
Breast Angiosarcoma: Case Series and Expression of Vascular Endothelial Growth Factor

Rondeep Brar^a Robert West^b Daniela Witten^d
Bhargav Raman^e Charlotte Jacobs^c Kristen Ganjoo^c

Departments of ^aInternal Medicine, ^bSurgical Pathology, and ^cMedical Oncology,
Stanford University Medical Center, ^dDepartment of Statistics, Stanford
University, and ^eStanford University School of Medicine, Stanford, Calif., USA

Key Words

Breast · Angiosarcoma · Vascular · Endothelial · Angiogenesis

Abstract

Purpose: Angiosarcoma of the breast is a rare, malignant tumor for which little is known regarding prognostic indicators and optimal therapeutic regimens. To address this issue, we performed a retrospective analysis of breast angiosarcoma cases seen at Stanford University along with immunohistochemical analysis for markers of angiogenesis.

Methods: Breast angiosarcoma cases seen between 1980 and 2008 were examined. Viable tissue blocks were analyzed for expression of vascular endothelial growth factor and its receptors.

Results: A total of 16 cases were identified. Data was collected regarding epidemiology, treatment, response rates, disease-free survival, and the use of various imaging modalities. Five tissue blocks remained viable for immunohistochemical analysis. Vascular endothelial growth factor-A was positively expressed in 3 of these samples.

Conclusion: Angiosarcoma of the breast is an aggressive malignancy with a propensity for both local recurrence and distant metastases. Angiogenesis inhibition may represent a novel therapeutic modality in this rare, vascular malignancy.

Introduction

Sarcomas of the breast are rare, malignant tumors of mesenchymal origin. Within this cohort, angiosarcoma represents one of the most common histological subtypes. Unfortunately, these tumors tend to be aggressive with high recurrence rates and an overall poor prognosis. Total mastectomy remains the primary treatment for breast

angiosarcoma (BAs). The use of neoadjuvant and adjuvant cytotoxic chemotherapy, typically with anthracycline-ifosfamide and gemcitabine-taxane regimens, has been previously reported with variable success [1]. Given the endothelial origin of BAs, angiogenesis inhibition represents a potentially attractive therapeutic modality.

The present study is a single-institution, retrospective analysis of all BAs cases seen at Stanford University Medical Center (SUMC). Clinical and pathologic data along with immunohistochemical (IHC) profiling of vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFR) will be presented.

Materials and Methods

Databases within SUMC's divisions of pathology, oncology, and radiation oncology were independently searched to extract all known BAs patients seen between 1980 and 2008. Various tumor characteristics, including location, size, grade, and stage, were examined. In those patients with a history of prior breast malignancy, efforts were made to determine their location, histological subtype, treatment, and complications, including significant lymphedema.

Primary treatment, including radiation, surgery, and chemotherapy, was documented. Disease-free dates were defined as the date of primary surgical intervention in patients with negative pathologic margins and without known metastases. In instances of disease recurrence, salvage therapies and response were documented. Disease-free survival (DFS) was defined as the date of pathologic diagnosis to the date of pathologically confirmed disease recurrence.

The use of various imaging modalities in establishing the diagnosis of BAs, including mammography, ultrasonography, and breast magnetic resonance imaging (MRI) was also evaluated. Finally, menopausal status at diagnosis and pertinent familial histories of breast cancer and sarcoma were established.

For immunohistochemistry, slides were cut at 4 mm, deparaffinized in xylene and hydrated in a graded series of alcohol. The primary antibodies used were: rabbit anti-human VEGFA (A-20) polyclonal antibody (Santa Cruz Biotechnology, Inc., Santa Cruz, Calif., USA; unit # sc-152), goat anti-human VEGFB (N-19) polyclonal antibody (Santa Cruz Biotechnology, Inc.; unit # sc-1878), goat anti-human VEGFC (C-20) polyclonal antibody (Santa Cruz Biotechnology, Inc.; unit # sc-1881), goat anti-human VEGFD (N-19) polyclonal antibody (Santa Cruz Biotechnology, Inc.; unit # sc-7603), mouse anti-human VEGFR1 monoclonal antibody (Santa Cruz Biotechnology, Inc.; unit # sc-65442), rabbit anti-human VEGFR2 polyclonal antibody (Abcam, Cambridge, UK; unit # ab45010), and mouse anti-human VEGFR3 monoclonal antibody (Abcam; unit # ab51496). The antigen retrieval solution was EDTA, pH 8. Slides were boiled by microwaving in antigen retrieval solution for 12 min. IHC reactions were visualized using rabbit, goat, or mouse versions of the biotin-free EnVision + system (DAKO, Carpinteria, Calif., USA) using diaminobenzidine.

Results

A total of 16 female patients with pathologic diagnoses of BAs were identified. Epidemiologic and pathologic data are presented in [table 1](#). Prior breast malignancies were present in 8 patients, of which 6 were infiltrating ductal carcinomas and 2 were infiltrating lobular carcinomas. Only 1 patient had a prior history of longstanding lymphedema. Previous ipsilateral breast irradiation was seen in 6 cases, and these patients tended to present at an older age (median 74 years, range 63–80 years). The average latency from irradiation to diagnosis of angiosarcoma in this cohort was 78 months (range 56–134 months).

Primary and salvage surgery, chemotherapy, and radiotherapy are presented in [table 2](#). Disease recurrence was documented in 5 of 16 patients at a median interval of 7 months (range 1–22 months). The Kaplan-Meier curve for DFS is depicted in [fig. 1](#).

Five tissue blocks of adequate viability were available for IHC analysis. Several antibodies were tested, including those against VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGFR-1, VEGFR-2, and VEGFR-3. Of these, clear positive and negative staining on archival tissue was demonstrated only for VEGF-A, VEGF-B, and VEGFR-2. Positive VEGF-A staining was noted in 3 of the 5 samples. VEGF-B and VEGFR-2 staining was negative in all 5 samples. Representative IHC sections are shown in [fig. 2](#).

Discussion

Sarcomas of the breast are rare, malignant tumors that occur at an annual frequency of 4.5 cases per 1 million women [2]. Within this group, angiosarcoma occurs with an annual incidence between 0.002 and 0.005% [3]. A recent review of BAs cases published to date established a median age at presentation of 70 (63 in the present study) and a median latency from prior radiotherapy to diagnosis of BAs as 72 months (78 months in the present study) [4].

In our series, the predominant imaging modalities prior to diagnosis were mammography and ultrasonography, whereas MRI was performed in only 1 patient. The optimal type of imaging for diagnosis of BAs is not known. Mammography may fail to identify 33% of BAs in contrast to only 9% of breast carcinomas [5, 6]. Using ultrasound, BAs may appear hyperechogenic and well circumscribed with posterior shadowing and, uncommonly, coarse calcification. Using MRI, BAs may have striking T2 signal, peripheral vascular channels, and either non-enhancement or enhancement without washout due to the presence of blood-filled vascular spaces. [Fig. 3](#) highlights representative radiologic findings in a 31-year-old female with primary BAs.

An interesting departure of our data from that previously published is a relatively lower burden of recurrent disease. Here, we report a recurrence rate of 37.5% over a median follow-up interval of 8 months. Previous estimates have reported variable recurrence rates ranging from 25–73% [3, 7]. This may partially be explained by our shorter follow-up interval. However, our population also contained a relatively greater percentage of patients treated with modified radical mastectomy (25%) over simple mastectomy (75%). Since the optimal extent of primary surgical resection has never been prospectively examined, it is difficult to gauge the magnitude of this effect. Previous retrospective analyses have reported 5 year DFS and overall survival of 44 and 61%, respectively [1]. Collectively, our data confirm BAs as an aggressive vascular malignancy of elderly women with a propensity for both local recurrence and distant metastases.

VEGF and VEGFR represent critical components in the process of angiogenesis, vascular permeability, and metastasis [8]. The VEGF structural family includes VEGF-A, VEGF-B, VEGF-C, and VEGF-D. Of these, VEGF-A is the major proangiogenic agent through its interactions with VEGFR-2, also known as kinase-insert domain-containing receptor (kdr). Although VEGF-A binds VEGFR-1, also known as fms-like tyrosine kinase (flt), the role of this interaction remains unclear.

Our series did not suggest widespread VEGF-A, VEGF-B, or VEGFR-2 expression in BAs. One of the 3 patients with positive VEGF-A staining in our series was a previously healthy 31-year-old female with primary BAs. It remains unclear whether primary BAs is a distinct clinical entity in comparison to secondary BAs in the previously irradiated breast. A prior report comparing 32 primary BAs cases with 23 secondary cases in previously irradiated patients found the former group to have better DFS and overall survival within the first 3 years, but no difference in overall survival curves [9].

The possibility of targeted anti-angiogenic therapy in the treatment of BAs remains intriguing. Recent IHC data from Itakura et al. [10] demonstrated positive VEGF-A expression in 32 of 34 (94%) angiosarcomas, although none of these were breast malignancies. A previous study demonstrated positive VEGF staining in 5 of 6 (83%) BAs, although correlating clinicopathologic and epidemiologic data were not presented [11].

The absence of widespread VEGF positivity in the current study does not preclude the use of anti-angiogenic agents in BAs treatment. For example, data from other tumor models has suggested that VEGF levels may not be predictive of clinical response to bevacizumab (Genentech, South San Francisco, Calif., USA), a monoclonal antibody against VEGF approved for treatment in metastatic breast, lung, and colon cancer [12].

Furthermore, therapy with paclitaxel, an alkaloid ester derived from the yew tree, has demonstrated efficacy in angiosarcoma. A phase II clinical trial of weekly paclitaxel for patients with metastatic or unresectable angiosarcoma has been completed [13]. In this analysis, a 19% overall response rate and 24% non-progression rate were observed at 6 months. Additionally, 3 patients who were unresectable at diagnosis achieved a partial response, permitting curative intent surgery. Two of these patients attained a complete remission, highlighting the mainstay of surgical therapy as primary treatment. Paclitaxel's cytotoxic effects have traditionally been ascribed to enhanced tubulin polymerization resulting in mitotic arrest [14]. However, paclitaxel has also been noted to have intrinsic anti-angiogenic activity that, at low concentrations, occurs without effecting microtubule function [15]. Hence, angiogenesis inhibition via anti-VEGF therapy may indeed represent a viable treatment. An open-label phase II study of single agent bevacizumab in angiosarcoma is currently ongoing.

Although this vascular malignancy remains rare, the increasing use of breast-conserving therapy with adjuvant radiotherapy may contribute to a rising incidence in the coming decades. Larger descriptive series, particularly documenting outcomes with neoadjuvant and adjuvant chemo- and radiotherapy, are needed. The ultimate efficacy of targeted anti-VEGF treatment will depend upon data from ongoing clinical trials.

Table 1. Epidemiologic and pathologic data

Age at diagnosis, years	
Range	23–80
Median	63
Gender	
Female	16 (100%)
Tumor size, cm	
Range	1.5–16.6
Median	5.5
Tumor grade	
High	6 (37.5%)
Intermediate	3 (18.75%)
Low	4 (25%)
Unavailable	3 (18.75%)
Overall stage	
I	2 (12.5%)
II	8 (50%)
III	0 (0%)
IV	1 (6.25%)
Incomplete	5 (31.25%)
Breast location	
Right	7 (43.75%)
Left	9 (56.25%)
History of prior ipsilateral breast malignancy	
IDC	6 (37.5%)
ILC	2 (12.5%)
History of prior ipsilateral breast irradiation	6 (37.5%)
History of significant lymphedema	1 (6.25%)
History of malignancy in 1st degree relative	
Sarcoma	0 (0%)
Breast	2 (12.5%)
Menopausal status at diagnosis	
Pre	6 (37.5%)
Post	9 (56.25%)
Unavailable	1 (6.25%)
Imaging modalities prior to diagnosis	
Ultrasound	2 (12.5%)
Mammography	9 (56.25%)
Ultrasound and mammography	3 (18.75%)
Breast MRI	1 (6.25%)

IDC = Infiltrating ductal carcinoma; ILC = infiltrating lobular carcinoma.

Table 2. Primary and salvage therapies

Primary surgical therapy	
SM	12 (75%)
MRM	4 (25%)
Primary adjuvant chemotherapy	
DC	1 (6.25%)
DI	1 (6.25%)
EI	1 (6.25%)
Primary radiotherapy	3 (18.75%)
Recurrence of disease	
Total	6 (37.5%)
Chest wall	4 (25%)
Liver	2 (12.5%)
Lungs	2 (12.5%)
Brain	1 (6.25%)
Tonsil	1 (6.25%)
Salvage surgery	
Total	4
Local excision	2 (12.5%)
Radical chest dissection	1 (6.25%)
Stereotactic intracranial resection	1 (6.25%)
Salvage radiotherapy	1 (6.25%)
Salvage chemotherapy	2 (12.5%)
Response to salvage therapy	
Progression	4 (25%)
Disease-free	1 (6.25%)

SM = Simple mastectomy; MRM = modified radical mastectomy; DC = doxorubicin/cyclophosphamide; DI = doxorubicin/ifosfamide; EI = epirubicin/ifosfamide.

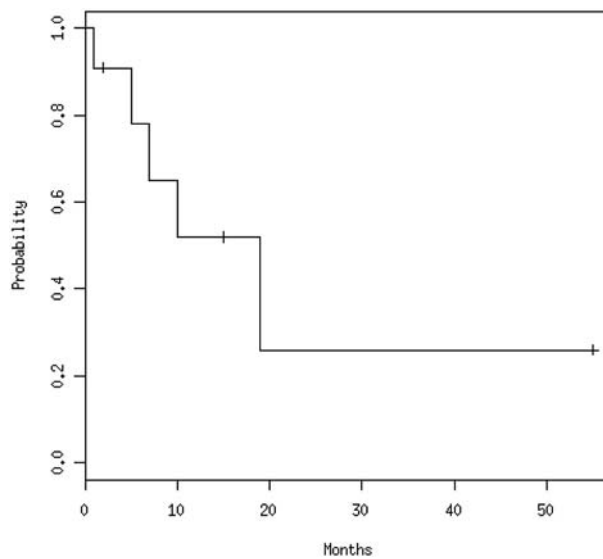
Fig. 1. Kaplan-Meier curve depicting disease-free survival.

Fig. 2. VEGF immunostaining in representative full cross-sections of angiosarcoma cases. **a** High-level immunostaining for VEGF-A; **b** low-level immunostaining for VEGF-A; **c** absence of staining for VEGF-B; **d** absence of staining for VEGFR-2. All images at 400×.

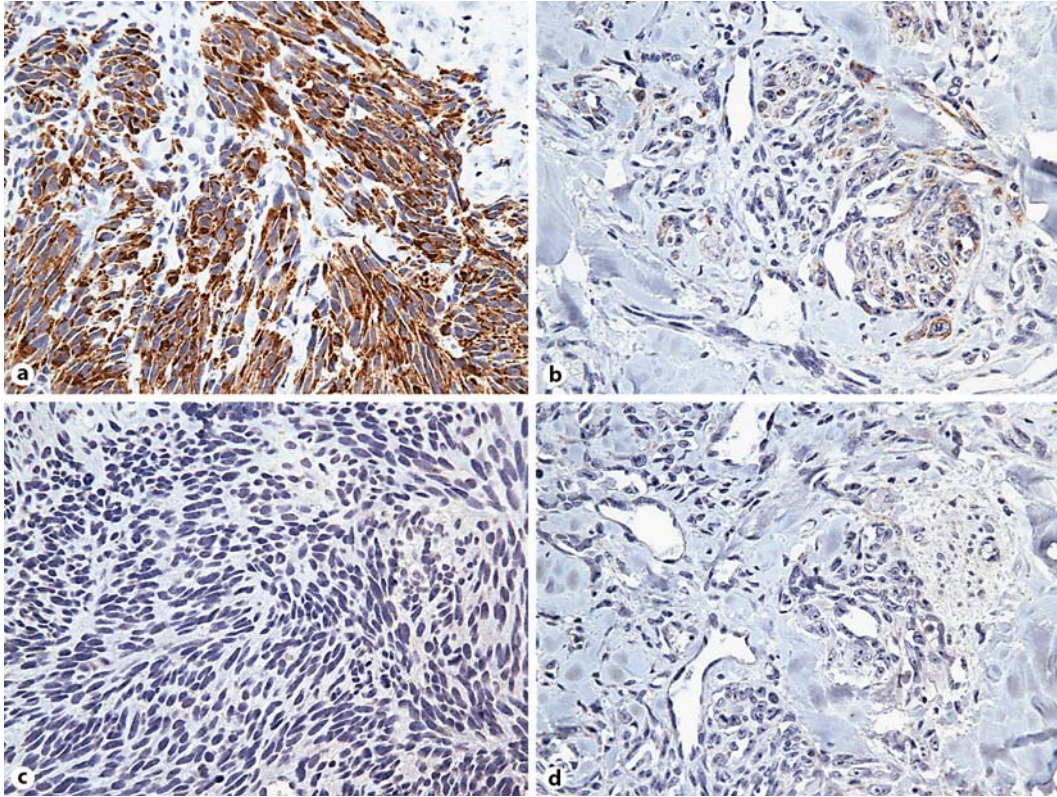
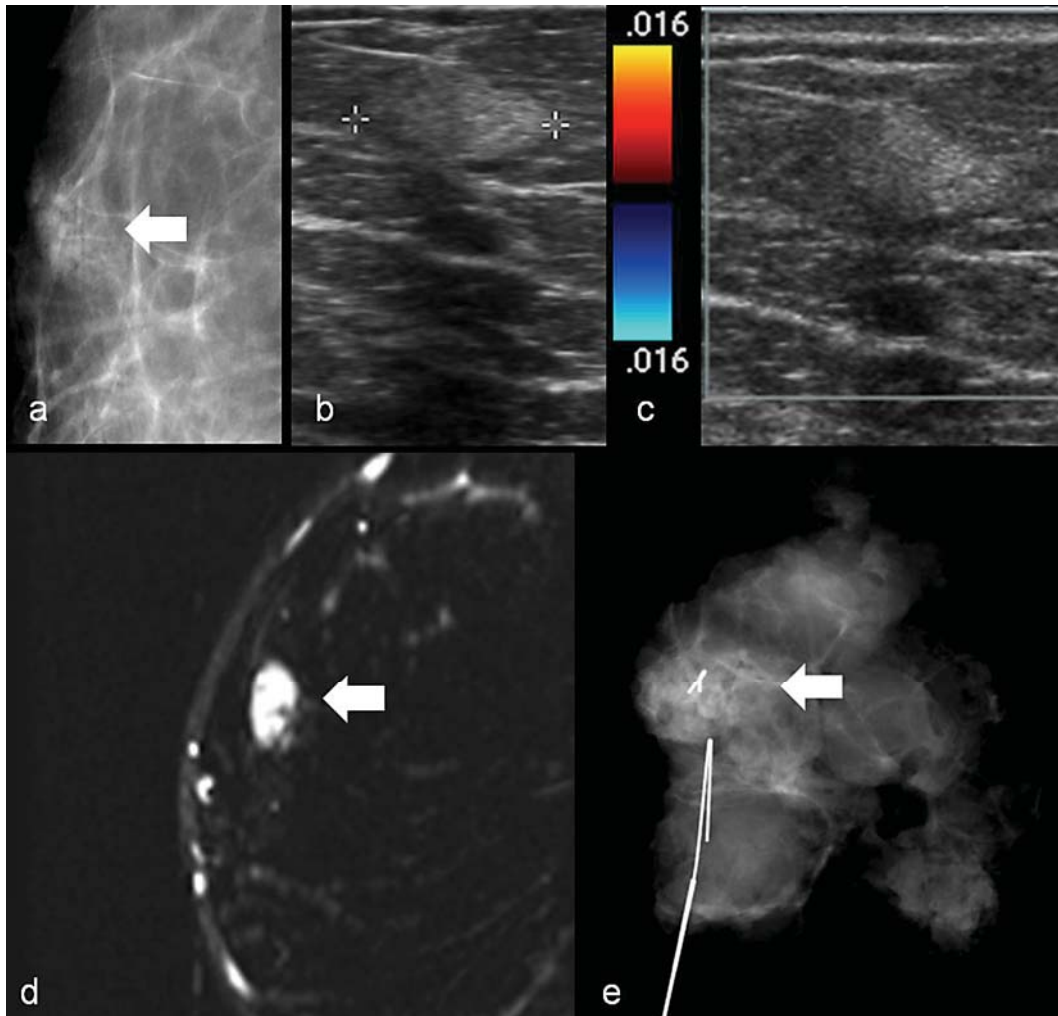


Fig. 3. Primary angiosarcoma of the left breast in a 31-year-old female. Initial mammography and ductogram were negative. However, spot images from the post-ductogram mammographic study (**a**) revealed a subtle mixed density lesion with both lucent and dense foci and lobulated, well-circumscribed margins (arrow) that were not appreciated on the initial mammogram. Ultrasound (**b, c**) of this location revealed a well-circumscribed heterogeneously echogenic lesion with posterior shadowing but no detectable flow. MRI (**d**) demonstrated a 1.3-cm lesion with high T2 signal but no significant enhancement (arrow). Mammogram of the post-excision specimen (**e**) demonstrates the sharply marginated mass with coarse heterogeneous stroma (arrow). Pathology indicated that this angiosarcoma was low-grade, which may account for the lack of vascularity and enhancement on ultrasound and MRI.



References

- 1 Sher T, Hennessy BT, Valero V, Broglio K, Woodward WA, Trent J, Hunt KK, Hortobagyi GN, Gonzalez-Angulo AM: Primary angiosarcomas of the breast. *Cancer* 2007;110:173–178.
- 2 Oberman HA: Sarcomas of the breast. *Cancer* 1965;18:1233–1243.
- 3 Luini A, Gatti G, Diaz J, Botteri E, Oliveira E, Cecilio Sahium de Almeida R, Veronesi P, Intra M, Pagani G, Naninato P, Viale G: Angiosarcoma of the breast: the experience of the European Institute of Oncology and a review of the literature. *Breast Cancer Res Treat* 2007;105:81–85.
- 4 Abbott R, Palmieri C: Angiosarcoma of the breast following surgery and radiotherapy for breast cancer. *Nat Clin Pract Oncol* 2008;5:727–736.
- 5 Liberman L, Dershaw DD, Kaufman RJ, Rosen PP: Angiosarcoma of the breast. *Radiology* 1992;183:649–654.
- 6 Baker LH: Breast cancer detection demonstration project: five-year summary report. *CA Cancer J Clin* 1982;32:194–225.
- 7 Monroe AT, Feigenberg SJ, Mendenhall NP: Angiosarcoma after breast-conserving therapy. *Cancer* 2003;97:1832–1840.
- 8 Stacker SA, Achen MG, Jussila L, Baldwin ME, Alitalo K: Lymphangiogenesis and cancer metastasis. *Nat Rev Cancer* 2002;2:573–583.
- 9 Vorburger SA, Xing Y, Hunt KK, Lakin GL, Benjamin RS, Feig BW, Pisters PW, Ballo MT, Chen L, Trent J, Burgess M, Patel S, Pollock R, Cormier JN: Angiosarcoma of the breast. *Cancer* 2005;104:2682–2688.
- 10 Itakura E, Yamamoto H, Oda Y, Tsuneyoshi M: Detection and characterization of vascular endothelial growth factors and their receptors in a series of angiosarcomas. *J Surg Oncol* 2008;97:74–81.
- 11 Zietz C, Rössle M, Haas C, Sendelhofert A, Hirschmann A, Stürzl M, Löhrs U: MDM-2 oncoprotein overexpression, p53 gene mutation, and VEGF up-regulation in angiosarcomas. *Am J Pathol* 1998;153:1425–1433.
- 12 Jubb AM, Hurwitz HI, Bai W, Holmgren EB, Tobin P, Guerrero AS, Kabbinarav F, Holden SN, Novotny WF, Frantz GD, Hillan KJ, Koeppe H: Impact of vascular endothelial growth factor-A expression, thrombospondin-2 expression, and microvessel density on the treatment effect of bevacizumab in metastatic colorectal cancer. *J Clin Oncol* 2006;24:217–227.
- 13 Penel N, Bui BN, Bay JO, Cupissol D, Ray-Coquard I, Piperno-Neumann S, Kerbrat P, Fournier C, Taieb S, Jimenez M, Isambert N, Peyrade F, Chevreau C, Bompas E, Brain EG, Blay JY: Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *J Clin Oncol* 2008;26:5269–5274.
- 14 Jordan MA, Toso RJ, Thrower D, Wilson L: Mechanism of mitotic block and inhibition of cell proliferation by taxol at low concentrations. *Proc Natl Acad Sci USA* 1993;90:9552–9556.
- 15 Wang J, Lou P, Lesniewski R, Henkin J: Paclitaxel at ultra low concentrations inhibits angiogenesis without affecting cellular microtubule assembly. *Anticancer Drugs* 2003;13:13–19.