A Gynecologic Oncology Group Study of Platinum-DNA Adducts and Excision Repair Cross-Complementation Group 1 Expression in Optimal, Stage III Epithelial Ovarian Cancer Treated with Platinum-Taxane Chemotherapy

Kathleen M. Darcy, Chunqiao Tian, and Eddie Reed

Abstract

To determine whether platinum-DNA adducts and/or mRNA expression of the excision nuclease excision repair cross-complementation group 1 (ERCC1) from peripheral blood leukocytes (PBL) were associated with clinical outcome in women with epithelial ovarian cancer (EOC), participants that had previously untreated, optimally resected, stage III EOC were randomized to paclitaxel plus cisplatin or carboplatin. DNA and RNA were extracted from PBLs collected 20 to 28 h post–drug infusion. DNA adducts were measured by atomic absorption spectroscopy. ERCC1 expression was evaluated by reverse transcription-PCR. There were 170 cases fully evaluable for DNA adducts and ERCC1 mRNA expression. Adduct levels ranged from 0.43 to 13 fmol platinum/µg DNA in 140 samples; and adducts were not detectable in 30 samples. ERCC1 mRNA was detectable in 132 samples and undetectable in 38. ERCC1 mRNA expression in PBLs was not associated with any clinical end point measured. The presence of detectable versus undetectable adducts was associated with longer median progression-free survival (20.4 versus 15.6 months; \( P = 0.084 \)) and overall survival (60.3 versus 36.3 months; \( P = 0.029 \)), respectively. Unadjusted Cox regression modeling indicated a trend toward a reduced risk of disease progression [hazard ratio (HR), 0.686; 95% confidence interval (95% CI), 0.447–1.054; \( P = 0.086 \)] and a statistically significant reduction in the risk of death (HR, 0.607; 95% CI, 0.385–0.958; \( P = 0.032 \)) for women with detectable versus undetectable adducts. After adjusting for clinicopathologic variables, detectable adducts were not an independent predictor of progression-free survival or overall survival. The presence of platinum-DNA adducts, but not ERCC1 mRNA expression, in PBLs was associated with better survival, but was not an independent predictor of clinical outcome in optimal advanced EOC. [Cancer Res 2007;67(9):4474–81]

Introduction

Ovarian cancer is currently the fifth leading cause of death in women in the United States, and an estimated 22,430 new ovarian cancer cases will be diagnosed, and 15,280 women will die of ovarian cancer in this country in 2007 (1). Currently, 68% of ovarian cancers are diagnosed at an advanced stage, and women with this diagnosis have a 5-year survival rate of 29% (1). Staging laparotomy with cytoreduction followed by platinum-taxane chemotherapy is currently the standard of care for women with previously untreated, advanced-stage disease in the United States (2–7). Although we currently lack useful means of predicting which ovarian cancer patients are most likely to benefit from platinum-plus-taxane–based chemotherapy, such a capability could theoretically allow us to selectively treat patients, depending on their likelihood to have a favorable clinical response and long-term survival, thus bringing novel treatments up front and avoiding unnecessary adverse effects in those unlikely to respond to standard therapy.

Research on the molecular and biochemical mechanisms that underlie resistance to platinum agents and their biological effect suggests the possibility of defining which patients are at increased risk for responding or not responding to platinum-based chemotherapy by measuring platinum-DNA adduct levels in peripheral blood leukocytes (PBL). The level of platinum-DNA adducts in PBL has been shown either to be positively correlated with disease response in a number of cancers, including testicular, breast, colon, lung, esophageal, and ovarian cancer (8–14), or with the degree of myelosuppression in children with cancer receiving cisplatin therapy (15), to be negatively correlated with disease response in advanced germ cell cancer (16) or to not be associated with disease response in patients with testicular, ovarian, or breast cancer (12, 17, 18). Furthermore, a positive association has not only been shown between platinum-DNA adducts in buccal cells and disease response in a variety of cancers, including testicular, breast, ovarian, and colon cancer (19), but also between platinum-DNA adducts in buccal cells and better OS in non–small cell lung cancer (NSCLC; ref. 20) and between platinum-DNA adducts in tumor tissue and better progression-free survival (PFS) in head and neck squamous cell carcinoma (HNSCC; ref. 21).

Given the evidence that was available in 1997, the Gynecologic Oncology Group (GOG) amended the randomized phase III trial it was conducting at the time, GOG protocol 158 (GOG-0158), to prospectively test the hypothesis that higher adduct levels are associated with better clinical outcome in women with epithelial ovarian cancer (EOC). Participants had previously untreated, stage III, optimally debulked EOC and were randomized to paclitaxel and either cisplatin or carboplatin. The end points in this trial included the assessment of PFS and overall survival (OS). Second-look laparotomy (SLL) was not required for this protocol, but was allowed when declared at the time of protocol enrollment as an option to assess disease status. Tumor response could not be evaluated in this study because the participants in this trial were not permitted to have residual tumor >1.0 cm following staging.

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laparotomy with cytoreduction. The results of the treatment components of this trial were published in separate reports (22, 23). Specifically, treatment with paclitaxel plus carboplatin was shown to be less toxic, easier to administer, and not inferior when compared with paclitaxel plus cisplatin chemotherapy in women with optimally resected, stage III EOC (22), and the performance of SLL did not seem to be associated with better survival (23). The presence and level of platinum-DNA represents the net balance between adduct formation and repair. Nucleotide excision repair (NER) is responsible for the repair of DNA damaged by platinum agents, including cisplatin and carboplatin (24, 25). Excision repair cross-complementation group 1 (ERCC1) is an excision nuclease that works in the repairosome responsible for excision of the covalent bulky damage to the DNA, the rate-limiting step in the NER process (26, 27). Studies in a variety of cancers including ovarian cancer have shown that ERCC1 expression correlates directly with resistance to platinum-based treatment, and that high ERCC1 expression (mRNA or protein) in tumor tissue was either associated with worse disease response, relapse-free survival, or OS (28–32), associated with a reduced risk of death (33), or was not associated with disease response (31, 33). More recently, a polymorphism in codon 118 of ERCC1 was shown to be an independent predictor of platinum resistance in ovarian cancer but was not associated with OS (34). In a study of 783 individuals with completely resected NSCLC, patients with ERCC1-negative tumors, but not those with ERCC1-positive tumors, seemed to benefit from adjuvant cisplatin-based chemotherapy and experience prolonged PFS as well as OS (35). Although platinum-DNA adducts in PBL have been shown to be an effective surrogate for platinum-DNA adduct assessments in tumor tissue (26), similar studies have yet to evaluate whether or not ERCC1 in PBL is a surrogate for ERCC1 assessments in tumor. ERCC1 expression was examined in RNA extracted from the PBL used to measure platinum-DNA adduct levels. Tumor tissue was not available from the women who participated in this protocol, which precluded an evaluation of tumor expression of ERCC1. Analyses were conducted to determine whether mRNA expression of ERCC1 in PBL collected 20 to 28 h after starting the first cycle of chemotherapy was associated with worse PFS and OS, and an increased risk of finding disease during SLL.

### Materials and Methods

**Eligibility criteria.** Women entered on the phase III treatment trial, GOG-0158 from April 1, 1997, to January 26, 1998, were eligible to participate in this translational research study. Participants were required to have a histologically confirmed diagnosis of EOC, stage III (optimal with V \_1 cm residual disease); an appropriate staging laparotomy with cytoreduction; adequate bone marrow, renal, and hepatic function; and an initial GOG performance score of 0, 1, or 2. The eligibility criteria also included three adenocarcinomas, not specified, two undifferentiated adenocarcinoma, two transitional cell carcinomas, and one small cell carcinoma.

**PLatinum-DNA adducts**
- **Undetectable:** 30 (17.6%)
- **Detectable:** 140 (82.4%)

**ERCC1 expression**
- **Negative:** 38 (22.4%)
- **Positive:** 132 (77.6%)

**Total:** 170 (100.0%)

*Median ± SD, 58.35 ± 11.15 yrs.

1 Includes three adenocarcinomas, not specified, two undifferentiated adenocarcinoma, two transitional cell carcinomas, and one small cell carcinoma.

2 Of those who opted to undergo SLL at enrollment, 5 women experienced disease progression before SLL, 10 women refused to undergo SLL, and 60 women underwent SLL.
required a suitable PBL (buffy-coat) specimen for testing, and written informed consent consistent with all federal, state, and local requirements to participate in the clinical and translational research components of this protocol. Eligibility was further contingent upon histologic confirmation of diagnosis by GOG Pathology Committee central review. The trial was done in accordance with the principles in the Declaration of Helsinki, and annual Institutional Review Board approval for this protocol was required for each of the GOG participating institutions and the testing laboratory.

**Stratification and treatment.** Patients on GOG-0158 were stratified by macroscopic residual disease status after their initial staging surgery, and a declaration of whether a reassessment (second-look) laparotomy would be done. Following enrollment on GOG-0158, women were randomly allocated to receive six cycles of $135$ mg/m$^2$ i.v. paclitaxel over 24 h starting on day 1 every 21 days, followed by $75$ mg/m$^2$ i.v. cisplatin on day 2 every 21 days or six cycles of $175$ mg/m$^2$ i.v. paclitaxel over 3 h on day 1 every 21 days, followed by a carboplatin area-under-the-curve (AUC) 7.5 i.v. on day 1 every 21 days.

**Specimen collection, shipping, and storage.** The protocol required the collection of a PBL (buffy-coat) specimen from each patient after initial staging laparotomy with cytoreduction and 24 h post–initial platinum infusion. In each case, $40$ to $50$ mL peripheral whole blood was collected in a purple-top Vacutainer tube with EDTA, a green-top Vacutainer tube with heparin, or a heparin syringe. The blood was drawn within 20 to 28 h of starting the initial platinum infusion during cycle 1. Recovered PBL were kept frozen less than $-70^\circ$C during shipment to the GOG Tissue Bank and then to Dr. Reed’s laboratory and storage before testing.

**DNA extraction and quantification of platinum-DNA adduct level.** DNA was extracted from lysed and digested PBL using CsCl density gradient

**Table 2. Association between categorized platinum-DNA adducts and ERCC1 expression**

<table>
<thead>
<tr>
<th>Platinum-DNA adducts</th>
<th>Undetectable cases, n (%)</th>
<th>Detectable cases, n (%)</th>
<th>Total cases</th>
</tr>
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<tr>
<td>ERCC1 expression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>6 (15.8)</td>
<td>32 (84.2)</td>
<td>38</td>
</tr>
<tr>
<td>Positive</td>
<td>24 (18.2)</td>
<td>108 (81.8)</td>
<td>132</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>140</td>
<td>170</td>
</tr>
</tbody>
</table>

NOTE: Row percentages are provided in parentheses. Fisher’s exact test; $P = 0.814$.

**Figure 2.** Kaplan-Meier estimate of PFS (A and C) and OS (B and D) for women with detectable compared with undetectable platinum-DNA adducts (A and B) or women with negative or positive ERCC1 mRNA expression (C and D). Legend inserted in (A). PFS distributions and median $\pm$ SE PFS times in months for women with detectable compared with undetectable platinum-DNA adducts, and the significance of the logrank test to evaluate the equality in PFS distributions for women with detectable compared with undetectable platinum-DNA adducts was $P = 0.084$. Censored, patients who were alive with no evidence of disease progression. Legend inserted in (B). Survival distributions and median $\pm$ SE survival times in months for women with detectable compared with undetectable platinum-DNA adducts. Significance of the logrank test to evaluate the equality in survival distributions for women with detectable compared with undetectable platinum-DNA adducts was $P = 0.029$. 
centrifugation and analyzed by atomic absorption spectroscopy using a Perkin-Elmer Zeeman 3030 Atomic Absorption Spectrophotometer with HGA 600 Graphite Furnace equipped with a platinum hollow cathode as described by Reed et al. (36). Serial aqueous dilutions from a stock solution of platinum (H2PtCl6·H2O) were used to generate a standard curve for comparison. The detection limit for this method is 10 fmol Pt/μg DNA and requires as little as 70 μg of DNA for testing.

**RNA extraction and quantitation of ERCC1 expression.** Total cellular RNA was extracted as previously described (37). cDNAs were generated using oligodeoxo-TMP primers from 5 μg total RNA per specimen. PCR was done for 35 cycles with cDNAs and appropriate primers using AmpliTag DNA polymerase (Perkin-Elmer). ERCC1 primers amplified a 239-bp segment from 394 to 633 bp of the ERCC1 cDNA. Primers for β-actin amplified a 731-bp segment extending from 269 to 1,535 bp of the coding region of the β-actin gene. Amplified DNAs were electrophoresed through a 1.5% agarose gel, transferred to a Hybond N+ membrane, hybridized to fluorescently labeled probes for ERCC1 and β-actin, and visualized using an enhanced chemiluminescence detection system. ERCC1 expression was quantified using the IPLab-Gel software (Scanalytics, Inc.), corrected based on β-actin expression, and presented as relative expression as compared with a human T-lymphocyte cell line control as reported previously (28, 29).

**Statistical methods and end points.** Biomarker and clinical data were analyzed using SPSS version 10.0 and SAS version 9.0. Estimates of the survival probabilities were calculated using the Kaplan-Meier method (38); the logrank test (39) was used to test the null hypothesis of equality in survival distributions among patient groups categorized by platinum-DNA adducts or ERCC1 expression. Unadjusted and adjusted Cox proportional hazards regression analyses (40) were done to model the association between platinum-DNA adducts or corrected ERCC1 expression expressed as continuous or categorized variables and either PFS or OS. The likelihood ratio test was used to evaluate the goodness of fit of each of the overall Cox models, and the Wald test was employed to assess the association between the individual covariates and outcome. Patients were followed quarterly for 2 years, semiannually for the next 3 years, and then annually until death. PFS was calculated as the time in months from enrollment on the GOG-0158 to disease progression or death for censored events, or to the date of last contact for censored events, that is, for patients alive with no evidence of disease progression. OS was calculated as the time from enrollment to death for censored events or to the date of last contact for censored events, that is, for patients alive, regardless of disease status. Cause of death was reported when available. As of August 23, 2006, 30 women were alive with no evidence of disease, 27 women were alive with disease progression, and 113 women died. Among those who died, 91.4% of the deaths were attributed to disease progression, whereas 1.9% of the deaths were due to treatment, 2.9% were due to a cause other than disease or treatment, and 3.8% were due to an unknown cause.

**Figure 2 Continued.** Legend inserted in (C), PFS distributions and median ± SE PFS times in months for women with negative or positive ERCC1 expression. Significance of the logrank test to evaluate the equality in PFS distributions for women with positive compared with negative ERCC1 expression was P = 0.993. Legend inserted in (D), survival distributions and median ± SE survival times in months for women with negative or positive ERCC1 expression. Significance of the logrank test to evaluate the equality in survival distributions for women with positive compared with negative ERCC1 expression was P = 0.809.
Unadjusted and adjusted logistic regression analyses (41) were conducted to examine the association between platinum-DNA adducts and the results of SLL. Disease status was classified as negative when there was no evidence of disease or positive when microscopic or macroscopic evidence of disease was observed during SLL.

Results

There were 316 women enrolled in GOG-0158 from April 1, 1997, to study closure on January 26, 1998, that were eligible to participate in this translational research study. Of these, there were 23 treatment protocol exclusions, including wrong tumor site, stage, or histologic subtype, EOC with low malignant potential, a previous invasive malignancy, and inadequate or improper surgery. There were an additional 93 cases that were excluded due to a problem associated with obtaining a suitable buffy-coat specimen for testing. Of these, the PBL (buffy-coat) specimen either was not collected, was improperly prepared, was received in unsatisfactory condition, or yielded insufficient DNA, poor-quality DNA, or insufficient high-quality RNA for testing. There were 170 cases with sufficient high-quality DNA and RNA for testing, and all provided evaluable results.

Among the 170 women who were evaluated for both platinum-DNA adducts and corrected ERCC1 expression, the median age at enrollment was 58 years, 88% were Caucasian, 73% had serous adenocarcinoma, 61% were poorly differentiated, and 61% had macroscopic gross residual disease following optimal cytoreductive surgery (Table 1). Detectable adducts were observed in 140 (82.4%) women, and levels ranged from 0.43 to 131 fmol platinum/μg DNA. Adducts were not detected in 30 (17.6%) cases. ERCC1 expression was detected in 132 (77.6%) women, and corrected levels ranged from 0.01 to 2.75. ERCC1 expression was not detected in 38 (22.4%) women. There was no evidence of a correlation between the level of corrected ERCC1 expression and platinum-DNA adducts (Fig. 1). In addition, categorized ERCC1 expression was not associated with categorized platinum-DNA adducts (Table 2).

The Kaplan-Meier method was used to model the time to disease progression or death in women categorized by the presence of platinum-DNA adducts or ERCC1 expression (Fig. 2). A trend suggesting a 4.8-month longer median PFS was observed in women with detectable compared with undetectable platinum-DNA adducts (P = 0.084; Fig. 2A). Moreover, median survival was 23.8 months longer in women with detectable compared with undetectable adducts (P = 0.029; Fig. 2B). In contrast, there was no evidence to suggest a difference in PFS (P = 0.993; Fig. 2C) or OS (P = 0.809; Fig. 2D) in women exhibiting positive compared with negative ERCC1 expression.

Unadjusted and adjusted Cox regression modeling was done to determine whether platinum-DNA adduct level or corrected ERCC1 expression was associated with PFS or OS. When expressed as a continuous variable, neither platinum-DNA adduct level nor corrected ERCC1 expression was associated with a change in the risk of disease progression or death (Table 3) in this cohort. Unadjusted Cox regression modeling indicated a trend toward a reduced risk of disease progression [hazard ratio (HR), 0.686; 95% confidence interval (95% CI), 0.447–1.054; P = 0.086] and a 39% reduction in the risk of death (95% CI, 0.385–0.958; P = 0.032) for women with detectable compared with undetectable platinum-DNA adducts. In contrast, positive compared with negative ERCC1 expression was not associated with an altered risk of disease progression (HR, 0.978; 95% CI, 0.655–1.461; P = 0.915) or death (HR, 1.026; 95% CI, 0.648–1.626; P = 0.912).

Cox regression analyses were then done with adjustments for clinicopathologic factors with prognostic and/or historical value in this patient population, including patient age, performance status, tumor grade, histologic subtype, residual disease status, and/or type of chemotherapy. The purpose of the first approach was to develop a reduced (parsimonious) Cox regression model for PFS or OS (Table 3) using a stepwise method to limit the clinicopathologic factors included in the model to those with prognostic value in this patient cohort. Variable inclusion was set at 0.1, with variable exclusion set at 0.15. The prognostic covariates were included during the first step, and the two biomarkers were added during the second step of model development. Residual disease status was the only clinicopathologic factor that satisfied the selection criteria for the reduced Cox regression model for PFS, whereas performance status, tumor grade, histologic subtype, and residual disease status were incorporated into the reduced model for OS. After adjusting for prognostic factors, the presence of platinum-DNA adducts and ERCC1 expression in peripheral leukocytes collected 20 to 28 h after the initiation of first-line combination chemotherapy were not independent predictors of PFS or OS in women with optimally debulked, advanced EOC (Table 3). A full Cox regression model was also developed with patient age, performance status, tumor grade, histologic subtype, residual disease status, and type of chemotherapy entered during the first step and both platinum-DNA adducts and corrected ERCC1 added during the second step. Similar results were obtained after adjusting for the full set of clinicopathologic factors. Neither categorized platinum-DNA adducts nor corrected ERCC1 expression added prognostic value to the full adjusted Cox regression model for PFS or OS (data not shown).

SLL was not required for this protocol, but was allowed when declared at the time of protocol enrollment as an option to assess disease status. Of the 170 women in this cohort, 75 elected to undergo SLL at enrollment. Ten women refused to undergo the procedure, and another five experienced disease progression before the scheduled SLL. Of the 60 women who underwent SLL, 34 (56.7%) showed no evidence of disease, and 26 (43.3%) exhibited microscopic or macroscopic evidence of disease. Unadjusted and adjusted logistic regression analyses were done to examine the association between platinum-DNA adducts or ERCC1 expression in PBL collected 20 to 28 h after starting cycle 1 of chemotherapy and the results of SLL. This modeling revealed that neither the level nor the presence of either platinum-DNA adducts or corrected ERCC1 expression was associated with a significant change in the estimated odds of observing evidence of disease during SLL as the confidence intervals surrounding these odds ratios overlapped 1.0 (Table 4).

Discussion

This is the first prospective study to evaluate the relationship between platinum-DNA adducts and either PFS or OS in a large cohort of women with ovarian cancer. This study was incorporated into a phase III treatment trial (GOG-0158; refs. 22, 23), and participants were enrolled by 32 parent and 48 affiliate GOG institutions. Platinum-DNA adducts were assessed in peripheral leukocytes 20 to 28 h post–initial infusion of the platinum agent during cycle 1 of chemotherapy using atomic absorbance spectroscopy. The participants had previously untreated, optimally debulked, stage III EOC and were randomized to chemotherapy with paclitaxel and cisplatin or paclitaxel and carboplatin. Women were required to have <1.0 cm of residual disease following surgical staging with cyto-reduction, and as such, tumor response was not
an end point in this trial. Previous studies evaluated the relationship between platinum-DNA adducts in peripheral leukocytes and disease response but not PFS or OS in a variety of cancers including ovarian cancer (8–14, 16–18) or between platinum-DNA adducts in either buccal cells or tumor and disease response in a variety of cancers (19), OS in NSCLC (20), or with PFS and OS in HNSCC (21). In these studies, platinum-DNA adducts were assessed using an ELISA (8–12, 14) atomic absorbance spectroscopy (12–14, 16, 17), inductively coupled plasma–mass spectroscopy (18), immunocytochemistry (19, 20), or ³²P postlabeling (21).

This study showed that the presence of platinum-DNA adducts in PBL 20 to 28 h after the first cycle of chemotherapy was associated with better OS, but not with PFS or the results of SLL. After adjusting for clinicopathologic factors, detectable compared with undetectable platinum-DNA adducts was not an independent predictor of clinical outcome in women with optimally debulked stage III EOC treated with platinum-taxane–based chemotherapy. When expressed as a continuous variable, the levels of platinum-DNA adducts were not associated with PFS, OS, or the results of SLL. Based on the limited sample size for this assessment, this study was only powered to detect a rather large change in the estimated odds of observing evidence of disease during SLL.

Although tumor response was not an end point in the study reported herein, SLL was allowed when declared at the time of protocol enrollment and provided an opportunity to evaluate disease status in this population with optimally debulked stage III EOC. There was no apparent evidence to suggest an association between either the level or the presence of platinum-DNA adducts and disease status following primary treatment with paclitaxel plus carboplatin (atomic absorbance spectroscopy versus immunocytochemistry assay versus ³²P postlabeling), type of sample (PBL versus buccal cells versus tumor tissue), time point for specimen collection (20 to 28 h after the start of the first cycle versus 1 h after the fifth cycle versus 23 h after the end of the first cycle), sample size (170 cases versus 27 cases versus 35 cases), and the type of treatment (paclitaxel plus cisplatin or carboplatin versus concurrent cisplatin radiation versus concurrent cisplatin radiation) in that described herein by van de Vaart et al. and by Hoebers et al., respectively.

Although tumor response was not an end point in the study reported herein, SLL was allowed when declared at the time of protocol enrollment and provided an opportunity to evaluate disease status in this population with optimally debulked stage III EOC. There was no apparent evidence to suggest an association between either the level or the presence of platinum-DNA adducts and disease status following primary treatment with paclitaxel plus carboplatin (atomic absorbance spectroscopy versus immunocytochemistry assay versus ³²P postlabeling), type of sample (PBL versus buccal cells versus tumor tissue), time point for specimen collection (20 to 28 h after the start of the first cycle versus 1 h after the fifth cycle versus 23 h after the end of the first cycle), sample size (170 cases versus 27 cases versus 35 cases), and the type of treatment (paclitaxel plus cisplatin or carboplatin versus concurrent cisplatin radiation versus concurrent cisplatin radiation) in that described herein by van de Vaart et al. and by Hoebers et al., respectively.
Categorized variables

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<th>Reduced model*</th>
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</tr>
<tr>
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<tr>
<td>Positive</td>
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<td>20</td>
<td>1.020 (0.304–3.423)</td>
</tr>
</tbody>
</table>

NOTE: NED, no evidence of disease; Positive, evidence of disease; OR, estimated odds ratio; AU, arbitrary units.

*Logistic regression analysis for modeling the relative odds of observing microscopic or macroscopic evidence of disease.

†Forward stepwise approach with input set at 0.10 and output set at 0.15. Adjustments were made for residual disease status (no versus yes) and treatment regimen (cisplatin plus paclitaxel versus carboplatin plus paclitaxel). Age at enrollment in years, performance status (asymptomatic versus symptomatic), tumor grade (well differentiated versus other grades), and histologic subtype (mucinous versus other histologic subtypes) did not satisfy the selection criteria for inclusion in these models.

A number of studies have evaluated the relationship between tumor expression ERCC1 and disease response, relapse-free survival or OS in ovarian cancer, gastric cancer, and colon cancer (28–33). The present study evaluated whether mRNA expression of ERCC1 in PBL collected 20 to 28 h after starting the first cycle of chemotherapy is associated with worse PFS and OS and an increased risk of finding disease during SLL. High ERCC1 expression (mRNA or protein) in tumor tissue was previously shown to be associated with resistance to platinum-based therapy (28–30, 32) or to not be associated with disease response (31, 33). In addition, the high expression of ERCC1 in tumor has been shown to be associated with shorter survival (30, 31) and a reduced risk of death (33). The study reported herein showed that neither the level nor the presence of ERCC1 in mRNA extracted from PBL collected 20 to 28 h after starting the first cycle of chemotherapy was associated with worse PFS and OS, or an increased risk of finding disease during SLL. Unfortunately, tumor tissue was not available from the women who participated in this clinical trial, and it was not possible to determine whether or not ERCC1 in PBL is a surrogate for ERCC1 in tumor tissue.

This study of molecular correlates of clinical outcome in EOC was conducted in the setting of a prospective randomized clinical trial. The data generated for ERCC1 mRNA levels suggest that leukocytes cannot be used to obtain clinically relevant information on ERCC1 mRNA in this setting. This is in contrast to studies of ERCC1 mRNA in tumor tissues (28–32, 35). We did not assess leukocytes for genomic polymorphisms such as ERCC1 codon 118, which has been associated with platinum sensitivity in lung cancer (42), colon cancer (43), and ovarian cancer (34). The data generated in this study for platinum-DNA adduct are consistent with previously published data in ovarian cancer (8, 9, 11, 12); in some studies of testicular cancer (8, 10); and in studies where platinum was used as the only chemotherapy (11, 13). As suggested in earlier studies, these data suggest that platinum-DNA adduct may go up or down concurrently in leukocytes and in malignant tissues in the same individuals. In addition, the positive correlation between adduct level and clinical outcome provides molecular support for the long-held clinical observation that platinum compounds may constitute the mainstay of treatment in EOC.

Appendix A. Members of the GOG

The following GOG member institutions participated in this translational research study: University of Alabama at Birmingham, Duke University Medical Center, Abington Memorial Hospital, University of Rochester Medical Center, Walter Reed Army Medical Center, Wayne State University, University of Minnesota Medical School, Emory University Clinic, 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, Georgetown University Hospital, University of Cincinnati, University of North Carolina School of Medicine, University of Iowa Hospitals and Clinics, University of Texas Southwest Medical Center at Dallas, Indiana University Medical Center, Wake Forest University School of Medicine, Albany Medical College, University of California Medical Center at Irvine, Tufts-New England Medical Center, Rush-Presbyterian-St. Luke's Medical Center, State University of New York Downstate Medical Center, University of Kentucky, Community Clinical Oncology Program, The Cleveland Clinic Foundation, Johns Hopkins Oncology Center, State University of New York at Stony Brook, Eastern Pennsylvania GYN/ONC Center, P.C., Washington University School of Medicine, Cooper Hospital/University Medical Center, Columbus Cancer Council, University of Massachusetts Medical Center, Fox Chase Cancer Center, Medical University of South Carolina, Women's Cancer Center, University of Oklahoma, University of Virginia, University of Chicago, Tacoma...
References


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