Published in final edited form as:

Gynecol Oncol. 2011 July ; 122(1): 89–94. doi:10.1016/j.ygyno.2011.03.013.

A Randomized Phase III Trial of IV Carboplatin and Paclitaxel x 3 Courses Followed by Observation Versus Weekly Maintenance Low Dose Paclitaxel in Patients with Early Stage Ovarian Carcinoma: a Gynecologic Oncology Group Study

Robert S Mannel, MD¹, Mark F Brady, PhD², Elise C. Kohn, MD³, Parviz Hanjani, MD⁴, Masamichi Hiura, MD⁵, Roger Lee, MD⁶, Koen DeGeest, MD⁷, David E Cohn, MD⁸, Bradley J. Monk, MD⁹, and Helen Michael, MD¹⁰

¹ University of Oklahoma, Oklahoma City, OK

² Gynecologic Oncology Group Statistical and Data Center

³ National Cancer Institute, Bethesda, MD

⁴ Abington Memorial Hospital, Abington, PA

⁵ Shikoku Cancer Center, Ehime, JAPAN

⁶ Tacoma General Hospital, Tacoma, WA

⁷ University of Iowa Hospitals and Clinics, Iowa City, IA

⁸ Ohio State University, Columbus, OH

⁹ University of California Medical Center Irvine, Orange, CA

¹⁰ Indiana University School of Medicine, Indianapolis, IN

Abstract

Purpose—To compare the recurrence-free interval (RFI), and safety profile in patients with completely resected high-risk early-stage ovarian cancer patients treated with intravenous (IV) carboplatin and paclitaxel with or without maintenance low-dose paclitaxel for 24 weeks.

© 2011 Elsevier Inc. All rights reserved.

Corresponding author: Robert S. Mannel, MD, University of Oklahoma, Health Sciences Center, OB/GYN, P.O. Box 26901, Williams Pavilion – Room WP-2410, Oklahoma City, OK 73190, Telephone: 405-271-8787, Fax: 405-271-8547, robert-mannel@ouhsc.edu.

Parts of this research were presented in abstract form at the Society of Gynecologic Oncologists Annual Meeting March 14–17, 2010, San Francisco, CA which was published in *Gynecol Oncol* 116(3): s1(SGO#1), 2010.

This trial was registered with the NCI on November 1, 1999 (NCT 00003644). Further details about the protocol are available at www.clinicaltrials.gov

CONFLICT OF INTEREST STATEMENT

The authors wish to report that there are no conflicts of interest with the exception of Dr. Helen Michael who reports that, although she is not aware of any financial relationships involving this study, she does hold stocks and/or bonds in the following companies: Johnson & Johnson, Amgen, Teva Pharmaceutical Industries ADR, Medtronic, Roche Holding ADR, Eli Lilly & Co, Pfizer, Abbott Laboratories, Becton Dickinson. Dr. Michael also reports that she does not select or manage her investments but rather an asset management company does that for her.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Methods—Eligibility was limited to patients with Stage I-A/B (Grade 3 or clear cell), all I-C or II epithelial ovarian cancer. All patients were to receive carboplatin AUC 6 and paclitaxel 175 mg/m² q 3 wks × 3 courses with random assignment to either observation or maintenance paclitaxel 40 mg/m²/wk × 24 wks. Recurrence required clinical or radiological evidence of new tumor.

Results—There were 571 patients enrolled onto this study, of whom 29 were deemed ineligible due to inappropriate stage or pathology, leaving 542 patients. At least 3 cycles of treatment were administered to 524/542 (97%) of patients, and among those assigned to maintenance paclitaxel, 80% completed the regimen. The incidence of grade 2 or worse peripheral neuropathy (15.5% vs 6%), infection/fever (19.9% vs 8.7%), and dermatologic events (70.8% vs 52.1%) were higher on the maintenance regimen ($p < 0.001$). The cumulative probability of recurring within 5 years for the maintenance paclitaxel regimen is 20% vs. 23% for surveillance (hazard ratio 0.807; 95% CI: 0.565–1.15). The probability of surviving 5 years was 85.4% and 86.2%, respectively.

Conclusion—Maintenance paclitaxel at 40 mg/m²/wk × 24 wks added to standard dose AUC6 and paclitaxel 175 mg/m² × 3 doses provides no significant increase in RFI.

INTRODUCTION

The management of early stage ovarian cancer (EOC) has gained a degree of consensus over the past decade. Patients with fully staged IA or IB disease with grade 1 or 2 non clear cell histology have a greater than 90% survival with surgery alone (1). For patients with stage IA or IB and an unfavorable histology including grade 3 and clear cell, stage IC, or stage II disease, the recurrence risk is 25 to 45% with adjuvant therapy (1–7). The 2004 Gynecologic Cancer Intergroup (GCI) Ovarian Cancer Consensus Conference recommended that patients with high risk early stage EOC receive at least 3 cycles of carboplatin therapy (8). Extrapolating data from advanced disease in which cisplatin/paclitaxel is superior to cisplatin/cyclophosphamide and that carboplatin is therapeutically equivalent to cisplatin with a superior toxicity profile, the Gynecologic Oncology Group (GOG) recommended carboplatin/paclitaxel for its standard arm (7,9,10).

GOG 157 compared 3 versus 6 cycles of carboplatin AUC 6 and paclitaxel 175 mg/m² every 3 weeks in high risk early stage EOC. There was no significant difference in the recurrence free interval (RFI) or overall survival (OS) (7). Grade 3 or 4 neurotoxicity was significantly increased from 2% to 11% in patients treated with 3 and 6 cycles of therapy respectively. Six cycles also caused significantly more granulocytopenia and anemia. Based upon these data, the GOG continued with 3 cycles of carboplatin/paclitaxel as the standard comparator arm.

Angiogenesis appears to play an important role in EOC and has been shown to be a marker of poor prognosis (11–14). The inclusion of an inhibitor of angiogenesis into a chemotherapeutic regimen for EOC may prevent outgrowth of microscopic remaining subclinical disease. Klauber and colleagues showed that paclitaxel at a dose lower than typically used for cytotoxic effects against cancer cells in mouse xenograft models may have an anti-angiogenic effect (15). Based on extrapolation from mouse dosing as well as phase I trials, the study postulated a dose of paclitaxel 40 mg/m² weekly may have similar actions in humans.

Another strategy of interest in managing ovarian cancer patients has been utilizing paclitaxel in a maintenance setting. GOG 178/Southwest Oncology Group (SWOG) 9701 demonstrated a significant increase in progression-free survival (PFS) for patients with advanced ovarian cancer in complete remission receiving 12 cycles compared to 3 cycles of monthly paclitaxel at 175 mg/m² in a maintenance setting (16). The trial initially utilized paclitaxel at 175 mg/m² but excessive toxicity resulted in a reduction to 135 mg/m². There

was, however, no significant improvement in OS perhaps secondary to crossover effect or the fact that the control arm had 3 cycles of therapy instead of observation alone. Several recent reports have also looked at the importance of schedule in paclitaxel administration. Katsumata et al reported that in advanced stage EOC dose dense paclitaxel at 80 mg/m² weekly × 3 combined with every three week carboplatin AUC 6 significantly improved PFS and OS when compared to standard every 3 week paclitaxel at 180 mg/m² and carboplatin AUC 6 (17).

In the current study, the choice of paclitaxel at 40 mg/m² given weekly for 24 weeks as maintenance therapy was made in an effort to take several of these strategies into consideration. The lower weekly dose could potentially exert an anti-angiogenic effect. At the same time, the total monthly dose of 160 mg/m² in the weekly regimen is almost 20% higher than the tolerable monthly dose of 135 mg/m² used in GOG 178/SWOG 9701 and approaches the percent increase used in the dose dense weekly paclitaxel strategy reported in advanced disease. The objective of this study was to compare RFI, and the safety profile of 3 cycles of carboplatin AUC 6/paclitaxel 175 mg/m² with or without maintenance low dose paclitaxel of 40 mg/m² weekly × 24 weeks in patients recently diagnosed with high-risk early stage EOC.

METHODS

Eligibility

Eligible patients were required to have a histologic diagnosis of EOC including serous, mucinous, endometrioid, clear cell, transitional cell, mixed epithelial, Brenner, and undifferentiated carcinoma. Borderline tumors were ineligible. Definitive surgical staging that followed GOG guidelines was to be done and included total abdominal hysterectomy, bilateral salpingo-oophorectomy, resection of all gross disease, infracolic omentectomy, selective pelvic and aortic node dissection, peritoneal biopsies from pelvic locations and bilateral paracolic areas, right diaphragm biopsy or cytology and aspiration of free fluid or abdominal washings for cytology. Patients were required to have completely resected stage IA or B grade 3 or clear cell subtype, or any stage IC, or stage II disease. The staging procedures and pathology materials for each patient were reviewed centrally by members of the GOG's Gynecologic Management and Pathology Committees. Those patients who were considered to have an ineligible histology, stage of disease, site of primary disease or inadequate tissue for documenting diagnosis are not included in the primary analyses. Other eligibility criteria included: no prior treatment for this malignancy, adequate bone marrow (WBC ≥ 3000 cells/mm³, platelets ≥ 100,000 cells/mm³, creatinine ≤ 2.0 mg%, and liver function bilirubin ≤ 1.5 × upper limit of normal (ULN), alkaline phosphatase and SGOT ≤ 3 × ULN. Patients with a history of another invasive malignancy in the past 5 years or GOG performance status of 4 or more were not eligible.

Participating institutions' Institutional Review Boards approved the study prior to enrolling any patients. All patients provided written informed consent in accordance with federal, state, local and institutional requirements and guidelines prior to enrollment. Patients had to be entered onto trial within 6 weeks of staging surgery.

Treatment assignment and dosing

All patients were registered and treatment was randomly assigned through the GOG Statistical and Data Center prior to receiving any chemotherapy. All patients were scheduled to receive 3 cycles of carboplatin AUC 6 IV, paclitaxel 175 mg/m² IV over 3 hours every 21 days followed by either observation or paclitaxel 40 mg/m² over 1 hour weekly for 24 weeks. Adverse events were categorized and graded according to Common Toxicity Criteria

(CTC) version 2.0 and all patients who received any study treatment are included in the summary of toxicities.

The treatment plan utilized the Calvert formula for AUC calculations with creatinine clearance calculated using the method of Jelliffe. The dose of carboplatin was recalculated for each cycle and a maximum body surface area (BSA) of 2.0 was used in paclitaxel dosing. Standard pretreatment regimen of dexamethasone, diphenhydramine, and cimetidine was used prior to paclitaxel administration.

All patients were monitored with weekly blood counts, and physical exam prior to each of the initial three cycles of carboplatin and paclitaxel. Patients randomized to weekly paclitaxel had monthly pretreatment CBC and physical exam prior to each four week cycle. Treatment modifications were employed in a sequential manner using course delay, dose reduction, and addition of granulocyte colony stimulating factor (G-CSF). Minimum blood counts required for treatment were absolute neutrophil count (ANC) ≥ 1500 cells/mm³ and platelets $\geq 100,000$ cells/mm³. No dose modifications were made for uncomplicated nadirs. Patients with grade 4 thrombocytopenia, febrile neutropenia, or delay > 2 weeks underwent dose reduction. G-CSF was used only in situations of recurrent delays or neutropenic complications after appropriate dose reductions.

A study regimen was assigned to each enrolling patient from pre-allocated, randomly permuted blocks of the treatments. Separate treatment lists were maintained for each stage of disease. The treatment assignment was not revealed until after the patient was successfully registered onto the study and this report includes an accounting of every patient who was registered. For the purpose of this report, results are presented according to each patient's randomized treatment assignment regardless of the amount of study treatment received.

Statistics

The primary question assessed by this trial was whether the addition of low dose paclitaxel following 3 courses of carboplatin/paclitaxel reduces the recurrence rate. Recurrence was defined as any clinical or radiographic evidence of new tumor. CA-125 elevation alone was not sufficient evidence of recurrence. After completion of chemotherapy patients were evaluated quarterly for 2 years, then semi-annually for 3 years, then annually thereafter. Time to recurrence and OS was assessed from the date the patient was registered onto the study to the date of recurrence or the date of last contact if no recurrence was observed. A logrank test (18) was used to assess the hypothesis that the two study treatments have equivalent recurrence rates. The study was designed to provide 85% chance of detecting a true 50% decrease in the recurrence rate while the type I error was limited to 5% for a one-tail test (19). This effect size is comparable to increasing expected proportion recurrence-free at 5 years from 77% to 88%. In anticipation that there would be loss of statistical power, if patients withdrew from treatment early, the study design provided guidelines for adjusting to the sample size to compensate. An interim analysis was scheduled to be performed when at least 30 recurrences were reported among those randomized to the reference regimen (3 cycles of carboplatin and paclitaxel) in order to assess for either extreme differences or futility which could warrant early accrual termination. For the purposes of this report, all reported p-values are two-sided. For the purposes of this report the study data was frozen and locked Jan-2010.

RESULTS

Patients

Between September of 1998 and December of 2006, 571 patients were enrolled into this study, of whom 542 (95%) are included in the current efficacy analysis. The reasons for excluding cases following centralized pathologic and surgical review are listed in the CONSORT diagram (Figure 1). Of the 542 eligible patients, 72% were stage I and 28% were stage II. Table 1 describes the characteristics of the study sample.

Completion of therapy

Of the 542 eligible patients, 268 were randomly assigned to the observation arm and 274 to the weekly paclitaxel $\times$ 24 arm. The proportion of patients completing at least 3 cycles of treatment was 97% of those assigned to 3 cycles, compared to 96% for those assigned to weekly paclitaxel. Among those patients randomized to the additional 24 weeks of paclitaxel, 86% completed at least 12 additional weeks and 79% completed the entire 24 weeks of treatment. There was approximately 1% attrition per week of the maintenance paclitaxel therapy. Table 2 summarizes the reasons for terminating the study treatment for both groups.

Outcome

The median duration of follow-up for the 445 patients who were alive at last contact is 6.7 years. There have been 122 reported recurrences. The percent recurring within 5 years for those assigned to observation was 23.2% (95% CI: 18.4–28.9) and 20.4% (95% CI: 15.9–25.9) for those assigned to 24 weeks of paclitaxel. Adjusted for stage of disease and tumor grade, the recurrence rate was 19.3% lower for those randomized to weekly paclitaxel, hazard ratio (HR) 0.807 (95% CI: 0.565 – 1.15, $p=0.24$). Figure 2 displays the estimated cumulative incidence of recurrence for the two groups. The probability of surviving 5 years was 85.4% for surveillance and 86.2% for extended weekly paclitaxel (Figure 3). The overall death rate was very similar for the two treatment groups (HR 0.781; 95% CI: 0.522–1.17, $p=0.23$).

Figure 4 displays the estimated treatment HR by disease stage (a), histology (b) and grade (c), respectively (Figure 4a,b,c, online only). The slight variation in the treatment hazard ratios across these subgroups of patients can be reasonably attributed to random variation. Patients with clear cell histology had a HR of 0.981 (95% CI: 0.490 – 2.96) when comparing extended weekly paclitaxel to surveillance. While patients with grade 3 disease had a HR of 0.759 (95% CI: 0.439 – 1.31) favoring extended weekly paclitaxel therapy. The overall cumulative incidence of recurrence within 5 years was 16.5% for stage I and 35.7% for stage II disease. The estimated probability of surviving 5 years was 88.8% and 78.9%, respectively.

Toxicity

Table 3 summarizes the toxicities (CTC version 2.0) for the 536 patients who received any study therapy. There were 6 patients who did not receive any study treatment and are not included in the summary of adverse events. The incidence of grade 2 or worse peripheral neuropathy (15.5% vs 6.0%), infection or fever (19.9% vs 8.7%), and dermatologic events (70.8% vs 52.1%) were significantly higher among patients treated on the maintenance weekly paclitaxel regimen ($p<0.001$). There was also a slightly greater incidence of grade 2 or worse cardiovascular events (8.1% vs 3.8%, $p=0.044$) among those on the maintenance regimen. Grade 3 or 4 peripheral neuropathy was reported in 0.7% of the observation group compared to 4.4% of the maintenance paclitaxel group ($p=0.012$). Twenty-one patients (10

on weekly paclitaxel and 11 on observation arm) developed a second primary cancer during follow-up. There were no treatment-related deaths reported.

DISCUSSION

This multi-institutional, prospective, randomized phase III trial demonstrates that adding 24 weeks of weekly paclitaxel at 40 mg/m² to the standard 3 cycles of carboplatin plus paclitaxel does not significantly impact RFI in patients with high risk early stage EOC. The addition of 24 weeks of low dose paclitaxel did lead to significantly increased toxicity with respect to neurotoxicity, infection, and dermatologic events, as well as possible cardiovascular events. Overall, there was an approximate 1% patient attrition per week of maintenance paclitaxel therapy with 79% of patients completing the entire 24 weeks of additional therapy. The most important difference in toxicity was an increase in grade 3 and 4 peripheral neuropathy from 0.7% in the observation arm to 4.4% in the maintenance arm. In the absence of proven benefit, the additional therapy cannot be recommended. The increase in toxicity was modest, however, and the maintenance regimen should be considered tolerable for future trials if applied to a different patient population.

A number of previous trials in patients with early stage EOC have reported a 5 year recurrence-free survival of 75–80% using a variety of post surgical treatment strategies including melphalan, intraperitoneal phosphorous-32, cisplatin, carboplatin, cisplatin plus cyclophosphamide, and carboplatin plus paclitaxel (1–7). GOG 157 targeted the same patient population randomizing between 3 or 6 cycles of carboplatin plus paclitaxel. The 5 year recurrence-free survival was 74.6% and 79.9% for 3 or 6 cycles of treatment (7). The current trial's 5 year recurrence-free survival of 76.8% and 80.0% for observation and maintenance paclitaxel falls within the reported range of previous studies.

An exploratory analysis of GOG 157 sought to identify subsets of patients who may benefit from more cycles of chemotherapy (20). The relative risk of recurrence for those who received 6 versus 3 cycles of chemotherapy was not different based on age, race, performance status, stage, grade, presence of ascites, ovarian rupture, or cytology. Differences were seen in histology, however, as women with serous tumors had a significantly decreased risk of recurrence with 6 compared to 3 cycles of chemotherapy (HR=0.33, 95% CI: 0.14–0.77). This difference was not seen in non-serous tumors. In the current study, patients with serous tumors had treatment HR of 0.822 (95% CI: 0.438 – 1.54), Figure 4b.

The dose in the current trial of 40 mg/m² weekly was chosen in an effort to minimize toxicity while at the same time maintaining reasonable dose intensity and taking advantage of a potential anti-angiogenic effect of lower dose paclitaxel. In advanced stage EOC patients, GOG 178/SWOG-9701 demonstrated that patients with a complete response to initial carboplatin/paclitaxel therapy, maintenance therapy with paclitaxel at 135 mg/m² monthly for 12 cycles versus 3 cycles provided significant increase in PFS (HR=0.68, p=0.004) (16). The dose used in the current trial, 40 mg/m² weekly, equates to a dose density of 160 mg/m² per month which is a 20% increase in dose over that used in GOG 178/SWOG-9701. The lack of benefit on recurrence or survival seen in the current study may be a function of the substantially different patient population seen in early stage EOC trials compared to advanced disease.

Recent genomic analysis indicates that histology and grade are better differentiators than stage with regard to non-hierarchical clustering of genomic patterns in ovarian cancers (21–23). High grade serous tumors cluster together regardless of stage and appear different than low grade serous tumors. Clear cell tumors of the ovary cluster with renal and endometrial

clear cell tumors rather than serous tumors of the ovary suggest a basic biologic difference which may impact response to therapy. These findings are important when analyzing early stage EOC trials. In the current study, less than 30% of the patients had serous histology. The most common cell type was clear cell (31%). This is in clear distinction to the histologic prevalence of patients with papillary serous recently reported in GOG 182 (24). That trial enrolled over 4,000 patients with stage III and IV EOC of which 80% were serous histology and only 3% were clear cell. In addition, 12% of the tumors in the present trial were grade 1. This substantial difference in histology with a much greater preponderance of clear cell, endometrioid, mucinous, and low grade tumors in the early stage EOC patient population may negatively impact a trial designed to evaluate the effectiveness of extended platinum/taxane based therapy. Indeed, poor response of clear cell, mucinous and low grade tumors to standard carboplatin/paclitaxel therapy has been seen in multiple trials (25-2-7). This poor response rate suggests that future treatment trials target ovarian cancer patients based on histology.

In conclusion, 3 cycles of carboplatin and paclitaxel continue to be shown as a reasonable treatment for women with high risk early stage EOC. The strategy of maintenance therapy using paclitaxel at 40 mg/m² weekly for 24 weeks showed little benefit for the group as a whole and was associated with increased toxicity. However, an increased understanding of the importance of grade and histology in determining treatment response and prognosis may suggest a different management strategy in epithelial ovarian cancer patients in general. There is evidence from other studies that clear cell, mucinous, and low grade tumors of the ovary may need a different treatment strategy than serous high grade tumors and this may need to be taken into consideration in future trial designs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by National Cancer Institute grants to the Gynecologic Oncology Group Administrative Office (CA 27469) and the Gynecologic Oncology Group Statistical Office (CA 37517).

The following Gynecologic Oncology Group (GOG) institutions participated in this study: Roswell Park Cancer Institute, University of Alabama at Birmingham, Duke University Medical Center, Abington Memorial Hospital, Walter Reed Army Medical Center, Wayne State University, University of Minnesota Medical School, University of Mississippi Medical Center, Colorado Gynecologic Oncology Group P.C., University of California at Los Angeles, University of Washington, University of Pennsylvania Cancer Center, Milton S. Hershey Medical Center, University of Cincinnati, University of North Carolina School of Medicine, University of Iowa Hospitals and Clinics, University of Texas Southwestern Medical Center of Dallas, Indiana University Medical Center, Wake Forest University School of Medicine, University of California Medical Center at Irvine, Rush-Presbyterian-St. Luke's Medical Center, University of Kentucky, University of New Mexico Health Sciences Center, The Cleveland Clinic Foundation, SUNY at Stony Brook, Southwest Oncology Group, Washington University School of Medicine, Memorial Sloan-Kettering Cancer Center, Cooper Hospital/University Medical Center, Columbus Cancer Council, University of Massachusetts Medical Center, Fox Chase Cancer Center, Women's Cancer Center, University of Nevada, University of Oklahoma, University of Chicago, Mayo Clinic, Case Western Reserve University, Tampa Bay Cancer Consortium, Gynecologic Oncology Network/Brody School of Medicine, Yale University School of Medicine, GOG Japan-Saitama Medical University International Medical Center and University of Texas – Galveston, Community Clinical Oncology Program.

References

1. Young RC, Walton LA, Ellenberg SS, et al. Adjuvant therapy in stage I and stage II epithelial ovarian cancer. *N Engl J Med.* 1990; 322:1021–27. [PubMed: 2181310]

2. Young RC, Brady MF, Nieberg RM, et al. Adjuvant treatment for early ovarian cancer: a randomized phase III trial of intraperitoneal ^{32}P or intravenous cyclophosphamide and cisplatin: a Gynecologic Oncology Group study. *J Clin Oncol.* 2003; 21:4350–55. [PubMed: 14645424]
3. Bolis G, Colombo N, Pecorelli S, et al. Adjuvant treatment for early epithelial ovarian cancer results of two randomized clinical trials comparing cisplatin to no further treatment of chronic phosphate (^{32}P). GICOG: Gruppo Interregionale Collaborativo in Ginecologia Oncologica. *Ann Oncol.* 1995; 6:887–93. [PubMed: 8624291]
4. Vergote IB, Vergote-De Vos LN, Abeler VM, et al. Randomized trial comparing cisplatin with radioactive phosphorus or whole-abdomen irradiation as adjuvant treatment of ovarian cancer. *Cancer.* 1992; 69:741–49. [PubMed: 1730124]
5. Trimbos JB, Parmar M, Vergote I, et al. International collaborative ovarian neoplasm trial I and adjuvant chemotherapy in ovarian neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in early-stage ovarian carcinoma. *J Natl Cancer Inst.* 2003; 5:105–12. [PubMed: 12529343]
6. Trimbos JB, Vergote I, Bolis G, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organization for Research and Treatment of Cancer – adjuvant chemotherapy in ovarian neoplasm trial. *J Natl Cancer Inst.* 2003; 95:113–25. [PubMed: 12529344]
7. Bell J, Brady MF, Young RC, et al. Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early-stage ovarian carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2006; 102:432–39. [PubMed: 16860852]
8. duBois A, Quinn M, Thigpen T, et al. 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCI GOCCC 2004). *Ann Oncol.* 2004; 16:viii7–viii12. 10.1093.
9. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med.* 1996; 334:1–6. [PubMed: 7494563]
10. Ozols R, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally-resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 2003; 21:3194–200. [PubMed: 12860964]
11. Paley PJ, Staskus KA, Gebhard K, et al. Vascular endothelial growth factor expression in early-stage ovarian cancer. *Cancer.* 1997; 80:98–106. [PubMed: 9210714]
12. Hollingsworth HC, Kohn EC, Steinberg SM, et al. Tumor angiogenesis in advanced stage ovarian carcinoma. *Am J Path.* 1995; 147:33–41. [PubMed: 7541612]
13. Belotti D, Vergani V, Drudis T, et al. The microtubule-affecting drug paclitaxel has antiangiogenic activity. *Clin Cancer Res.* 1996; 2:1843–49. [PubMed: 9816139]
14. Wang J, Lou P, Lesniewski R, et al. Paclitaxel at ultra low concentrations inhibits angiogenesis without affecting cellular microtubule assembly. *Anticancer Drugs.* 2003; 14:13–19. [PubMed: 12544254]
15. Klauber N, Parangi S, Flynn E, et al. Inhibition of angiogenesis and breast cancer in mice by the microtubule inhibitors 2-methoxyestradiol and taxol. *Cancer Res.* 1997; 57:81–86. [PubMed: 8988045]
16. Markman M, Liu PY, Wilczynski S, et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. *J Clin Oncol.* 2003; 21:2460–65. [PubMed: 12829663]
17. Katsumata N, Yasuda M, Takahasi F, et al. Dose-dense paclitaxel once-a-week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase III, open-label, randomized controlled trial. *Lancet.* 2009; 374:1331–338. [PubMed: 19767092]
18. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Rep.* 1966; 50:163–170.
19. Schoenfeld D. The asymptotic properties of comparative tests for comparing survival distributions. *Biometrika.* 1981; 68:316–19.

20. Chan JK, Tian C, Fleming GF, et al. The potential benefit of six versus three cycles of chemotherapy in subsets of women with early-stage high risk epithelial ovarian cancer: an exploratory analysis of a Gynecologic Oncology Group study. *Gynecol Oncol.* 2010; 116:301–306. [PubMed: 19945740]
21. Zorn KK, Bonome T, Gangi L, et al. Gene expression profiles of serous, endometrioid, and clear cell subtypes of ovarian and endometrial cancer. *Clin Cancer Res.* 2005; 11:6422–430. [PubMed: 16166416]
22. Stany MP, Bonome T, Wamunyokoli F, et al. Classification of ovarian cancer: a genomic analysis. *Adv Exp Med Biol.* 2008; 622:22–33.
23. Farley J, Ozbun LL, Birrer MJ. Genomic analysis of epithelial ovarian cancer. *Cell Res.* 2008; 18:538–48. [PubMed: 18427574]
24. Bookman M, Brady M, McGuire W, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a phase III trial of the Gynecologic Cancer Intergroup. *J Clin Oncol.* 2009; 27:1419–425. [PubMed: 19224846]
25. Takano M, Sugiyama T, Yaegashi N, et al. Progression-free survival and overall survival of patients with clear cell carcinoma of the ovary treated with paclitaxel-carboplatin or irinotecan-cisplatin: retrospective analysis. *Int J Clin Oncol.* 2007; 12:256–60. [PubMed: 17701003]
26. Kurman RJ, Shih IeM. Pathogenesis of ovarian cancer: lessons from morphology and molecular biology and their clinical implications. *Int J Gynecol Pathol.* 2008; 27:151–60. [PubMed: 18317228]
27. Yoshida S, Furukawa N, Haruta S, et al. Theoretical model of treatment strategies for clear cell carcinoma of the ovary: focus on perspectives. *Cancer Treat Rev.* 2009; 35:608–15. [PubMed: 19665848]

Research Highlights

- Maintenance paclitaxel does not improve survival in early stage ovarian cancer
- 3 cycles of carboplatin and paclitaxel is preferred for early stage ovarian cancer
- Maintenance paclitaxel given weekly is well tolerated

Figure 1.
 GOG – 175 Consort Diagram

Cumulative Incidence of Recurrence By Randomized Treatment Group

Figure 2.
C = carboplatin, T = paclitaxel, wkly = weekly

Figure 3.
C = carboplatin, T = paclitaxel

Table 1

Patient Characteristics

Characteristics	Treatment			
	CT + weekly T × 24 cycles		CT 3 cycles	
	N = 274	%	N = 268	%
Age				
Median (years)	55.1		56.0	
<40	22	8.0	21	7.9
40–49	66	24.1	56	20.9
50–59	88	32.1	98	36.6
60–69	64	23.4	57	21.3
≥70	34	12.4	36	13.5
Race				
Non-Hispanic Black	5	1.8	8	3.0
Non-Hispanic White	230	83.9	233	86.9
Hispanic	12	4.4	5	1.9
Native American	2	0.7	1	0.4
Asian/Pacific Islander	25	9.1	21	7.8
Stage				
I	194	70.8	195	72.8
II	80	29.2	73	27.2
Cell Type				
Serous adenocarcinoma	73	26.6	78	29.1
Endometrioid adenocarcinoma	57	20.8	55	20.5
Mucinous adenocarcinoma	13	4.7	18	6.7
Clear cell adenocarcinoma	88	32.1	82	30.6
Adenocarcinoma unspecified	8	2.9	4	1.5
Mixed epithelial	30	10.9	24	9.0
Other	5	1.9	7	2.6
Grade of Primary Tumor				
1	28	10.2	38	14.2
2	60	21.9	69	25.7
3	98	35.8	79	29.5
Clear cell (no grade)	88	32.1	82	30.6

C = carboplatin, T = paclitaxel

Table 2

Reason for discontinuing study regimen

Reason for discontinuing study regimen	Treatment			
	CT + weekly T × 24 cycles		CT × 3 cycles	
	N = 274	%	N = 268	%
Completed treatment regimen	218	79.6	260	97.0
Progression	6	2.2	0	0
Patient refused	26	9.5	4	1.5
Toxicity	19	6.9	3	0.8
Other reasons	5	1.8	1	0.8

C = carboplatin, T = paclitaxel

Table 3

Frequency of adverse events by maximum grade and study treatment

Adverse Event	CT × 3 + weekly T × 24 cycles N = 271						CT × 3 cycles + surveillance N = 265					
	0	1	2	3	4	5	0	1	2	3	4	5
Leukopenia	24	49	124	72	2	29	52	98	82	4		
Thrombocytopenia	149	95	15	10	2	156	80	13	15	1		
Neutropenia	16	13	39	78	125	18	18	33	85	111		
Anemia	52	159	56	4	0	56	149	58	2	0		
Other hematologic	258	1	5	7	0	252	5	4	4	0		
Allergy	232	17	14	7	1	241	12	5	7	0		
Auditory	254	4	13	0	0	258	2	5	0	0		
Cardiovascular	219	30	10	11	1	243	12	3	6	1		
Coagulation	268	3	0	0	0	261	2	0	2	0		
Constitutional	89	111	64	7	0	106	112	40	7	0		
Dermatologic	56	23	190	2	0	82	45	135	2	1		
Endocrine	239	14	18	0	0	246	6	13	0	0		
Gastrointestinal	78	100	81	10	2	85	118	51	10	1		
Genitourinary/Renal	222	34	14	1	0	226	22	14	3	0		
Hemorrhage	253	16	1	1	0	254	9	2	0	0		
Hepatic	244	23	3	1	0	243	17	4	1	0		
Infection/Fever	210	7	39	15	0	240	2	12	11	0		
Metabolic	218	30	13	9	1	231	21	8	5	0		
Musculoskeletal	240	19	9	3	0	242	16	7	0	0		
Peripheral neuropathy	115	114	30	12	0	157	92	14	2	0		
Other neurologic	198	49	19	4	1	215	31	11	6	2		
Ocular/Visual	244	14	12	1	0	244	12	9	0	0		
Pain	107	95	54	15	0	115	87	51	12	0		
Pulmonary	230	17	23	1	0	245	7	13	0	0		
Sexual	258	6	7	0	0	254	9	2	0	0		

C = carboplatin and T=paclitaxel

Six patients who did not receive study treatment are not included in this summary of adverse events. The incidence of peripheral neuropathy, infection or fever, dermatologic events and cardiovascular events were higher among patients treated on the prolonged regimen of paclitaxel ($p < 0.005$). Twenty-one patients (10 on CT+Tx24 and 11 on CT+surveillance) developed a 2nd primary cancer during follow-up.