Title

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 evalua...

Journal

Gynecologic oncology, 119(3)

ISSN

0090-8258

Authors

Hurteau, Jean A
Brady, Mark F
Darcy, Kathleen M
et al.

Publication Date

2010-12-01

DOI

10.1016/j.ygyno.2010.08.002

Gynecologic Oncology 119 (2010) 444–450

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

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 ☆,☆☆

Jean A. Hurteau [a,*], Mark F. Brady [b], Kathleen M. Darcy [b], William P. McGuire [c], Pamela Edmonds [d,1], Michael L. Pearl [e], Iouri Ivanov [f], Krishnansu S. Tewari [g], Robert S. Mannel [h], Kristine Zanotti [i], Doris M. Benbrook [j]

[a] NorthShore University Health System Division of GYN Oncology, Department of Obstetrics and Gynecology, University of Chicago Pritzker School of Medicine, Evanston Hospital, Evanston, IL 60201, USA
[b] Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY 14263, USA
[c] Harry & Jeanette Weinberg Cancer Institute, Baltimore, MD 21237, USA
[d] Department of Pathology, Thomas Jefferson University, Philadelphia, PA 19107, USA
[e] Department of Obstetrics and Gynecology, Stony Brook, Stony Brook, NY 11794, USA
[f] Pathology Department, Columbus Cancer Council, Columbus, OH 43210, USA
[g] Department of Obstetrics and Gynecology, University of California Medical Center at Irvine, Chao Family Comprehensive Cancer Center, Orange, CA 92868, USA
[h] Department of Gynecologic Oncology, University of Oklahoma, Oklahoma City, OK 73190, USA
[i] Department of GYN/ONC, University Hospitals Case Medical Center, Cleveland, OH 44106, USA
[j] Department of Gynecologic Oncology, Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190, USA

ARTICLE INFO

Article history:
Received 19 May 2010
Available online 17 September 2010

Keywords:
Ovarian cancer
Thalidomide
Tamoxifen
VEGF
CA-125
Recurrence

ABSTRACT

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, histologically 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%),

☆ This study was supported by the National Cancer Institute grants to the Gynecologic Oncology Group (GOG) Administrative Office (CA 27469), the GOG Tissue Bank (CA 27469 and CA 11479) and the GOG Statistical and Data Center (CA 37517).

☆☆ The following GOG member institutions participated in this protocol: Duke University Medical Center; Walter Reed Army Medical Center; University of Minnesota Medical School; University of Mississippi; Colorado Gynecologic Oncology Group, UCCC; University of California at Los Angeles; University of Cincinnati Medical Center; University of North Carolina; Southwestern Medical Center of Texas; Indiana University Cancer Center; Wake Forest University School of Medicine; University of California Medical Center at Irvine; Tufts-New England Medical Center; Rush University Medical Center; State University of New York at Brooklyn; University of Kentucky; University of New Mexico Health Sciences Center; Cleveland Clinic Foundation; State University of New York at Stony Brook; Washington University School of Medicine; Cooper Hospital/University Medical Center; Columbus Cancer Council/Ohio State; M.D. Anderson Cancer Center; Fox Chase Cancer Center; Women's Cancer Center, University of Nevada; University of Oklahoma; University of Virginia Health Sciences Center; University of Chicago; Mayo Clinic; Case Western Reserve University; Tampa Bay Cancer Consortium; Gynecologic Oncology Network/Brody School of Medicine; Yale University; University of Wisconsin Hospital; Cancer Trials Support Unit; Women and Infants Hospital; The Hospital of Central Connecticut at New Britain General Hospital; and Community Clinical Oncology Program.

* Corresponding author. University of Chicago Pritzker School of Medicine, NorthShore University Health System, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Evanston Hospital, 2650 Ridge Avenue, Walgreen Building Suite 1507, Evanston, IL 60201, USA. Fax: +1 847 733 5358.
E-mail address: jhurteau@uchicago.edu (J.A. Hurteau).

[1] Dr. Edmonds is now at Abington Memorial Hospital, Abington, PA 19001.

0090-8258/$ – see front matter
doi:10.1016/j.ygyno.2010.08.002

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.

Introduction

Current therapy for patients with advanced epithelial ovarian, primary peritoneal or fallopian tube carcinoma (EOC/PPC/FTC) includes cytoreductive surgery followed by platinum/paclitaxel-based chemotherapy. This multi-modality approach achieves clinical responses in about 70% of patients, although a majority of women eventually relapse and die of disease progression. The first sign of relapse can be a progressively rising CA-125 [1]. Biochemical-recurrent EOC is defined as CA-125 elevation above normal values without clinical evidence of disease, and can predate clinical disease by approximately 3–6 months [1]. Even if CA-125 elevation is a harbinger of EOC relapse, the question remains as to whether early therapeutic intervention can translate into extending the duration of clinical remission.

Table 1
Patient characteristics and treatment duration.

Characteristic	Thalidomide		Tamoxifen	
	Cases	%	Cases	%
Age				
<50	7	10.3	12	17.1
50–59	17	25.0	14	20.0
60–69	22	32.4	28	40.0
70–79	17	25.0	15	21.4
80–89	5	7.4	1	1.4
Race				
Non-Hispanic—White	66	97.0	65	92.9
Non-Hispanic—Black	0	0.0	2	2.9
Hispanic	1	1.5	1	1.4
American Indian	0	0.0	1	1.4
Asian/Pacific Islander	1	1.5	1	1.4
Performance Status				
0–asymptomatic	63	92.6	67	95.7
1–symptomatic	5	7.4	3	4.3
Histology*				
Serous adenocarcinoma	56	82.4	63	90.0
Endometrioid	2	2.9	1	1.4
Adenocarcinoma, not specified	2	2.9	2	2.9
Mixed epithelial	7	10.3	2	2.9
Other	1	1.5	2	2.9
Primary Site of Disease				
Ovary	58	85.3	59	84.3
Peritoneum	10	14.7	10	14.3
Fallopian Tube	0	0	1	1.4
Prior Treatment Free Interval				
<6 months	12	17.6	14	20.0
6–12 months	27	39.7	28	40.0
>12 months	29	42.6	28	40.0
Tumor grade				
1	6	8.8	3	4.3
2	17	25.0	20	28.6
3	45	66.1	47	67.1
Number of cycles				
0	1	1.5	1	1.4
1	18	26.9	6	8.6
2	15	20.9	8	11.4
3	17	25.4	15	21.4
4	6	9.0	9	12.9
5	3	4.5	7	10.0
6	3	4.5	11	15.7
>6	5	7.5	13	18.6
Total	68		70	

The Gynecologic Oncology Group (GOG) has focused considerable effort on extending the duration of remission and improving survival through the evaluation of novel agents as well as different routes of chemotherapy administration, combinations, sequences and types of consolidation/maintenance regimens. In 2003, the GOG initiated this study, GOG#198, in response to a paucity of data from clinical trials evaluating the benefit of early therapeutic intervention in patients with asymptomatic biochemical-recurrent EOC/PPC/FTC. Since then, trial results in this disease setting are beginning to emerge.

The randomized trial of early treatment with unspecified-chemotherapy based on rising CA-125 in comparison to delayed treatment with unspecified-chemotherapy until documented disease progression in the United Kingdom (Medical Research Council and European Organization for Research and Treatment of Cancer; protocol OV05/EORCT 55955) showed no survival benefit and was presented at the 2009 American Society of Clinical Oncologists (ASCO) Annual Meeting [2]. In contrast, the randomized, double-blinded, placebo-controlled phase II trial of the anti-angiogenic urokinase plasminogen inhibitor Å6 showed a higher proportion of patients with longer progression-free survival (PFS) when treated with Å6 versus placebo in patients ($n=22$) with biochemical-recurrent EOC [3].

The GOG carefully considered the treatment arms to be evaluated in GOG#198. A no treatment arm when this study was initiated was deemed to be unacceptable due to patient anxiety over a rising CA-125 compelling a significant proportion of physicians in the United States to intervene therapeutically. The use of tamoxifen as the reference arm seemed justified based on a favorable toxicity profile compared with available cytotoxic agents and the lack of interference with subsequent interventions after documentation of clinical progression [4]. Studies

Table 2
Number of patients experiencing all CTC graded adverse events.

Adverse event	Thalidomide ($n=67$)					Tamoxifen ($n=69$)				
	CTC grade					CTC grade				
	0	1	2	3	4	0	1	2	3	4
Leukopenia*	42	19	5	1	0	61	8	0	0	0
Neutropenia*	46	12	7	2	0	64	3	2	0	0
Thrombocytopenia	61	5	0	1	0	65	4	0	0	0
Anemia	52	11	4	0	0	59	9	1	0	0
Auditory	64	1	2	0	0	68	1	0	0	0
DVT/thrombosis	63	0	0	2	2[a]	68	0	0	0	1
Other cardiovascular	56	7	4	0	0	63	4	2	0	0
Constitutional*	25	18	16	8	0	51	14	4	0	0
Dermatologic*	45	10	7	5	0	65	3	1	0	0
Endocrine*	66	0	1	0	0	45	13	11	0	0
Gastrointestinal*	25	16	23	3	0	46	17	5	1	0
Genitourinary/renal	64	1	2	0	0	64	4	1	0	0
Hepatic	65	2	0	0	0	66	2	1	0	0
Metabolic	59	6	1	1	0	61	8	0	0	0
Musculoskeletal	65	1	1	0	0	65	4	0	0	0
Somnolence*	50	4	5	7	1	69	0	0	0	0
Other neurologic*	35	13	15	4	0	67	1	1	0	0
Peripheral neurologic*	35	16	12	3	1	60	8	1	0	0
Ocular/visual	56	6	4	1	0	67	2	0	0	0
Pain	41	14	9	3	0	50	13	6	0	0
Pulmonary*	56	1	4	6	0	68	0	1	0	0

[a] One patient developed bilateral deep vein thrombosis and pulmonary emboli, placed on Coumadin, but died 7 days later.

* $p<0.005$ for an exact trend test of the hypothesis that CTC adverse event grade is independent of treatment.

Table 3
Pre-treatment serum VEGF Concentrations and baseline characteristics.

Baseline characteristics	Cases	Pre-treatment serum VEGF concentration (pg/ml)		*p*-value
		Median	1st–3rd quartiles	
Patient age (years)				
<60	46	163.2	65.3–374.9	0.265
60–69	39	187.0	96.4–354.3	
≥70	26	115.1	29.6–306.4	
Site of primary disease				
Ovary	96	146.7	60.0–369.5	0.221
Fallopian tube/peritonium	15	250.0	134.4–354.3	
Tumor stage				
Stage III	96	170.5	73.1–368.5	0.167
Stage IV	15	102.2	27.6–273.8	
Prior treatment free interval (months)				
<6	20	258.9	90.6–423.7	0.315
6–12	43	137.8	47.1–273.8	
>12	48	151.0	73.1–371.3	
Total	111	164.3	62.2–366.8	

Kruskal–Wallis test [34].
Pre-treatment serum VEGF concentrations are available for 111 patients.

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 extend PFS and overall survival (OS) in this patient population.

The primary objective of GOG 198 was to compare the PFS of women receiving tamoxifen or thalidomide who are in complete clinical remission following front line treatment for EOC/PPC/FTC but have a rising CA-125 (biochemical recurrence). A secondary objective was to compare toxicities of these treatments. Translational objectives were to determine whether changes in VEGF in serum were independent of randomization treatment, or associated with PFS. VEGF is a potent pro-angiogenic factor [17] with prognostic value in primary EOC [18–24]. Its value in recurrent EOC is not well understood [25–29].

Methods

Patients

Eligible patients had histologically confirmed FIGO stage III or IV, EOC/PPC/FTC and had received only one (platinum/taxane-based) first-line chemotherapy. Eligibility was confirmed by the Pathology Review Committee. The patients had to be clinically and radiologically without evidence of measurable or non-measurable disease as defined by RECIST 1.0 criteria. Ascites and/or pleural effusions were defined as non-measurable disease, and were not exclusion criteria if asymptomatic. Patients must have had adequate bone marrow, renal and hepatic functions that included an absolute neutrophil count (ANC) greater than or equal to 1,500/μl, platelets greater than or equal to 100,000/μl, a creatinine less than or equal to 1.5× institutional upper limit normal (ULN) and bilirubin less than or equal to 1.5× ULN with SGOT and alkaline phosphatase less than or equal to 2.5× ULN. Patients were ineligible if they had a history of venous thromboembolism (VTE), cerebral vascular accident (CVA), brain metastasis or were on full dose anticoagulation, anti-seizure medications or receiving any biphosphanates such as zoledronic acid.

Biochemical-recurrent ovarian cancer was defined as a CA-125 that exceeded twice the upper limit of normal. The patient's CA-125 levels must have normalized during first-line therapy. For patients with CA-125 levels <100 U/ml at study registration, a second confirmatory measurement within a period of not more than 4 weeks was required. Patients with CA-125 levels ≥100 U/ml were eligible without a confirmatory measurement. All women provided written informed consent and participating institutions obtained annual institutional review board (IRB) approval for this study in accordance with federal, state, local and institutional requirements and guidelines.

Drug administration

Patients were randomized to either thalidomide at 200 mg orally daily with weekly dose escalation of 100 mg to a maximum dose of 400 mg or tamoxifen at 20 mg orally twice daily for up to twelve 28-day cycles, 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 $VEGF_{165}$ standard as recommended by the manufacturer (R&D Systems, Inc., Minneapolis, MN).

Statistical considerations

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.

Results

Patient characteristics and treatment

Of the 139 patients registered onto the study between February of 2003 and July 2007, 138 were eligible and one was excluded due to an inappropriate primary diagnosis. Patient characteristics are listed in Table 1. Median age was 63.7 years and 86% had a diagnosis of serous adenocarcinoma. There were 6 (4%) patients who received maintenance treatment (paclitaxel) prior to enrollment. Overall, prior TFI was <6 months for 19% and >12 months for 41% of patients. There were 68 and 70 patients randomly assigned to thalidomide and tamoxifen, respectively. Overall, patients received more cycles of tamoxifen than thalidomide (Table 1). Specifically, 78% of patients received ≥3 cycles of tamoxifen whereas only 50% of patients received ≥3 cycles of thalidomide. Disease progression was the primary reason for discontinuing study treatment in 81% of tamoxifen and 57% of thalidomide treated patients. Adverse events necessitated discontinuing treatment in 1% of tamoxifen and 31% of thalidomide treated patients.

Adverse events

Adverse events are summarized in Table 2. There were more grades 3 and 4 toxicities in the thalidomide arm than the tamoxifen arm (55% versus 3%). The most common grades 3 and 4 toxicities with thalidomide were constitutional (12%), somnolence (12%), pulmonary (9%), venous thromboembolism (VTE) (6%) and peripheral neurologic (6%) and with tamoxifen, VTE (1.4%) and gastrointestinal (1.4%). One patient on thalidomide developed bilateral deep vein thrombosis and pulmonary emboli but unfortunately expired despite anticoagulation. Overall, leucopenia, neutropenia, constitutional, dermatologic, gastrointestinal and pulmonary adverse events occurred more frequently and with greater severity with thalidomide that with tamoxifen. In addition, somnolence, peripheral neuropathy, other neurotoxicity and endocrine adverse events occurred more frequently and more severely with thalidomide.

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] = 0.928–1.85), 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 (III versus 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

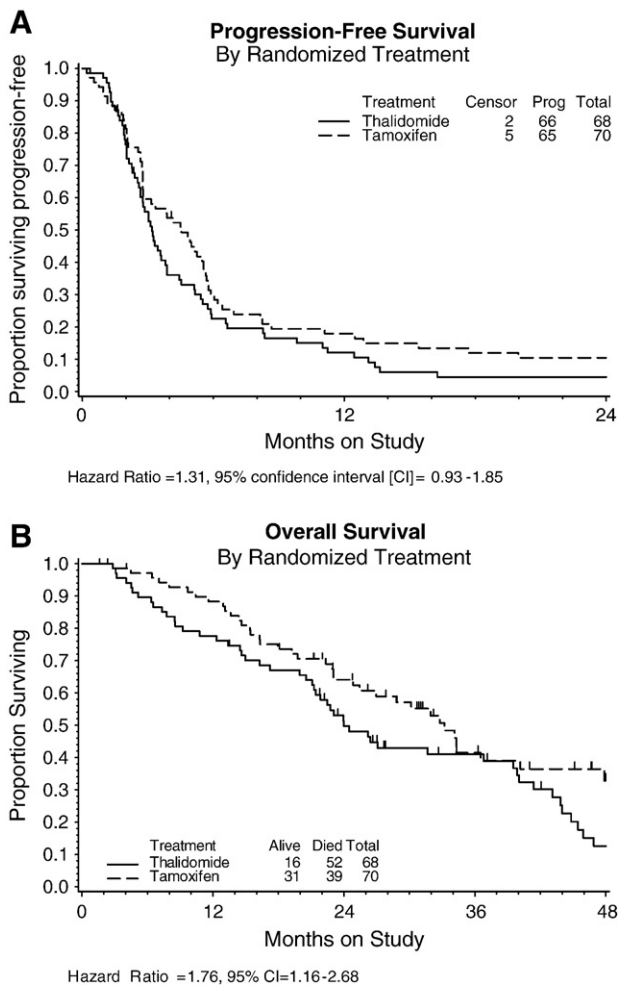

Fig. 1. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B) by randomized treatment group.

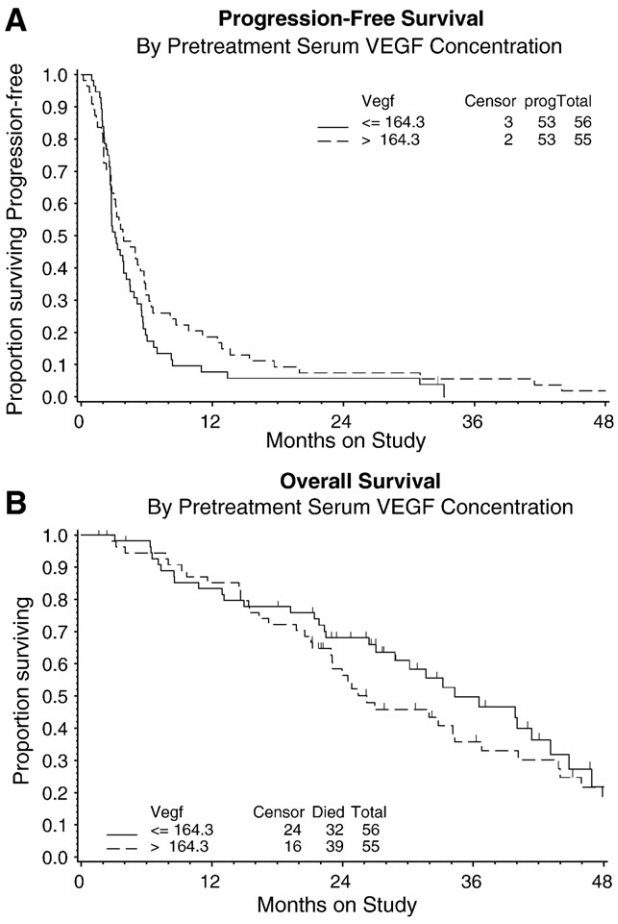

Fig. 2. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B) by pre-treatment serum VEGF concentration categorized at the median as low (≤164.3 pg/ml) or high (>164.3 pg/ml). Log-rank test was used to evaluate the differences in progression-free survival ($p=0.161$) and overall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

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 anti-angiogenic 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

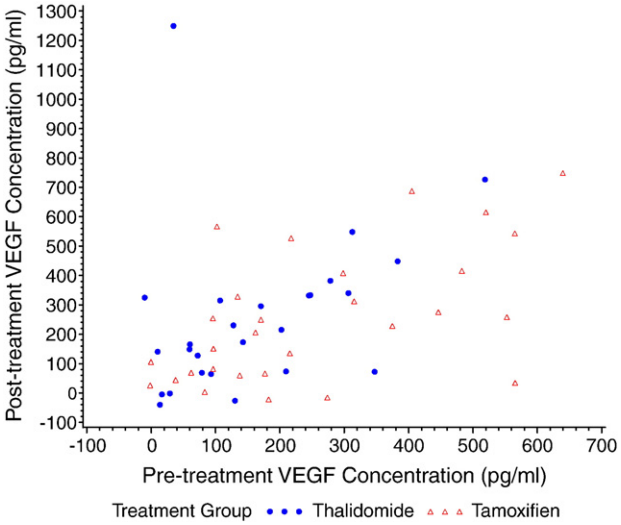

Fig. 3. Scatter plot for VEGF concentration in pre-treatment and post-treatment sera by treatment regimen for the 55 patients with matched specimens. Descriptive statistics (1st quartile, median, 3rd quartile) are also available for VEGF concentrations in the 111 patients with pre-treatment serum (62.2 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 anti-angiogenic properties like thalidomide [12] or tamoxifen [6,11], or be associated with thalidomide-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 PFS, 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.

Acknowledgments

The authors thank Anne Reardon for her assistance in formatting and editing this manuscript and Suzanne Baskerville for coordinating the clinical data for this study. We also thank the GOG Publications Subcommittee for their critical review of and thoughtful suggestions for the manuscript.

References

[1] Tuxen MK, Soletormos G, Dombernowsky P. Serum tumor marker CA 125 for monitoring ovarian cancer during follow-up. Scand J Clin Lab Invest 2002;62:177–88.
[2] Rustin GJ, van der Burg ME. A randomized trial in ovarian cancer of early treatment of relapse based on CA125 level alone versus delayed treatment based on conventional clinical indicators (MRC OVO5/EORTC 55955 trials). J Clin Oncol 2009;27(18S):793s.
[3] Ghamande SA, Silverman MH, Huh W, Behbakht K, Ball G, Cuasay L, et al. A phase 2, randomized, double-blind, placebo-controlled trial of clinical activity and safety of subcutaneous A6 in women with asymptomatic CA125 progression after first-line chemotherapy of epithelial ovarian cancer. Gynecol Oncol 2008;111:89–94.
[4] Hatch KD, Beecham JB, Blessing JA, Creasman WT. Responsiveness of patients with advanced ovarian carcinoma to tamoxifen. A Gynecologic Oncology Group study of second-line therapy in 105 patients. Cancer 1991;68:269–71.
[5] Markman M, Iseminger KA, Hatch KD, Creasman WT, Barnes W, Dubeshter B. Tamoxifen in platinum-refractory ovarian cancer: a Gynecologic Oncology Group Ancillary Report. Gynecol Oncol 1996;62:4–6.
[6] Hyder SM, Nawaz Z, Chiappetta C, Stancel GM. Identification of functional estrogen response elements in the gene coding for the potent angiogenic factor vascular endothelial growth factor. Cancer Res 2000;60:3183–90.
[7] Jordan VC, Gapstur S, Morrow M. Selective estrogen receptor modulation and reduction in risk of breast cancer, osteoporosis, and coronary heart disease. J Natl Cancer Inst 2001;93:1449–57.
[8] Matthews J, Gustafsson JA. Estrogen signaling: a subtle balance between ER alpha and ER beta. Mol Interv 2003;3:281–92.
[9] Levin ER. Integration of the extranuclear and nuclear actions of estrogen. Mol Endocrinol 2005;19:1951–9.
[10] Zhao C, Dahlman-Wright K, Gustafsson JA. Estrogen receptor beta: an overview and update. Nucl Recept Signal 2008;6:e003.
[11] Applanat MP, Buteau-Lozano H, Herve MA, Corpet A. Vascular endothelial growth factor is a target gene for estrogen receptor and contributes to breast cancer progression. Adv Exp Med Biol 2008;617:437–44.
[12] D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci USA 1994;91:4082–5.
[13] Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med 1995;1:27–31.
[14] McBride WG. Thalidomide and congenital abnormalities. Lancet 1961;2:1358.
[15] Lenz W. Thalidomide and congenital abnormalities. Lancet 1962;1:45.
[16] Kamat AA, Kim TJ, Landen Jr CN, Lu C, Han LY, Lin YG, et al. Metronomic chemotherapy enhances the efficacy of antivascular therapy in ovarian cancer. Cancer Res 2007;67:281–8.
[17] Nagy JA, Dvorak AM, Dvorak HF. VEGF-A and the induction of pathological angiogenesis. Annu Rev Pathol 2007;2:251–75.
[18] Tempfer C, Obermair A, Hefler L, Haeusler G, Gitsch G, Kainz C. Vascular endothelial growth factor serum concentrations in ovarian cancer. Obstet Gynecol 1998;92:360–3.
[19] Chen CA, Cheng WF, Lee CN, Chen TM, Kung CC, Hsieh FJ, et al. Serum vascular endothelial growth factor in epithelial ovarian neoplasms: correlation with patient survival. Gynecol Oncol 1999;74:235–40.
[20] Oehler MK, Caffier H. Prognostic relevance of serum vascular endothelial growth factor in ovarian cancer. Anticancer Res 2000;20(6D):5109–12.
[21] Cooper BC, Ritchie JM, Broghammer CL, Coffin J, Sorosky JI, Buller RE, et al. Preoperative serum vascular endothelial growth factor levels: significance in ovarian cancer. Clin Cancer Res 2002;8:3193–7.
[22] Harlozinska A, Sedlaczek P, Kulpa J, Grybos M, Wójcik E, Van Dalen A, et al. Vascular endothelial growth factor (VEGF) concentration in sera and tumor effusions from patients with ovarian carcinoma. Anticancer Res 2004;24:1149–57.
[23] Li L, Wang L, Zhang W, Tang B, Zhang J, Song H, et al. Correlation of serum VEGF levels with clinical stage, therapy efficacy, tumor metastasis and patient survival in ovarian cancer. Anticancer Res 2004;24(3b):1973–9.
[24] Hefler LA, Zeillinger R, Grimm C, Sood AK, Cheng WF, Gadducci A, et al. Preoperative serum vascular endothelial growth factor as a prognostic parameter in ovarian cancer. Gynecol Oncol 2006;103:512–7.
[25] Abendstein B, Daxenbichler G, Windbichler G, Zeimet AG, Geurts A, Sweep F, et al. Predictive value of uPA, PAI-1, HER-2 and VEGF in the serum of ovarian cancer patients. Anticancer Res 2000;20(1B):569–72.
[26] Alvarez Secord A, Sayer R, Snyder SA, Broadwater G, Rodriguez GC, Berchuck A, et al. The relationship between serum vascular endothelial growth factor, persistent disease, and survival at second-look laparotomy in ovarian cancer. Gynecol Oncol 2004;94:74–9.
[27] Garcia AA, Hirte H, Fleming G, Yang D, Tsao-Wei DD, Roman L, et al. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. J Clin Oncol 2008;26:76–82.
[28] Schilder RJ, Sill MW, Lee RB, Shaw TJ, Senterman MK, Klein-Szanto AJ, et al. Phase II evaluation of imatinib mesylate in the treatment of recurrent or persistent epithelial ovarian or primary peritoneal carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 2008;26:3418–25.
[29] Han ES, Burger RA, Darcy KM, Sill MW, Greer BE, Sorosky JI, et al. Relationship between angiogenic markers and clinicopathologic factors/outcome in GOG-170D, a phase II trial of bevacizumab (Bev) in recurrent or persistent epithelial ovarian cancer (EOC) and primary peritoneal cancer (PPC). J Clin Oncol 2008;26 (ASCO Abstract #5577).
[30] Dmoszyńska A, Bojarska-Junak A, Domański D, Roliński J, Hus M, Soroka-Wojtaszko M. Production of proangiogenic cytokines during thalidomide treatment of multiple myeloma. Leuk Lymphoma 2002;43:401–6.

[31] Melchert M, List A. The thalidomide saga. Int J Biochem Cell Biol 2007;39: 1489–99.
[32] Blackwell KL, Haroon ZA, Shan S, Saito W, Broadwater G, Greenberg CS, et al. Tamoxifen inhibits angiogenesis in estrogen receptor-negative animal models. Clin Cancer Res 2000;6:4359–64.
[33] Yin Y, Wang S, Sun Y, Matt Y, Colburn NH, Shu Y, et al. JNK/AP-1 pathway is involved in tumor necrosis factor-alpha induced expression of vascular endothelial growth factor in MCF7 cells. Biomed Pharmacother 2009;63:429–35.
[34] Kruskal WH, Wallis WA. Use of ranks on one-criterion variance analysis. J Am Stat Assoc 1952;47:583–21.