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Randomized phase III trial of tamoxifen versus thalidomide in women with biochemical-recurrent-only epithelial ovarian, fallopian tube or primary peritoneal carcinoma after a complete response to first-line platinum/taxane chemotherapy with an evaluation of serum vascular endothelial growth factor (VEGF): A Gynecologic Oncology Group Study☆☆

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Purpose. To compare progression-free survival (PFS), overall survival (OS) and toxicities of thalidomide versus tamoxifen and to evaluate serum vascular endothelial growth factor (VEGF) in biochemical-recurrent epithelial ovarian cancer, primary peritoneal cancer or fallopian tube carcinoma (EOC/PPC/FTC).

Methods. Biochemical recurrence was defined as a rising CA-125 exceeding twice the upper limit of normal without evidence of disease as defined by RECIST 1.0 criteria. Women with FIGO stages III and IV, historically confirmed EOC/PPC/FTC who were free of disease following first-line chemotherapy were randomized to oral thalidomide 200 mg daily with escalation to a maximum of 400 mg or tamoxifen 20 mg orally twice daily for up to 1 year, progression or adverse effect prohibited further treatment. VEGF was quantified by ELISA in pre and post-treatment serum.

Results. Of the 139 women randomized, 138 were eligible. Interim analysis showed that thalidomide did not reduce the recurrence rate relative to tamoxifen, and the trial was closed. Thalidomide versus tamoxifen was associated with a similar risk of progression (HR = 1.31, 95% confidence interval [CI] = 0.93–1.85), an increased risk of death (HR = 1.76, 95% CI = 1.16–2.68) and more grades 3 and 4 toxicities (55% versus 3%). The most common grades 3 and 4 toxicities were constitutional (12%), somnolence (12%), pulmonary (9%), venous (3%), diarrhea (5%), and menses pain (3%). There were 16 deaths in the tamoxifen arm and 13 deaths in the thalidomide arm. Biochemical recurrence was defined by CA-125 elevation exceeding twice the upper limit of normal in the context of a rising CA-125 of at least 10%. There was no difference in the proportion of women with biochemical recurrence exceeding twice the upper limit of normal (HR = 1.61, 95% CI = 0.77–3.38) and there was no difference in overall survival between the two arms (HR = 1.10, 95% CI = 0.59–2.08).

Conclusions. Thalidomide was not superior to tamoxifen for the treatment of women with biochemical-recurrent ovarian, fallopian tube or primary peritoneal carcinoma following first-line platinum/taxane chemotherapy.
venous thromboembolism (VTE) (6%) and peripheral neurologic (6%) for thalidomide, with VTE (1.4%) and gastrointestinal (1.4%) for tamoxifen. Serum VEGF was not associated with clinical characteristics, treatment, PFS or OS.

**Conclusion.** Thalidomide was not more effective than tamoxifen in delaying recurrence or death but was more toxic. VEGF was not prognostic in this cohort.

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supporting the use of tamoxifen showed a 17% response rate in measurable recurrent disease (17%) [4], 13% response rate in platinum-resistant disease [5], observed stable disease in 38% of patients lasting a median of 3 months [4] and diverse estrogen receptor (ER)-dependent and ER-independent mechanisms of action [6-11] including anti-angiogenic activity [6,11]. Agents that inhibited tumor angiogenesis and invasion were considered to be ideal candidates for the experimental arm for GOG#198 given their potential to extend the duration of remission and disease progression while exhibiting a more favorable toxicity profile than cytotoxic drugs given at maximally tolerated doses. Thalidomide, an old drug with potent anti-angiogenic activity [12,13], emerged as a viable experimental agent for GOG#198. Thalidomide gained notoriety in the 1960s when it was administered to women in their first trimester of pregnancy and found to cause limb defects at birth [14,15]. These potent teratogenic effects on fetal limbs were the result of thalidomide's anti-angiogenic activity. Thalidomide given at a continuous low dose [16] was thought to be less toxic than current chemotherapy agents and might be considered to be ideal candidates for the experimental arm for GOG#198 given their potential to extend the duration of remission and disease progression or adverse effects prohibit additional therapy.

Clinical management, assessments and testing

Pre-treatment evaluation consisted of history and physical exam, assessment of GOG performance status, chest x-ray, electrocardiogram, complete blood count (CBC), serum chemistries (electrolytes, creatinine, magnesium, calcium, phosphate and liver function test), urinalysis, CA-125 and documentation of lack of measurable disease by CT scan. During the study, interval history, physical examination, toxicity assessment, CBC and serum chemistries were obtained at the start of each cycle. Patients were seen every 4 weeks to assess toxicities according to the National Cancer Institute Common Toxicity Criteria (CTC) Version 2. Tumor assessment was to be performed every 12 weeks with CT scan unless indicated by new complaints or symptoms. Disease progression was based on RECIST 1.0 criteria. CA-125 levels were measured every 12 weeks. Changes in CA-125 were not used to document disease progression or discontinue treatment.

Clinical end points

Patients were followed quarterly for 2 years, semi-annually for 3 years and then annually until death from completion of treatment. PFS was calculated as the time in months from study enrollment to disease progression or death, or date of last contact for those who were alive, without evidence of disease progression. Duration of survival was calculated as the time from enrollment to death or to the date of last contact for those who were still alive. Death due to any cause was considered an uncensored event. Treatment-free interval (TFI) was defined as the time from completing first-line platinum/taxane chemotherapy until enrollment onto this study. For the six patients who received prior maintenance therapy TFI was measured from the date of the last cycle of maintenance therapy.

Enzyme-linked immunosorbent assay

VEGF concentration was assessed in duplicate in pre- and post-treatment serum in a single batch experiment using the validated Quantikine Human VEGF Immunoassay Kit (DVE00) and a VEGF standard as recommended by the manufacturer (R&D Systems, Inc., Minneapolis, MN).
The study treatments were allocated sequentially from concealed permuted blocks within TFI strata (<6 months versus 6 to 12 months versus >12 months). The primary analysis of PFS in this study was to include all eligible patients. The null hypothesis to be tested was: thalidomide does not reduce the recurrence rate relative to tamoxifen treated patients. The relative event rates were to be estimated with a proportional hazards model adjusted for TFI.

The targeted sample size was 260 patients. The first interim analysis was to occur after the first 105 patients had experienced either progression or death and include an assessment of thalidomide superiority and futility. Accounting for the interim analyses, the overall study design provided a 90% chance of declaring thalidomide active, if it truly reduced the PFS event rate by 33%, while type I error was limited to 5% for a one-tailed test. An exact trend test was used to assess the hypothesis that the grade of each adverse event was independent of study treatment. Since there are several adverse event categories and a precise hypothesis was not prespecified, the critical \( p \)-value for statistical significance for these tests is set to 0.005 (two-sided).

Mean serum VEGF was calculated from duplicate measurements used to evaluate reproducibility. A Kruskal–Wallis test was used to assess the relationship between VEGF and disease characteristics. Mean VEGF concentration was included in a proportional hazards model first as a continuous value, categorized at the median and then transformed to quartile scores. The Spearman’s rank correlation coefficient was used to assess the relationship between VEGF in matched pre- and post-treatment sera and to pre-treatment CA-125.

**Clinical end points**

Conditioned on the available data, the probability that this study would conclude that thalidomide was superior to tamoxifen at the final analysis was about 2.5%, even if the future data supported the alternative hypothesis, that is, thalidomide truly reduces the PFS event rate by 33%.

The first scheduled interim analysis of this study was conducted in July 2007. At that time, the PFS event rate was 38% higher and death rate was 39% higher among those randomized to thalidomide when compared to tamoxifen. Based on a review of the data available for the interim analysis, the GOG Data Monitoring Committee voted to terminate accrual onto this study, but to continue the follow-up on those already enrolled.

At the time of the current analysis, the median duration of follow-up among the 47 women alive at last contact was 31 months. Women randomized to thalidomide experienced statistically similar PFS (Fig. 1A) but shorter OS (Fig. 1B) compared to tamoxifen. The median PFS was 3.2 and 4.5 months while median survival duration was 24.0 and 33.2 months for the thalidomide and tamoxifen arms, respectively. After adjusting for prior TFI, thalidomide was associated with a similar risk of disease progression (hazard ratio [HR] = 1.31, 95% confidence interval [CI] = 0.92–1.85), but an increased risk of death (HR = 1.76, 95% CI = 1.16–2.68) compared with tamoxifen. A strong association was observed between prior TFI and both PFS and OS (\( p < 0.001 \)). Specifically, median PFS and OS were 2 and 14.5 month for women with TFI ≤6 months, 3.8 and 27 months for those with TFI from 6 to 12 months, and 4.9 and 45 months for those with a TFI >12 months, respectively.

**Translational end points**

VEGF concentration was quantified pre-treatment in duplicate in 111 women with a median of 164.3 pg/ml, an intra-class correlation coefficient (reliability) of 0.75, and evidence of heteroscedasticity (variance between duplicates was proportional to VEGF concentration) (Table 3). Pre-treatment VEGF concentration did not appear to vary by patient age (<60 versus 60 to 69, versus ≥70 years), site of primary tumor (ovary versus fallopian tube or peritoneum), stage at diagnosis (II vs III vs IV) or prior TFI (<6 versus 6 to 12 versus >12 months). When categorized at median (164.3 pg/ml), women with low versus high pre-treatment serum VEGF had similar PFS (Fig. 2A, \( p = 0.161 \)) and OS (Fig. 2B, \( p = 0.366 \)). Exploratory analyses with a proportional hazards model indicated that pre-treatment VEGF concentration (expressed as a continuous variable, dichotomized at the median or categorized into quartiles) was not associated with either risk of disease progression or death. Moreover, within each treatment group, pre-treatment VEGF concentration was not associated with either PFS or OS duration. There were 55 patients with matched pre- and post-treatment sera (Fig. 3). A direct correlation was observed for serum VEGF pre- and post-treatment (Spearman’s correlation coefficient = 0.503, \( p < 0.001 \)). There was no evidence to suggest that changes in VEGF were dependent on treatment, or were associated with PFS or OS. Also, there was no association between pre-treatment CA-125 values and VEGF (Spearman’s correlation coefficient = −0.085, \( p = 0.381 \)).

**Discussion**

In this study, thalidomide at a dose of 200–400 mg/day was not more effective than tamoxifen in delaying disease recurrence among women with biochemical-recurrent EOC/PPC/FTC. Women randomized to thalidomide experienced statistically similar PFS (Fig. 1A), 9-month shorter median survival, worse OS (Fig. 1B) and an increased risk of death (HR = 1.76, 95% CI = 1.16–2.68) compared with tamoxifen. How to account for these survival differences remains unclear at this time. It is possible that tamoxifen may have positive ER-dependent and/or -independent effects [6–11] on this patient population accounting for the survival difference. Should this truly be
the case, this finding might be of significance as the recent MRC/EORTC findings presented at the 2009 ASCO meeting showed that early treatment of this patient population had no survival benefit compared to a reference arm of delayed treatment [2]. The lack of standardized treatment arms in the EORTC trial, however, might have diluted the chance of observing a clinical benefit with early treatment. Given that GOG#198 did not include a no treatment arm and that the MRC/EORTC trial did not include a tamoxifen treatment arm, these trials are difficult to compare. It will, however, be interesting to review the type of treatments employed and toxicity generated by the chemotherapy arm in the MRC OV05/EORTC 55955 protocol [2]. Alternatively, thalidomide may have promoted disease progression in this patient population via regulation of cytokines, chemokines and/or angiogenic factors other than VEGF thus accounting for the increase death rate in this group. Further study of tamoxifen in this patient population would be warranted to determine whether the survival benefit is clinically meaningful and whether tamoxifen can play a role in the adjuvant treatment of ER-positive EOC/PPC/FTC as is does in ER-positive breast cancer.

Both agents in this trial have been shown to exhibit antiangiogenic activity [6,11,12,30–32]. Thalidomide inhibits expression of the pro-angiogenic factors VEGF and basic fibroblast growth factor (bFGF) via mechanisms involving tumor necrosis factor-alpha (TNF-alpha) [12,30–32] and transcriptional activation of the VEGF promoter [33]. Tamoxifen inhibits angiogenesis and VEGF by ER-dependent

[6,11] and -independent mechanisms [32]. Translational objectives were prospectively embedded into the current study to examine the prognostic relevance of VEGF as previously documented for previously

Fig. 1. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B) by randomized treatment group.

Fig. 2. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B) by pretreatment serum VEGF concentration categorized at the median as low (<164.3 pg/ml) or high (≥164.3 pg/ml). Log-rank test was used to evaluate the differences in progression-free survival (p = 0.161) and overall survival (p = 0.366) distributions by low versus high VEGF.

Fig. 3. Scatter plot for VEGF concentration in pre-treatment and post-treatment sera by treatment regimen for the 55 patients with matched specimens. Descriptive statistics (1st quartile, median, 3rd quartile) are also available for VEGF concentrations in the 111 patients with pre-treatment serum (62.2 pg/ml, 164.3 pg/ml and 366.8 pg/ml) and the 60 women with post-treatment serum (69.2 pg/ml, 221.7 pg/ml and 352.3 pg/ml).
untreated primary EOC [18–24], and to test the hypothesis that elevated VEGF levels in association with a rising CA-125 may herald a particularly aggressive recurrent tumor that might benefit from early intervention with agents that have antiangiogenic properties like thalidomide [12] or tamoxifen [6,11], or be associated with thalido-
mide-resistance and production of pro-angiogenic cytokines during thalidomide treatment as observed in relapsing and resistant multiple myeloma [30]. In GOG#198, neither pre-treatment VEGF nor changes in VEGF concentration (pre- and post-treatment) were associated with DFS, OS or treatment. These results are consistent with two studies in recurrent ovarian cancer [24,27] but differ from other studies in women with previously untreated [18–24] or recurrent [26,28,29] EOC. Type of specimen, time point, disease status, sample size, detection method or treatment regimen may have contributed to the observed disparity between studies. In addition, pre-treatment serum VEGF concentrations did not significantly correlate with TFI. Though an 8-month difference was noted in median survival in women with low compared to high VEGF levels (34 versus 26 months, respectively) this difference was not statistically significant (p = 0.366). The stability of the VEGF levels between pre- and post-treatment serum samples is consistent with the poor outcome of this patient population in both treatment arms. Longitudinal expression of VEGF, other angiogenic markers and cytokines alone and in combination with CA-125 are also being examined in GOG#198 sera.

This study did show the strong association between shorter TFI and worse outcome. In fact, patients with a prior TFI of >6 versus >12 months had a 30-month shorter median survival time and 3-month shorter median PFS time. This supports the contention that biology of disease has an important influence on overall prognosis.

Tamoxifen exhibited a relatively low toxicity profile in this trial. Thalidomide was significantly more toxic with a higher proportion of patients experiencing grades 3 and 4 toxicities (55% versus 3%) and discontinuing therapy due to adverse events (16% versus 1%) compared to tamoxifen. Specifically, 78% of patients received ≥3 cycles of tamoxifen whereas only 50% of patients received ≥3 cycles of thalidomide. The imbalance in treatment allowed more patients in the thalidomide group to come off study earlier and receive second line chemotherapy agents. One would think that the thalidomide group would have a PFS and OS benefit due to earlier treatment with chemotherapy compared to tamoxifen. However, this was not the case and this potentially supports the concept that tamoxifen may indeed have a positive overall effect on this patient population.

In summary, early therapeutic intervention using thalidomide in biochemical-recurrent EOC/PPC/FTC did not delay recurrence or death compared with tamoxifen. In fact, a qualitative comparison of times to progression or death favored tamoxifen. The lower toxicity of tamoxifen makes it an attractive treatment option in this patient population especially if future studies can show it to be more effective than a no treatment arm or other active agents in this setting. Treatment in the setting of biochemical-recurrent EOC/PPC/FTC should have a low toxicity index while achieving maximal effect.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

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