Published in final edited form as:
Int J Gynecol Cancer. 2013 November ; 23(9): . doi:10.1097/IGC.0b013e3182a809e0.

A Phase II Study of Oxaliplatin Combined with Continuous Infusion Topotecan for Patients with Previously Treated Ovarian Cancer

Stacey M. Stein[1], **Amy Tiersten**[2], **Howard S. Hochster**[1], **Stephanie V. Blank**[3], **Bhavana Pothuri**[3], **John Curtin**[3], **Ilan Shapira**[4], **Benjamin Levinson**[5], **Percy Ivy**[6], **Benson Joseph**[2], **Achuta K. Guddati**[7], and **Franco Muggia**[2]

[1]Division of Medical Oncology, Department of Medicine, Yale School of Medicine, New Haven, CT

[2]Division of Medical Oncology, Department of Medicine, New York University School of Medicine, New York, NY

[3]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, New York University School of Medicine, New York, NY

[4]Beth Israel Cancer Center, Albert Einstein College of Medicine, NY, USA, New York University School of Medicine, New York, NY

[5]Division of Biostatistics, Department of Population Health, New York University School of Medicine, New York, NY

[6]Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD

[7]Department of Internal Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Abstract

Background—Phase II trials suggest that prolonged intravenous (IV) infusion of the topoisomerase-1 inhibitor topotecan may be less toxic than when given by standard IV bolus 5-day administration. Oxaliplatin exhibits efficacy in platinum- pretreated disease and shows preclinical synergy with topoisomerase-I inhibitors. We sought to determine the efficacy and safety of oxaliplatin plus infusion topotecan in recurrent platinum-pretreated ovarian cancer.

Methods—Patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers previously treated with 1–2 prior regimens including a platinum and taxane received oxaliplatin (85 mg/m^2 day 1, 15) and topotecan (0.4 mg/m^2/day) by continuous IV infusion over 14 days every 4 weeks. The primary objective of the trial was to estimate the objective response rate in platinum-resistant disease (stratum I) and in platinum-sensitive disease (stratum II). Toxicities were assessed in all patients.

Results—Thirty-eight patients received 144 cycles of therapy (median 4, range 1–6). The most common grade 3/4 toxicities included thrombocytopenia (37% grade 3, 19% grade 4), neutropenia (37% grade 3, 11% grade 4) and anemia (15% grade 3). Response occurred in 4 of 19 patients in stratum I (21%, 95% confidence intervals [CI] 6%, 46%) and 9 of 19 patients in stratum II (47%, 95% CI 24%, 71%). Three in each stratum had lengthy complete responses.

Presented in part at the American Society of Clinical Oncology June 2010 Meeting

Disclosures: The authors report no disclosures or conflicts of interest.

Conclusions—Biweekly oxaliplatin plus a 14-day continuous IV infusion of topotecan, given monthly, is an active regimen in platinum-pretreated ovarian cancer and merits additional evaluation.

Introduction

Epithelial carcinoma of the ovary, fallopian tube, or peritoneum is the fifth leading cause of cancer death among women in western countries [1, 2]. Most patients present with advanced stages: 75% of patients are stage III or IV at diagnosis with only 18% of stage IV patients expected to be alive 5 years after diagnosis [3]. Carboplatin and paclitaxel have become the current standard first-line chemotherapy treatment after optimal debulking surgery. While this treatment yields high response rates, the disease usually recurs [4]. New salvage therapies are needed, particularly for ovarian cancer that is platinum-resistant (usually defined as a platinum free interval of less than 6 months).

Oxaliplatin, a DACH (diaminocyclohexane) substituted platinum, creates DNA-platinum adducts bulkier and more hydrophobic than cisplatin, that are not easily excised by DNA mismatch repair mechanisms [5]. In addition, ovarian cell lines resistant to cisplatin and carboplatin can still be sensitive to oxaliplatin [6]. In fact, oxaliplatin has been shown to have some activity in both platinum-sensitive and platinum-resistant disease [7].

In an earlier study with a 21-day topotecan infusion in heavily pretreated ovarian cancer patients we obtained an overall response rate (ORR) of 38% (CR 24%) with a favorable toxicity profile [8, 9]. Continuous infusion topotecan was shown to cause increased enzyme depletion of topoisomerase-I, the target of topotecan [9]. In subsequent studies of continuous topotecan infusion combined with cisplatin as first-line therapy [10] or with pegylated liposomal doxorubicin in pretreated patients [11], the regimens were found to have considerable anti-tumor activity but with myelosuppression often dose-limiting. In a subsequent phase I study, continuous topotecan was coupled with oxaliplatin for patients with previous treated ovarian cancer [12]: it was given by continuous IV infusion over 14 days and combined with oxaliplatin given on days 1 and 15 every 28 days. A recommended phase II dose for both oxaliplatin (85 mg/m^2) and topotecan (0.4 mg/m^2/day x 14 days)[12] was defined. This regimen was tolerable and less myelosuppressive than in the preceding study of topotecan combined with cisplatin [10, 12] in a less pretreated population; objective responses were observed at all dose levels: six of 22 patients (RR 27%, 95% confidence intervals 11%, 50%) with platinum-pretreated disease, and five of the responses were complete. Therefore, we sought to initiate this phase II trial and explore its activity in this recurrent setting stratified by whether these were considered platinum-sensitive or platinum-resistant.

Materials and Methods

Patients

This was a single arm non-randomized phase II trial with the primary objective of assessing response rates stratified separately in platinum-resistant, and platinum-sensitive cohorts. A two-stage design was applied in each stratum with response rates after 2 cycles of treatment as a criterion for going on to a second stage (see statistical considerations). Stratum I (platinum-resistant) included patients recurring after a disease-free interval following platinum-based therapy of less than or equal to 6 months and/or progression on a platinum-containing regimen. Stratum II (platinum-sensitive) included patients with a disease-free interval following platinum-based therapy of greater than 6 months. Patients had histologically or cytologically proven, previously treated, epithelial ovarian, primary peritoneal, or fallopian tube cancer. Eligibility criteria also included age ≥ 18 years old,

minimum life expectancy of 4 months, and a Karnofsky Performance Status >/= 70. Adequate hematopoietic (absolute neutrophil count >/=1500/mm^3, platelet count >/= 100,000/μL), hepatic [bilirubin <1.5 times the institutional upper limit of normal (IULN) or aspartate and alanine aminotransferases <2.5 times the IULN (unless liver metastases were present and documented at baseline by radiographic images, and then the patient was eligible unless these levels were > 5 times the IULN)], and renal (creatinine <1.5 times the IULN and creatinine clearance >40) function was also required. Growth factors were only used if a patient was hospitalized for febrile neutropenia; otherwise patients were delayed.

Measurable or evaluable disease was required as defined by the RECIST criteria, version 1.0 [13]. Measurable disease was characterized as lesions reproducibly measurable in one dimension according to RECIST criteria. Evaluable (non-measurable) disease included CA125 levels >50 U/ml on two occasions at least one week apart. The number of allowed prior chemotherapy regimens were two: the initial (required) taxane- and platinum-based regimen (including intraperitoneal or IV consolidation) and an additional non-platinum and non-topotecan chemotherapy regimen. In addition, any number of biologic therapies were permitted.

Patients with measurable disease were assessed using RECIST criteria for determination of response/progression. Patients with evaluable disease were assessed for response/progression by using the Gynecologic Cancer Intergroup Committee (GCIC) including CA-125 measurements [14]. Patients with elevated CA-125 at entry were considered to have a partial response if the CA-125 decreased by >50% but remained above the upper limit of normal range (35 U/ml) and confirmed on a subsequent determination at least one month later. Patients with an abnormal baseline CA-125 decreasing to the normal range confirmed one month later were considered to have a complete response. Progressive disease (PD) was defined on the basis of a confirmed doubling of CA-125 levels from the upper limit of normal or the nadir CA-125 level, confirmed one month later. Stable disease included any CA125 change that did not fit the definition of PD, PR, or CR. In patients with both measurable and evaluable disease, the overall clinical response was the worst of the two confirmed observed responses [13, 15].

Treatment

Oxaliplatin 85 mg/m^2 was given as a 2 hour infusion on Day 1 and Day 15 of each 4 week cycle. For patients with a creatinine clearance > 60, topotecan 0.4 mg/m^2/day was given as a continuous infusion for 14 days beginning on Day 1. Topotecan was administered by Computerized Ambulatory Drug Delivery (CADD) pump in 50 ml of D5W for the correct dose to be infused at 6 ml/day x 7 days with weekly cassette changes. For patients with a creatinine clearance between 40 – 60 ml/min, the topotecan starting dose was 0.3 mg/m^2/day. Therapy consisted of a maximum of six four-week treatment cycles. Treatment was discontinued at disease progression. During treatment, disease response was assessed every two treatment cycles.

Dose modifications

New cycles were not started until the neutrophil count was >= 1,500/mm^3 and platelet count was >= 100,000/μL, recovery from mucositis or diarrhea to grade 1 or less had occurred, as well as recovery from skin toxicity to grade 1 or less. If the Day 1 dose of oxaliplatin was held, then topotecan was also held. Day 8 topotecan infusion was interrupted for ANC <500/μL, platelets < 50,000/μL, or a grade 3 nonhematologic toxicity. Day 15 oxaliplatin dose was given only if ANC >1.0/mm^3 and platelets > 100,000/μL.

Statistical considerations

For each stratum, the minimax two-stage design for phase II clinical trials was used to determine sample size [16]. For stratum I, a response rate at 2 cycles of at least 20% would justify further study of this treatment regimen whereas a rate of 5% or less would be considered uninteresting. The sample size at first stage for stratum I was set at 13, where 1 or more responses observed at 2 cycles would warrant continuing to the second stage with an additional 14 patients. Four or more responses observed at 2 cycles among the total of 27 patients from both stages would be considered sufficiently active to warrant further study in future trials. For this design the alpha error probability was 0.05 and the beta error probability was 0.20. For stratum II, a response rate at 2 cycles of at least 30% would justify further study of this treatment regimen whereas a rate of 10% or less would be considered uninteresting. The first stage was set at 15, where 2 or more responses observed at 2 cycles would warrant continuing to the second stage with an additional 10 patients. Six or more responses observed at 2 cycles among the total of 25 patients from both stages would be considered sufficiently active to warrant further study in future trials. For this design the alpha error probability was also 0.05 and the beta error probability was 0.20. The probabilities for early closure of stratum I with a true response of 5% was 0.51 for stratum I, and for early closure of stratum II with a true response rate of 10% was 0.55. We sought substantial improvements in baseline (i.e., topotecan alone) expectations upon adding oxaliplatin. The best data for the activity of topotecan in relation to platinum sensitivity comes from the second-line trial of Gordon et al comparing topotecan with Doxil[17]. We assumed that baseline topotecan response would be lower because of the additional lines of therapy, particularly in the platinum-sensitive stratum. The overall response rate was estimated in each stratum, with an exact 95% confidence interval. Patients with PD status at the time of assessment along with patients who did not complete 2 cycles of treatment were considered as non-responders. Time to progression (TTP) was calculated in each of the strata from the first date on study to date of progression or death (any cause) whichever occurred first. Any patient with PD, either by RECIST or CA125 criteria, before or after 2 cycles was counted as an event. For the purposes of the statistical analysis, the date of the actual scan (using RECIST) or blood test (using CA-125) were used as date of progression; a patient alive and progression-free at the end of study was censored. All treated patients were included in Kaplan-Meier analyses and patients alive and progression-free at the end of study were censored. The Kaplan-Meier method was used to plot the TTP curve and to estimate the median TTP with a 95% Confidence Interval (based on the sign test) in each of the two strata. Overall survival (OS) was also calculated from the date on study to date of death (any cause).

Informed consent and regulatory approval

The study was reviewed and approved by the Cancer Evaluation Therapy Program of the National Cancer Institute (P56317), and by the institutional review board (IRB) at each participating institution (ClinicalTrials.gov identifier NCT00313612).

Results

Patient characteristics

Thirty-eight patients entered the study between January 2006 and March 2010 at 3 institutions, and their characteristics are shown in Table 1. Nineteen patients were enrolled in stratum I (platinum-resistant) and 19 in stratum II (platinum- sensitive). The median age was 60 (range, 38 to 80 years). Nineteen patients had 1 prior regimen and 19 patients had 2; 32 patients had epithelial ovarian cancer, 4 had primary peritoneal cancer and 2 patients had fallopian cancer.

Treatment administered

The 38 treated patients received 144 cycles of therapy. The median number of treatment cycles was 4 (range 1–6 cycles). Reasons for discontinuing therapy included toxicity, patient preference to not have a pump, and progression of disease. Eight patients discontinued before 2 cycles (4 for predefined toxicity, 3 by patient/physician choice, 1 had progressive disease). Twenty-seven patients had day 15 oxaliplatin held at least once, 13 patients required dose reductions, and 30 patients had treatment delays, mainly for thrombocytopenia. No patients had neutropenic fever.

Toxicity

Hematological toxicities were the most common adverse events. Both hematological and nonhematological toxicities are shown in Table 2. The most common grade 3 and 4 toxicities included thrombocytopenia (21% grade 3, 18% grade 4), neutropenia (26% grade 3, 13% grade 4) and anemia (13% grade 3). Five patients in the platinum resistant group received a total of 14 units of packed red blood cells and 1 patient received platelet transfusions. Four patients in the platinum sensitive group received a total of 8 units of packed red blood cells and two patients each received platelet transfusions. After three patients required platelet transfusion we noted that among patients entered there were 3 with a creatinine clearance between 40–60 ml/min, two of whom developed grade 4 thrombocytopenia. Accordingly, the protocol was amended to decrease the dose of topotecan to 0.3 mg/m^2/day in patients with borderline decreases in renal function. However, all patients enrolled after the amendment had creatinine clearances >60.

Response data

The response data are shown in Table 3. Activity after cycle 2 assessments to proceed to a second stage were met for both strata (2 CR and 2 PR of 13 for stratum I, and 2 CR and 6 PR out of 15 in stratum II). Response eventually occurred in 4 of 19 patients in stratum I (21%, Exact 95% confidence intervals [CI] 6%, 46%) and 9 of 19 patients in stratum II (47%, Exact 95% CI 24%, 71%). Noteworthy were 6 complete responses out of 38 patients (16%) with 3 CRs that were eventually documented in each stratum, with 1 CR in each having taken place at subsequent reassessments in responding patients. In stratum I, a patient was lost to follow-up 8 months after achieving a CR after completing treatment; while the two other patients showed progression at 8 months in one, and continued CR at 57 months in the other. The PR in this stratum lasted 5 months, whereas 7 were stable 3 to 7.5 months and an additional patient for 18 months. In the platinum sensitive stratum two of the CRs lasted 13 months each, and one remains in CR 64 months after protocol treatment. In these platinum-sensitive patients five PRs lasted from 5, 6, 14, 16, and 19.5 months, and a sixth PR patient refusing further assessments at 16 months. Stable disease was documented to last 3, 4, 14, and 15.5 months before progressing. Informal analysis of these data (readily available to the lead investigator) indicated sufficient activity including complete responses to encourage further exploration of this regimen in either stratum. Accordingly, with sufficient tolerance data and upon reaching this conclusion, we decided to close the study before reaching the original target accruals (27 in stratum I & 25 in stratum II).

Time to progression and overall survival

The median time to progression (TTP) in stratum I was 6.3 months (95% CI: 2.6, 7.1) and in stratum II was 12.6 months (95% CI: (4.3, 16.2). The median overall survival (OS) in stratum I was 15.9 months (95% CI: 9.7, NA) and in stratum II: 22.7 months (95% CI: 15.5, 37.5).

Discussion

Previous phase I trials of oxaliplatin and topotecan in recurrent ovarian cancer found maximum tolerated doses at less than the individual fully tolerated doses for both topotecan, using the bolus schedule, and oxaliplatin [18, 19]. The dose limiting toxicities were neutropenia, thrombocytopenia, and diarrhea. Our group had previously conducted a phase I trial of single agent low-dose continuous infusion of topotecan which showed a twenty-one day topotecan infusion was well tolerated at 0.53 mg/m^2 [12]. The dose limiting toxicity was hematologic, most significantly, thrombocytopenia. In addition, a phase I study of combining topotecan infusion with bolus cisplatin in the first line treatment of ovarian cancer showed similar endpoints as taxane and platinum combinations but with greater hematologic toxicity [10]. To attempt to gain the same effect with less toxicity, a phase I study combining infusion topotecan with bolus oxaliplatin was performed which showed no grade 4 hematologic events and resulted in a recommendation for phase II studies to use topotecan 0.4 mg/m^2 on days 1–15 and oxaliplatin 85 mg/m^2 on days 1 and 15 [12] which was used in this study. The combination of oxaliplatin and continuous infusion topotecan in the current phase II study has now yielded TTP and OS rates that compare favorably with other combination regimens. In this study we found median TTP of 6.3 and 12.6 months with median OS of 15.9 and 22.7 months for the platinum-resistant and -sensitive strata respectively, which compare favorably to the reported outcomes above. In this study, the main cause of treatment delay was hematologic, mainly thrombocytopenia. Thirty nine percent of patients had grade 3 or 4 thrombocytopenia. While myelosuppression was frequent, it did not cause clinical complications and was easily managed with dose modification.

Many combinations have been tested in both the platinum-sensitive and platinum-refractory setting. In platinum-sensitive patients, carboplatin-containing doublets have been compared to carboplatin alone and to other doublets. A randomized phase III study of gemcitabine plus carboplatin vs. carboplatin in platinum sensitive patients showed improvement of PFS (8.6 months vs. 5.8 months) versus carboplatin alone [19]. Also, a phase II trial with gemcitabine and epirubicin in second line treatment for relapses occurring after less than 12 months showed a response rate of 42% with a median TTP of 7.2 months. The response rate and median duration of responses were 37.5% in the platinum-resistant patients and 50% and 8.8 months in the platinum sensitive patients. Fifty six percent of patients had grade 3 or 4 neutropenia [20]. In a group of platinum resistant patients, a combination of gemcitabine and oxaliplatin showed a PFS and OS of 4.6 months and 11.4 months, respectively. The rate of grade 3–4 neutropenia was 33% [21]. Therefore, re-treating with a regimen containing a platinum agent has shown a wide range of response rates [22] and further emphasized in a pooled analysis of the AGO-OVAR and ICON studies that demonstrated that paclitaxel plus platinum was an improvement over platinum alone both in progression free survival and overall survival [23]. The CALYPSO study has now shown a longer PFS when liposomal doxorubicin with carboplatin is compared to paclitaxel and carboplatin in these platinum sensitive patients (11.3 vs. 9.4 months) [24, 25], and the OCEANS study indicates a lengthening of PFS when bevacizumab in combination with carboplatin and gemcitabine for platinum sensitive patients (12.4 months vs. 8.4 months)[26].

In platinum-resistant disease paclitaxel, pegylated liposomal doxorubicin (PLD), altretamine, and topotecan are approved by the US Food and Drug Administration (FDA) for second line use[17]. Randomized data to support one regimen over another is lacking; however, the recent AURELIA trial data indicates best response rates and PFS are obtained when bevacizumab is added to paclitaxel, pegylated liposomal doxorubicin, or topotecan, with the combination with paclitaxel providing the most favorable data [(bevacizumab +chemotherapy vs. chemotherapy) ORR: 30.9 vs. 12.6; PFS: 6.7 vs. 3.4 months] [27].

In summary, the results of the current study lead us to conclude that this regimen should be studied further in both strata. Nevertheless, toxicity and practical issues must also be resolved to pursue such studies: about 20% of patients experience severe, mostly hematologic toxicities. After noting greater toxicity in patients with glomerular filtration rates calculated to be less than 60, the protocol was amended to decrease the dose of topotecan to 0.3 mg/m^2/day in such patients; however, all patients enrolled after the amendment had creatinine clearances >60. While the response rates and OS are encouraging, further studies would require dosage adjustments to decrease hematologic toxicity. Treatment dose modifications and delays for grade 3 or 4 thrombocytopenia were required in 39% of patients. While such myelosuppression was frequent, only rarely did it lead to hospitalization or transfusions and could be managed with dose modifications. The use of prolonged infusion for topotecan is another practical issue that must be addressed in planning future trials. We conclude that in both platinum-sensitive and platinum-resistant settings, this novel regimen combining continuous infusion topotecan with oxaliplatin has encouraging activity and relatively similar or more favorable outcomes when compared to other regimens for recurrent ovarian cancer after platinum-based therapy.

Acknowledgments

Supported by the Department of Health and Human Services, National Cancer Institute contract number N01-CM-62204, New York Cancer Consortium (PI: Joseph A. Sparano, MD)

The authors acknowledge the late Dr. Scott Wadler, our colleague and friend, who conceived of and founded the New York Cancer Consortium and who played a key role in the development of this trial.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005; 55:74–108. [PubMed: 15761078]
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010; 60:277–300. [PubMed: 20610543]
3. Huang L, Cronin KA, Johnson KA, et al. Improved survival time: what can survival cure models tell us about population-based survival improvements in late-stage colorectal, ovarian, and testicular cancer? Cancer. 2008; 112:2289–300. [PubMed: 18393325]
4. Cannistra SA. Cancer of the ovary. N Engl J Med. 2004; 351:2519–29. [PubMed: 15590954]
5. Raymond E, Faivre S, Woynarowski JM, Chaney SG. Oxaliplatin: mechanism of action and antineoplastic activity. Semin Oncol. 1998; 25:4–12. [PubMed: 9609103]
6. Rixe O, Ortuzar W, Alvarez M, et al. Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. Biochem Pharmacol. 1996; 52:1855–65. [PubMed: 8951344]
7. Chollet P, Bensmaine MA, Brienza S, et al. Single agent activity of oxaliplatin in heavily pretreated advanced epithelial ovarian cancer. Ann Oncol. 1996; 7:1065–70. [PubMed: 9037366]
8. Hochster H, Wadler S, Runowicz C, et al. Activity and pharmacodynamics of 21-Day topotecan infusion in patients with ovarian cancer previously treated with platinum-based chemotherapy. New York Gynecologic Oncology Group. J Clin Oncol. 1999; 17:2553–61. [PubMed: 10561322]
9. Hochster H, Liebes L, Speyer J, et al. Effect of prolonged topotecan infusion on topoisomerase 1 levels: a phase I and pharmacodynamic study. Clin Cancer Res. 1997; 3:1245–52. [PubMed: 9815806]
10. Hochster HSPE, Mandeli J, Wadler S, Runowicz C, Goldberg G, Speyer J, Wallach R, Muggia F. New York Gynecologic Oncology Group (and phase II consortium) and the Eastern Cooperative Oncology. Prolonged topotecan infusion with cisplatin in the first-line treatment of ovarian cancer: an NYGOG and ECOG study. Gynecologic Oncology. 2006; 100:324–9. [PubMed: 16253316]

11. Mirchandani D, Hochster H, Hamilton A, et al. Phase I study of combined pegylated liposomal doxorubicin with protracted daily topotecan for ovarian cancer. Clin Cancer Res. 2005; 11:5912–9. [PubMed: 16115933]
12. Hochster H, Chen TT, Lu JM, et al. Tolerance and activity of oxaliplatin with protracted topotecan infusion in patients with previously treated ovarian cancer. A phase I study. Gynecol Oncol. 2008; 108:500–4. [PubMed: 18191187]
13. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92:205–16. [PubMed: 10655437]
14. Rustin GJ, Bast RC Jr, Kelloff GJ, et al. Use of CA-125 in clinical trial evaluation of new therapeutic drugs for ovarian cancer. Clin Cancer Res. 2004; 10:3919–26. [PubMed: 15173101]
15. Rustin GJ. Use of CA-125 to assess response to new agents in ovarian cancer trials. J Clin Oncol. 2003; 21:187s–93s. [PubMed: 12743133]
16. Simon R. Optimal two-stage designs for phase II clinical trials. Controlled clinical trials. 1989; 10:1–10. [PubMed: 2702835]
17. Gordon AN, Fleagle JT, Guthrie D, et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol. 2001; 19:3312–22. [PubMed: 11454878]
18. Tortora G, Ciardiello F, Damiano V, et al. Preclinical and phase I study of oxaliplatin and topotecan in combination in human cancer. Ann Oncol. 2002; 13:392–8. [PubMed: 11996469]
19. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol. 2006; 24:4699–707. [PubMed: 16966687]
20. Murgia V, Sorio R, Griso C, et al. Multicenter phase 2 study of combined gemcitabine and epirubicin as second-line treatment for patients with advanced ovarian cancer. Int J Gynecol Cancer. 2010; 20:953–7. [PubMed: 20683401]
21. Ray-Coquard I, Weber B, Cretin J, et al. Gemcitabine-oxaliplatin combination for ovarian cancer resistant to taxane-platinum treatment: a phase II study from the GINECO group. Br J Cancer. 2009; 100:601–7. [PubMed: 19190632]
22. Guarneri V, Piacentini F, Barbieri E, Conte PF. Achievements and unmet needs in the management of advanced ovarian cancer. Gynecol Oncol. 2010; 117:152–8. [PubMed: 20056266]
23. Parmar MKLJ, Colombo N, du Bois A, Delaloye JF, Kristensen GB, Wheeler S, Swart AM, Qian W, Torri V, Floriani I, Jayson G, Lamont A, Tropé C. ICON and AGO Collaborators. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet. 2003; 361:2099–106. [PubMed: 12826431]
24. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, et al. Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol. 2010; 28:3323–9. [PubMed: 20498395]
25. Wagner U, Marth C, Largillier R, et al. Final overall survival results of phase III GCIG CALYPSO trial of pegylated liposomal doxorubicin and carboplatin vs paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients. Br J Cancer. 2012; 107:588–91. [PubMed: 22836511]
26. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012; 30:2039–45. [PubMed: 22529265]
27. Eric Pujade-Lauraine FH, Weber Béatrice, Reuss Alexander, Poveda Andres, Kristensen Gunnar, Sorio Roberto, Vergote Ignace B, Witteveen Petronella, Bamias Aristotelis, Pereira Deolinda, Wimberger Pauline, Oaknin Ana, Mirza Mansoor Raza, Follana Philippe, Bollag David T, Ray-Coquard Isabelle. AURELIA Investigators. AURELIA: A randomized phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT)-resistant recurrent ovarian cancer (OC). Journal of Clinical Oncology. 2012; 30(suppl):abstr LBA5002.

Table 1

Characteristics of enrolled patients.

	Stratum I (platinum resistant)	Stratum II (platinum sensitive)
Age		
Median	61 (38–80)	59 (40–71)
Range		
ECOG PS		
0	9	13
1	10	6
# of prior regimens		
1	12	7
2	7	12
Histology		
Ovarian	18	14
Primary peritoneal	1	3
Fallopian tube	0	2

Table 2

Toxicities of Treatment.

Grade 3/4 Toxicities			
All treated patients (n = 38)			
	Platinum resistant	**Platinum sensitive**	**Incidence of each toxicity as a % of the total**
Hematologic			
Febrile neutropenia	0	0	0 %
Neutropenia grade 3	2	8	26.3 %
Neutropenia grade 4	1	4	13.1 %
Anemia grade 3	4	1	13.1 %
RBC transfusion	5	4	23.6 %
Thrombocytopenia grade 3	2	6	21 %
Thrombocytopenia grade 4	3	4	18.4 %
Platelet transfusion	1	2	7.8 %
Nonhematologic			
Diarrhea grade 3	0	1	2.6 %
Fatigue grade 3	1	2	7.8 %
Constipation grade 3	1	1	5.2%
Elevated AST & ALT	1	0	2.6 %

Table 3

Responses by stratum*

	Platinum Resistant	Platinum Sensitive
No.	19	19
Complete Response (CR)	3	3
Partial Response (PR)	1	6
Stable Disease	8	4
Disease Progression	4	1
Response rate (CR + PR)	21% (95% CI 6%, 46%)	47% (95% CI 24%, 71%)

* see text for duration of response