</i>	15 (25)
<i>Neutropenia</i>	28 (47)
With fever	4 (7)
<i>Thrombocytopenia</i>	2 (3)
<i>Neurological</i>	10 (17)
Function	6 (10)
ADL	4 (7)
<i>Renal</i>	6 (10)
<i>Gastrointestinal</i>	17 (28)
<i>Metabolic</i>	3 (5)
<i>Thromboembolic event</i>	4 (7)
<i>Infection</i>	2 (3)
<i>Fatigue</i>	1 (2)

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**Table 4**  
**IP cycle administration and tolerability**

Measurement	Number (%)
<i>Tolerability</i>	
Cycles prescribed	328
Cycles completed	261 (80)
Patients completing all IP cycles	39 (65)
<i>Dose delay, reduction or alteration</i>	
Delay >1 week (total)	13
Reduction	6 (10)
Alteration (total)	38
<i>Reason for stopping therapy</i>	
Completion	39 (65)
Toxicity	20 (33)
Response plateau	1 (2)
<i>Response</i>	
Complete	53 (88)
Partial	4 (7)
Progression	3 (5)
<i>Status</i>	
No evidence of disease	26 (43)
Alive with disease	14 (23)
Deceased	16 (27)
Unknown	4 (7)

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