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# Phase I feasibility study of intraperitoneal cisplatin and intravenous paclitaxel followed by intraperitoneal paclitaxel in untreated ovarian, fallopian tube, and primary peritoneal carcinoma: A Gynecologic Oncology Group Study

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## Abstract

**Purpose—**Intraperitoneal chemotherapy has shown a survival advantage over intravenous chemotherapy for women with newly diagnosed optimally debulked epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. However, significant toxicity has limited its acceptance. In an effort to reduce toxicity, the Gynecologic Oncology Group conducted a Phase I study to evaluate the feasibility of day 1 intravenous (IV) paclitaxel and intraperitoneal (IP) cisplatin followed by day 8 IP paclitaxel on an every 21-day cycle.

**Methods—**Patients with Stage IIB-IV epithelial ovarian, fallopian tube, primary peritoneal carcinomas or carcinosarcoma received paclitaxel 135 mg/m$^2$ IV over 3 hours followed by cisplatin 75 mg/m$^2$ IP on day 1 and paclitaxel 60 mg/m$^2$ IP on day 8 of a 21 day cycle with 6



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**CONFLICT OF INTEREST STATEMENT**
The authors wish to report that there are no conflicts of interest.

cycles planned. Dose-limiting toxicity (DLT) was defined as febrile neutropenia or dose-delay of greater than 2 weeks due to failure to recover counts, or Grade 3-5 non-hematologic toxicity occurring within the first 4 cycles of treatment.

**Results—**Twenty of 23 patients enrolled were evaluable and nineteen (95%) completed all six cycles of therapy. Three patients experienced a DLT consisting of infection with normal absolute neutrophil count, grade 3 hyperglycemia, and grade 4 abdominal pain.

**Conclusions—**This modified IP regimen which administers both IV paclitaxel and IP cisplatin on day one, followed by IP paclitaxel on day eight, of a twenty-one day cycle appears feasible and is an attractive alternative to the intraperitoneal treatment regimen administered in GOG-0172.

### Keywords

Ovarian cancer; intraperitoneal chemotherapy; cisplatin; paclitaxel; phase I trial

## INTRODUCTION

Ovarian cancer affects nearly 22,000 women on an annual basis and is the cause of death in approximately 14,000 each year.[1] Currently, the optimal management approach requires surgical cytoreduction followed by platinum-taxane based therapy. For those women who have undergone successful surgical cytoreduction to no more than 1cm residual disease, treatment incorporating intraperitoneal (IP) therapy has become an accepted standard of care option.[2] The Gynecologic Oncology Group (GOG) has run the largest Phase III trials of intraperitoneal chemotherapy in ovarian cancer, and each has shown a survival advantage when IP therapy was compared to an IV-only regimen.[3,4,5] The most recent Phase III trial reported was GOG-0172, which compared IV paclitaxel 135 mg/m2 on day 1 and IV cisplatin 100 mg/m2 on day 2, to a regimen of intravenous paclitaxel 135 mg/m2 on day 1, intraperitoneal cisplatin 100 mg/m2 on day 2, followed by intraperitoneal paclitaxel 60 mg/m2 on day 8, with each arm administered on a 21-day cycle.[5] The median progression-free survival for the intravenous and intraperitoneal arms was 18.3 and 23.8 months, respectively. The relative risk of progression was 0.79 (95% CI: 0.63, 0.99) for the intraperitoneal group (p = 0.027, one-sided log-rank test). The median survival for the intravenous and the intraperitoneal arms was 49.7 and 65.6 months, respectively. The relative risk of death was 0.71 (95% CI: 0.54, 0.94) for the intraperitoneal group (p = 0.03, two-sided log-rank test).

Despite these results, the toxicity and port complications associated with the intraperitoneal-containing regimen in GOG 172 was significant. Only 42% of women on the IP arm of GOG-0172 completed the planned 6 cycles of therapy.[5, 6] Long-term sequelae were also problematic with patient-reported neurotoxicity significantly worse for the IP study arm one year post-treatment (p=0.0018).[7] These treatment-related complications ultimately did affect quality of life; compared to those receiving standard intravenous therapy, the IP therapy group had significantly worse quality of life (QOL) prior to cycle 4 (p<0.0001) and 3-6 weeks post-treatment (p=0.0035).[7] However, there were no significant overall QOL differences between arms one year post-treatment.[7]

Efforts to reduce the toxicity of treatment have been a major emphasis on current intraperitoneal trials conducted by the Phase I Subcommittee of the GOG. One potential means of improving intraperitoneal treatment would be to deliver combined intravenous and intraperitoneal treatment on the same day, which would negate the need for hospital admission or an additional day of outpatient therapy in the first week. While paclitaxel infusion of 175 mg/m2 over three hours has been shown to be equivalent to 24-hr paclitaxel infusion of 135 mg/m2 in platinum regimens, there remains a concern over prohibitive

neurotoxicity when cisplatin is given on the same day as the taxane.[8,9] However, given that the pharmacokinetics of intraperitoneal cisplatin administration shows delayed absorption compared to intravenous administration, we hypothesized that the neuropathy risk may be minimized with same day administration.[10, 11, 12] Additionally, cisplatin-related toxicities should be further ameliorated by reducing the dose to 75 mg/m2, from 100 mg/m2 used in GOG 172. This together with standard pre- and post-hydration should reduce the metabolic and renal complications of treatment.

We report the results of a Phase I feasibility study to evaluate an alternative regimen to GOG 172 conducted in the Phase I Subcommittee of the Gynecologic Oncology Group.

## PATIENTS AND METHODS

### Eligibility Criteria

Patients with a histologic diagnosis of epithelial ovarian carcinoma, fallopian tube adenocarcinoma, peritoneal primary carcinoma or carcinosarcoma, as verified by submission of the local institutional pathology report, were eligible. International Federation of Gynecology and Obstetrics (FIGO, 1985 Staging System) Stages IIB, IIC, III or IV were included, and patients could have had either optimal or suboptimal residual disease. All patients must have undergone an appropriate debulking surgery and enrolled within 12 weeks of surgery. All patients were required to have a GOG performance status of 0, 1, or 2, and measurable disease was not required. Laboratory criteria for eligibility included an absolute neutrophil count (ANC) ≥ 1,500/μL, platelet count ≥ 100,000/μL, creatinine ≤ 1.5 times upper limit of normal (ULN), bilirubin ≤ 1.5 times ULN, alkaline phosphatase and aspartate aminotransferase (SGOT) ≤ 2.5 times ULN using the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI CTCAE v3). Patients with baseline hearing loss were allowed to participate provided they had a baseline audiogram; repeat evaluation was recommended after cycles three and six or with complaints of tinnitus or hearing loss. All patients gave written informed consent and authorization to release personal health information before study entry in compliance with institutional, state, and federal regulations. The study required IRB approval prior to local institutional enrollment.

### Treatment Plan

On day 1 of each 21-day cycle, patients received paclitaxel 135 mg/IV over 3 hours followed by cisplatin 75 mg/m$^2$ IP and returned on day 8 to received paclitaxel 60 mg/m$^2$ IP. Treatment was continued for a total of six cycles.

Routine premedication to prevent hypersensitivity, nausea, and vomiting was used and included steroids, histamine blocking agents and antiemetics. Intraperitoneal cisplatin or paclitaxel was reconstituted in 1 liter of warm normal saline and infused through the peritoneal catheter as rapidly as possible. It was preferred that the patient receive an additional liter of normal saline in the peritoneal cavity afterward. The patient was asked to change position at 15-minute intervals for two hours to ensure adequate intra-abdominal distribution. No attempt was made to retrieve infusate, although ascites could be drained prior to infusion if a large amount was present.

### Dose-Limiting Toxicity

The primary endpoint of the study was defined as the number of patients who experience at least one dose-limiting toxicity (DLT), using NCI CTCAE v 3.0 or delay in therapy for more than two weeks during the first four cycles of treatment. Any of the following deemed at least possibly related to the regimen constituted a DLT: febrile neutropenia of unknown origin without clinically or microbiologically documented infection when ANC is <1,000/

μL; grade 4 thrombocytopenia with platelet nadir of <25,000/μL or clinically significant bleeding with grade 3 thrombocytopenia; any treatment-related death; and any non-hematologic grade 3 or 4 adverse event with the exceptions of grade 3 fatigue or hypersensitivity reaction, grade 3 nausea and vomiting, grade 3 dehydration (as a result of nausea and vomiting), grade 3 constipation or anorexia, or grade 3 electrolyte abnormalities (hypocalcemia, hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia) lasting for less than 7 days. Patients who experienced catheter-related complications were non-evaluable and replaced.

## Treatment Evaluations

Laboratory parameters were obtained within 14 days prior to initiation of protocol therapy and repeated within 4 days of subsequent cycles. Toxicity assessments were collected prior to each cycle and all toxicity was followed to resolution. Patients enrolled with measurable disease were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) Criteria 1.0.[13] Imaging evaluations consisted of chest imaging (chest x-ray or computerized tomography [CT]) and CT of the abdomen and pelvis was required within 28 days of the start of protocol therapy and within 4 to 12 weeks of completion of treatment. Follow-up CT scans were performed otherwise if clinically indicated. Patients who received any treatment were evaluable for both toxicity and response (if measurable). Patients who withdrew from therapy before the completion of 4 cycles of therapy for reasons unrelated to treatment toxicity were considered inevaluable for DLT assessment (this included patients who withdrew for disease progression).

## Dose Adjustments

Day 1 treatment was delayed if any of the following toxicities were present on the day of treatment: absolute neutrophil count (ANC) less than 1,500 cells/μL (or 1000 cells/μL if patient had received filgrastim), platelet count less than 100,000 cells/μL, or creatinine greater than 2.0 mg%. However, day 8 treatment with paclitaxel was only delayed for grade 2 or greater neuropathy, catheter failure or acute abdominal pain.

Day 1 treatment was modified to paclitaxel administered intravenously at 110 mg/m2 and cisplatin at 50 mg/$m^2$ for the first occurrence of any of the following: grade 3 or greater febrile neutropenia, grade 4 neutropenia lasting more than 7 days, grade 3 thrombocytopenia with bleeding, or grade 4 thrombocytopenia. Patients experiencing grade 3 or 4 hepatotoxicity had a dose reduction of paclitaxel to 110 mg/$m^2$ but no change in the cisplatin dose. Patients experiencing grade 4 neuropathy were discontinued from protocol. There were no modifications made to day 8 intraperitoneal treatment with paclitaxel.

## Statistical Analysis

This study aimed to evaluate the feasibility of this regimen during the initial 4 cycles of therapy by assessing the tolerability through dose limiting toxicities. The study plan used a 2-stage group sequential design where twenty (20) patients were entered in each stage of the trial. If eight or more DLTs occurred in the first 20 patients treated, then the regimen was declared not feasible for Phase III investigation. If no more than four adverse events occurred in the first 20 patients treated and medical judgment indicated, then the trial was stopped with the regimen considered feasible for Phase III investigation. If there were between five and seven adverse events observed during the first stage of accrual and medical judgment indicated, the regimen would enroll a second cohort. If 12 or more adverse events occurred in a total of 40 patients, the regimen was considered not feasible. If 11 or fewer events occurred, the regimen was considered feasible for a Phase III investigation.

If the true event rate for this regimen is 40%, the design provided a 90.6% chance of classifying the regimen as not feasible, with a 58.4% chance reaching this conclusion before beginning the second stage. If the event rate is 20%, the design provided a 91.1% chance of classifying the regimen as feasible and a 63.0% chance of reaching this conclusion before beginning the second stage.[14, 15]

# RESULTS

## Patient Demographics

Between April and September 2009, twenty-three patients were enrolled. The demographics of this population are summarized in Table 1. The median age was 59 (range, 33-78) and the majority had a performance status of 0-1. All patients underwent a surgical debulking procedure. Seventy percent were Stage III at diagnosis and 17% were Stage IV. Seventeen patients (74%) had an ovarian primary tumor at diagnosis and 65% were serous histology. Nine (39%) were cytoreduced to no gross residual disease and 7/23 (30%) were reduced to <1cm at the end of surgery. The remaining 7 (30%) had 1cm (n=6) or >1cm (n=1) residual disease. Post-operative reports indicate that four patients (17.4%) had bowel surgery as part of their tumor debulking; 3 had a rectosigmoid resection and 1 patient had resection of the terminal ileum.

## Toxicities

Of the twenty-three patients enrolled in the first cohort, three were replaced due to a port malfunction prior to IP paclitaxel on cycle 3 day 8 (n=1), grade 4 hypersensitivity reaction to the first treatment of intravenous paclitaxel given on Day 1 (n=1), and refusal of further treatment after cycle 1 day 1 (n=1). The last patient required hospitalization one week after her first treatment with grade 3 nausea and vomiting, as well as grade 2 pain involving her chest and abdomen felt to be port-related, which prompted her refusal of further therapy. Subsequent to her withdrawal, she was diagnosed with a port-site cellulitis in the context of grade 3 neutropenia, which also required admission to the hospital for further treatment.

Of twenty evaluable patients, there were three DLTs. One patient experienced a grade 3 urinary tract infection with a normal absolute neutrophil count and another experienced grade 3 hyperglycemia. The last patient, who had undergone a rectosigmoid resection as part of her debulking surgery, experienced grade 4 constipation and abdominal pain which was listed as at least possibly related to her first dose of intraperitoneal cisplatin. She subsequently required emergent surgery for a presumed intestinal perforation. However, at surgery she was felt to have an anastomotic leak. This patient also experienced grade 4 thrombocytopenia, grade 3 anemia, and grade 3 leukopenia and was taken off protocol therapy. Given that only 3 DLTs occurred in these patients, the study enrollment was stopped and the regimen was considered feasible. Adverse events that occurred in the 20 evaluable patients are given in Table 2.

Among all patients (n=23) hematologic toxicity consisted of grade 3 anemia in 4 patients and grade 3-4 leukopenia in 4. Nine patients had neutropenia (grade 3 in five; grade 4 in four) though none persisted for greater than 14 days. There were no incidences of grade 3-4 thrombocytopenia. There were few serious non-hematologic toxicities noted. Five patients experienced grade 3 metabolic derangements (hypokalemia, hyponatremia, hypophosphatemia, and hypocalcemia) over the entire regimen. Gastrointestinal toxicities were the predominant toxicities, though these were mild in severity. Fourteen patients (61%) experienced sensory neuropathy which was grade 1-2 severity in all but one. Cumulative toxicity in all patients treated is given in Table 3.

### Response Rate

Eighteen of the 20 (90%) evaluable patients completed the protocol defined therapy of six cycles. One patient discontinued treatment after her fifth cycle due to progression of disease.

Nine of 20 evaluable patients had measurable disease at the beginning of treatment and of these, one partial response (11.1%) was confirmed; three additional partial responses were reported, but not confirmed on repeat imaging and are therefore reported as stable. Overall, four of 9 patients (44%) had stable disease and four progressed during treatment (44%). Because these patients were evaluated greater than two months after study entry, they are reported as "indeterminate" by RECIST. Eighteen of 23 patients were evaluable for response using GCIG criteria.[16] Twelve met criteria for a full response by CA-125 (67%) and an additional 2 patients (11%) had a partial response, for an overall response rate of 78%. Four others did not meet criteria for response; 2 did not experience a significant reduction in their CA-125 while on treatment and the other two had insufficient data to gauge their response by CA-125. Response data is summarized in Tables 4 and 5.

## DISCUSSION

This study represents a feasibility evaluation of an alternative IV/IP regimen from that used in GOG-0172. In this experience, we report that 90% of patients completed all six cycles of treatment with a manageable toxicity profile and few severe neuropathic adverse events. Thus, as planned in the statistical design of the study, it was closed in the first stage, as it fulfilled protocol criteria of a feasible regimen. It is noted that the threshold number of DLTs for opening the study to a second stage would have increased or stayed the same if the actual number of evaluable patients increased. Therefore, including or excluding the patient who withdrew from the therapy during cycle 1 and later experienced a grade 3 port-site cellulitis would have no impact on the study conclusions since the total number of DLTs was less than or equal to four.

Several interesting points are worthy of further mention. There were few port malfunctions experienced and only one patient was taken off the study due to port problems. This low rate of port malfunctions may be due to the more common placement of catheters at the time of initial surgery using the insertion procedure mandated by the GOG Surgical Manual and to the commitment to intraperitoneal therapy within the investigators and staff participating in limited institution GOG Phase I trials. In this study, the incidence of grade 3-4 neuropathy is 4.3%. This is lower than the neuropathic rate seen in the IV-only arm of GOG-0172, where the incidence of grade 3-4 neuropathy was 8.6%, as opposed to 19% IV/IP therapy.[5] Thus, it appears that this modification may also mitigate the neuropathic toxicity when delivering intraperitoneal cisplatin and paclitaxel.

The primary objective of this study was to assess feasibility of the schedule, not to evaluate response rate or survival. In addition, the majority of patients entered with no gross or optimally cytoreduced disease (69%) and less than half (43%) entered with measurable lesions on their post-operative CT scan. In light of this, we analyzed response by CA-125 using GCIG criteria, which has been shown to be both accurate and comparable to standard RECIST criteria.[17] Using CA-125, the overall response was 78% with 12 of 18 (67%) achieving a full response.

One of four patients who underwent a rectosigmoid resection as part of their primary surgery had an adverse event (Grade 4 constipation) and subsequently was found to have an anastomotic leak. Given this, further conclusions regarding IP treatment in the context of bowel resection cannot be drawn from this experience. Overall, however, there were little hematologic or non-hematologic toxicity reported with this modified regimen. Beyond

metabolic derangements, nausea and vomiting expected with cisplatin, the toxicity profile was tolerable and did not change significantly between the first four cycles or at the end of cycle 6. This likely explains the rate of completion of therapy, which at 90% improves on the completion rate of GOG-0172, where it was reported to be 42%,[5] and also exceeds that of IP carboplatin, reported at 75% in an earlier phase I study by Morgan, et al.[18]

There are several ongoing studies evaluating the optimal treatment of ovarian cancer. Among them, open to optimally resected patients, is GOG 252, a three-arm randomized study utilizing bevacizumab in combination with one of 3 regimens: IV carboplatin D1 with weekly IV paclitaxel D1, D8, D15, IP carboplatin and IP paclitaxel delivered on D1, or GOG-172 (IV paclitaxel D1, IP carboplatin D8, and IP paclitaxel D15).[19] Another ongoing study is looking at the triple angiokinase inhibitor, BIBF1120, in combination with IV carboplatin and IV paclitaxel.[20] Taken in this context, the role of IP therapy, whether using cisplatin or carboplatin, especially in combination with biologic agents such as the angiogenesis inhibitors, remains an area of active study. Still, in the face of the significant survival results reported by Armstrong et al. in GOG-172, any attempts to improve tolerability of IP treatment should be taken seriously.

In conclusion, this Phase I trial has identified a potentially feasible replacement regimen to GOG-0172. While the number of patients treated on this study was small, the endpoints met the protocol-defined criteria for consideration in a Phase III trial. Whether these results will be realized at institutions that do not routinely offer intraperitoneal treatment requires further scrutiny. Thus, it warrants further investigation as we aim to improve upon and increase physician acceptance of intraperitoneal therapy in ovarian, fallopian tube, and primary peritoneal cancers.

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1. We demonstrate that IP cisplatin delivered on the same day as IV paclitaxel, and then followed by IP paclitaxel on Day 8 is feasible.
2. The completion rate using this modified GOG-172 regimen was 95% (20 of 23 completing 6 planned cycles).
3. The rate of Grade 2 or greater sensory neuropathy was only 8% (2 of 23).

**Table 1**
**Patient and Clinical Demographics (n=23)**

| **Median Age (Range)** | **59 (33-78) N (%)** |
|---|---|
| RACE | |
| White | 22 (95) |
| African American | 1 (5) |
| PERFORMANCE STATUS | |
| 0 | 12 (52) |
| 1 | 10 (43) |
| 2 | 1 (4) |
| MEASURABLE DISEASE | |
| Yes | 10 (43) |
| No | 13 (57) |
| TUMOR ORIGIN | |
| Ovary | 17 (74) |
| Fallopian Tube | 1 (4) |
| Peritoneum | 5 (22) |
| STAGE | |
| II | 3 (13) |
| III | 16 (70) |
| IV | 4 (17) |
| CYTOREDUCTION STATUS | |
| No gross residual | 9 (39) |
| <1cm | 7 (30) |
| ≥1cm | 7 (30) |
| BOWEL RESECTION PERFORMED | |
| None | 19 (83) |
| Ileum | 1 (4) |
| Rectosigmoid | 3 (13) |
| TUMOR HISTOLOGY | |
| Serous | 15 (65) |
| Endometrioid | 2 (9) |
| Clear Cell | 3 (13) |
| Other | 3 (13) |
| TUMOR GRADE | |
| 1 | 2 (9) |
| 2 | 3 (13) |
| 3 | 18 (78) |

**Table 2**

**Cumulative Adverse Events in Evaluable Patients (n=20)**

| AE Category | CTCAE v3.0 Grade | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | Total |
| **Allergy/Immunology** | 15 | 4 | 0 | 1 | 0 | 0 | 20 |
| **Bone Marrow** | | | | | | | |
| Anemia | 0 | 8 | 8 | 4 | 0 | 0 | |
| Leukopenia | 3 | 7 | 7 | 1 | 2 | 0 | |
| Neutropenia | 8 | 0 | 4 | 5 | 3 | 0 | 20 |
| Thrombocytopenia | 13 | 7 | 0 | 0 | 0 | 0 | |
| Other | 19 | 1 | 0 | 0 | 0 | 0 | |
| **Auditory/Ear** | 17 | 0 | 3 | 0 | 0 | 0 | 20 |
| **Cardiac** | 19 | 1 | 0 | 0 | 0 | 0 | 20 |
| **Constitutional** | 3 | 12 | 4 | 1 | 0 | 0 | 20 |
| **Dermatologic** | 3 | 3 | 14 | 0 | 0 | 0 | 20 |
| **Gastrointestinal** | | | | | | | |
| Nausea | 4 | 14 | 1 | 1 | 0 | 0 | |
| Vomiting | 13 | 5 | 1 | 1 | 0 | 0 | 20 |
| Other | 0 | 13 | 6 | 0 | 1 | 0 | |
| **Infection** | 17 | 0 | 2 | 1 | 0 | 0 | 20 |
| **Lymphatic** | 19 | 1 | 0 | 0 | 0 | 0 | 20 |
| **Metabolic** | 5 | 5 | 7 | 3 | 0 | 0 | 20 |
| **Neurologic** | | | | | | | |
| Neurosensory | 9 | 10 | 1 | 0 | 0 | 0 | 20 |
| Other | 15 | 4 | 1 | 0 | 0 | 0 | |
| **Ocular/Visual** | 17 | 3 | 0 | 0 | 0 | 0 | 20 |
| **Pain** | 6 | 10 | 4 | 0 | 0 | 0 | 20 |
| **Pulmonary** | 17 | 2 | 1 | 0 | 0 | 0 | 20 |

Abbreviation: CTCAE v.3.0: National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 3.0

**Table 3**

**Cumulative Toxicity seen in All Patients (n=23)**

| AE Category | CTCAE v3.0 Grade | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | Total |
| **Allergy/Immunology** | 17 | 4 | 0 | 1 | 1 | 0 | 23 |
| **Bone Marrow** | | | | | | | |
| Anemia | 0 | 6 | 13 | 4 | 0 | 0 | |
| Leukopenia | 4 | 6 | 9 | 2 | 2 | 0 | |
| Neutropenia | 7 | 0 | 7 | 5 | 4 | 0 | 23 |
| Thrombocytopenia | 13 | 8 | 2 | 0 | 0 | 0 | |
| Other | 20 | 0 | 2 | 1 | 0 | 0 | |
| **Auditory/Ear** | 19 | 0 | 4 | 0 | 0 | 0 | 23 |
| **Cardiac** | 21 | 1 | 0 | 1 | 0 | 0 | 23 |
| **Constitutional** | 5 | 12 | 4 | 2 | 0 | 0 | 23 |
| **Dermatologic** | 4 | 4 | 15 | 0 | 0 | 0 | 23 |
| **Gastrointestinal** | | | | | | | |
| Nausea | 4 | 14 | 3 | 2 | 0 | 0 | |
| Vomiting | 9 | 9 | 3 | 2 | 0 | 0 | 23 |
| Other | 2 | 12 | 8 | 0 | 1 | 0 | |
| **Hemorrhage** | 22 | 1 | 0 | 0 | 0 | 0 | 23 |
| **Infection** | 16 | 0 | 4 | 3 | 0 | 0 | 23 |
| **Lymphatic** | 22 | 1 | 0 | 0 | 0 | 0 | 23 |
| **Metabolic** | 6 | 6 | 6 | 5 | 0 | 0 | 23 |
| **Neurologic** | | | | | | | |
| Neurosensory | 9 | 12 | 1 | 1 | 0 | 0 | 23 |
| Other | 17 | 5 | 1 | 0 | 0 | 0 | |
| **Ocular/Visual** | 20 | 3 | 0 | 0 | 0 | 0 | 23 |
| **Pain** | 5 | 12 | 5 | 1 | 0 | 0 | 23 |
| **Pulmonary** | 19 | 3 | 1 | 0 | 0 | 0 | 23 |

Abbreviation: CTCAE v.3.0: National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 3.0

## Table 4
**Overall Response Rate Among Measurable Patients (n=9)**

| Response category | N (%) |
|---|---|
| Complete response (CR) | 0 |
| Partial response (PR) | 1 (11.1) |
| Stable Disease (SD) | 4 (44.4) |
| Indeterminate (ID) | 4 (44.4) |

**Table 5**
**Overall Response Rate by GCIG CA-125 criteria (n=18)**

| Response category | N (%) |
|---|---|
| Full response | 12 (67) |
| Partial response | 2 (11) |
| Other | 4 (22) |
| Not Evaluable | 5 (28) |

GCIG, Gynecologic Cancer Intergroup