Bevacizumab Therapy in Patients with Recurrent Uterine Neoplasms

JASON D. WRIGHT[1], MATTHEW A. POWELL[2], JANET S. RADER[2], DAVID G. MUTCH[2] and RANDALL K. GIBB[3]

[1]*Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, NY;*
[2]*Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University School of Medicine, WA;* [3]*Billings Clinic Cancer Center, Billings, MT, U.S.A.*

Abstract. *Background: Angiogenesis plays an important role in endometrial carcinogenesis. We reviewed our experience with the anti-VEGF monoclonal antibody bevacizumab for the treatment of recurrent uterine neoplasms. Patients and Methods: A retrospective analysis of women with recurrent uterine neoplasms treated with bevacizumab was performed. Results: A total of 11 patients were identified, 9 with epithelial endometrial carcinomas and 2 with leiomyosarcomas. All patients had multi-site disease and were heavily pretreated with a median of 3 prior chemotherapy regimens. All received bevacizumab combination therapy which was well-tolerated. Two patients had partial responses, 3 had stable disease, while 5 patients progressed. One subject was not assessable for response. The median progression-free interval was 5.4 months for the entire cohort and 8.7 months for those who achieved clinical benefit (PR or SD). Conclusion: Bevacizumab was well-tolerated and displayed promising anti-neoplastic activity in patients with endometrial cancer and uterine leiomyosarcoma.*

Endometrial cancer is the most common gynecologic malignancy with nearly 41,200 cases expected in 2006 (1). Prognosis for patients with early stage disease confined to the uterus is excellent. However, the outcome for patients with recurrent, metastatic disease remains poor (2, 3). In a series of 379 patients with recurrent endometrial cancer the survival for women with pelvic recurrences was 12%. For patients with distant metastatic disease survival dropped to 5%, while only 2% of those with combined pelvic and distant failure were salvaged (2). Thus there is a clear need for agents with activity in the setting of recurrent disease.

Angiogenesis plays an important role in the development and progression of endometrial cancer (4-7). Abulafia *et al.* noted a progressive increase in microvessel density (MVD) with the progression from benign endometrium to hyperplasia to invasive cancer (8). Increased vascular density is also associated with a poor prognosis. The 5-year overall survival was 82% in a cohort of endometrial cancer patients with low microvessel density compared to only 52% for those with high MVD (5). Additionally, high VEGF expression and microvessel density are associated with lymphvascular space invasion, nodal metastases and advanced stage disease (6).

Angiogenesis therefore appears to be a potential therapeutic target for women with uterine neoplasms. Treatment with the monoclonal anti-VEGF antibody bevacizumab has demonstrated impressive results for a number of solid tumors (9, 10). Based upon these findings we have incorporated bevacizumab into the treatment of women with recurrent epithelial and mesenchymal uterine neoplasms. We describe the results of bevacizumab therapy for these patients, to our knowledge the first report of bevacizumab for uterine cancer.

Patients and Methods

Study approval was obtained from the Washington University Human Studies Committee. A review of institutional databases was then performed to identify patients with recurrent uterine tumors treated with the monoclonal, anti-vascular endothelial growth factor antibody bevacizumab between January 2005 and August 2006. Women with epithelial as well as mesenchymal lesions were included in the analysis. Patients treated with single agent bevacizumab as well as those treated with bevacizumab in combination with cytotoxic chemotherapy were examined.

Toxicity was assessed and documented according the National Cancer Institute's Common Toxicity Criteria version 3.0 guidelines. Response was determined based on radiographic evaluation. Response Criteria in Solid Tumors (RECIST) were utilized to

Correspondence to: Jason D. Wright, MD, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, 161 Fort Washington Ave, 8th Floor, New York, NY 10032, U.S.A. Tel: +1 212 305 3410, Fax: +1 212 305 3412, e-mail: jw2459@columbia.edu

Key Words: Bevacizumab, angiogenesis, endometrial cancer, uterine cancer.

Table I. *Demographic data.*

Characteristics	Patients, n=11
Age (years)	
Median	57
Range	38-70
Histology	
Endometrioid	4
Serous	2
Adenosquamous	1
Mixed epithelial	2
Leiomyosarcoma	2
Stage	
I	3
II	1
III	2
IV	5
Adjuvant therapy	
Radiation	3
Chemotherapy	7
Hormonal therapy	1
Recurrence location[1]	
Intraabdominal	7
Liver	8
Lung	4
Bone	1
Retroperitoneal nodes	5
Prior regimens	
Median	3
Range	1-12
Bevacizumab combination	
Cyclophosphamide	4
Paclitaxel	1
5-Fluorouracil	1
Capecitabine	1
Doxorubicin	1
Etoposide	1
Carboplatin/docetaxel	1
Gemcitibine/liposomal doxorubicin	1
Bevacizumab doses	
Median	6
Range	3-21
Bevacizumab administered (mg)	
Median	4,679
Range	990-13,315

[1]Several patients recurred in multiple locations.

Table II. *Incidence of grade >2 toxicity.*

	Patients, n		
	Grade 2	Grade 3	Grade 4
Neutropenia	0	2	0
Anemia	2	1	0
Thrombocytopenia	0	1	1
Fatigue	2	0	0
Mucositis	0	1	0
Nausea	2	1	0
Proteinuria	0	0	0
Hypertension	2	0	0
Bleeding	0	1	0
Thrombotic	0	0	0

Table III. *Response and outcome.*

	Patients, n
Response	
Complete response	0
Partial response	2
Stable disease	3
Progression	5
Not assessable	1
Vital Status	
Alive with disease	6
Dead of disease	5

document response. As patients were treated outside of the setting of a clinical trial, confirmatory imaging was not required. Overall (OS) and progression-free survival (PFS) were determined for each patient using standard definitions.

Results

Eleven patients with recurrent uterine tumors treated with bevacizumab were identified. The characteristics of the eleven subjects are displayed in Table I. The median age of the women was 57 years, ranging from 38 to 70. Nine patients had epithelial malignancies, including two papillary serous carcinomas and 2 mixed epithelial tumors that each contained serous elements. Two patients had uterine leiomyosarcomas. The initial stage at diagnosis was: I (3), II (1), III (2) and IV (5). All eleven women had multi-site recurrences. Additionally, all had received prior salvage therapy. The median number of prior chemotherapeutic regimens was 3 with a range of 1-12. At the initiation of therapy all women had measurable disease.

Bevacizumab was administered in combination with a cytotoxic agent in all eleven patients (Table I). The combination included oral cyclophosphamide in 4 women. Other combination regimens included weekly paclitaxel, 5-fluorouracil, capecitabine, doxorubicin, etoposide, carboplatin/docetaxel and gemcitabine/liposomal doxo-rubicin. The median cumulative dose of bevacizumab received by the patients was 4,679 mg. The toxicities encountered are shown in Table II. Overall the regimen was well-tolerated; the most common side-effects were anemia, nausea, neutropenia, thrombocytopenia, hypertension and fatigue. One episode of grade 4 thrombocytopenia was encountered. Although no

thromboembolic complications were identified, one case of a grade 3 gastrointestinal bleeding episode was noted. No gastrointestinal perforations occurred.

Ten patients were assessable for response. Two partial responses were seen, three women had stable disease and five progressed on treatment (Table III). One subject was not assessable for response. One PR was noted in a patient with an endometrioid endometrial carcinoma with widespread disease treated with combination bevacizumab and cyclophosphamide. The second PR was documented in a woman with pulmonary, vaginal and osseous metastases treated with bevacizumab/cyclophosphamide. When stratified by histology, one patient with leiomyosarcoma had stable disease while the other progressed. Among those with epithelial endometrial tumors, 2 patients had partial responses, 2 had stable disease and 4 progressed. The median progression-free interval for the entire cohort was 5.4 months. The median progression-free interval in the 5 patients with clinical benefit (PR or stable disease) was 8.7 months (range 6.7-12.5 months). At last follow-up, 6 women were alive with disease while 5 patients had died from progressive disease.

Discussion

In our cohort of patients with recurrent uterine cancer, bevacizumab therapy was well tolerated and displayed encouraging anti-tumor activity. Emerging preclinical data highlights the importance of VEGF during endometrial carcinogenesis. In an evaluation of 115 patients with normal endometria, endometrial hyperplasia and endometrial cancer VEGF expression was noted in 66% of the subjects with cancer, higher than seen in the women with CAH and benign endometrial findings (4). Likewise, Holland *et al.* demonstrated mRNA of VEGF-A in 100% of the endometrial cancers examined, but none of the CAH or benign endometrial specimens. The authors also characterized the expression of VEGF-B, a family member of VEGF-A. Interestingly, VEGF-B mRNA levels appeared to be lower in the cancers than in the benign endometrium. The authors hypothesized that VEGF-B contributes to endometrial cancer development through modulation of the availability of receptors for VEGF-A (11). These findings highlight the complex interplay of angiogenic factors that likely function in the endometrium.

Despite improvements in survival, treatment for recurrent endometrial cancer is usually palliative. Therapy typically employs either hormonal agents or cytotoxic chemotherapy. Active agents include doxorubicin, platinum compounds and taxanes. The Gynecologic Oncology Group recently reported the results a phase III trial comparing doxorubicin and cisplatin with or without paclitaxel for patients with advanced, recurrent or metastatic endometrial cancer. The addition of paclitaxel improved the response rate (57%), PFS (median 8.3 months) and OS (median 15.3 months) (12). Of note, enrollment was limited to chemotherapy-naïve women. Among the women with epithelial cancers assessable for response in our cohort, clinical benefit was seen in 4 (2 PR, 2 stable disease). These findings are particularly striking given that our cohort was heavily pretreated.

Our series included two patients with leiomyosarcomas. Angiogenesis also appears to play a prominent role in the carcinogenesis of leiomyosarcoma. In a large cohort of patients with soft tissue sarcomas, VEGF overexpression was identified in 25% of the leiomyosarcoma patients. More importantly, VEGF overexpression was associated with a shorter survival in this patient group (13). The outcome for patients with recurrent leiomyosarcoma remains poor (13). With a response rate of 25% and median survival of 7.7 months, doxorubicin appears to be the most active single agent (14). Hensley *et al.* reported the results of combination gemcitabine and docetaxel for leiomyosarcoma. The overall response rate was 53%, the median time to progression 5.6 months (15). Disease stabilization was achieved in one of our patients with leiomyosarcoma. The patient had multiple pulmonary metastases and had failed four prior cytotoxic regimens. She achieved a progression-free interval of 6.7 months on treatment.

This series represents the first report of bevacizumab for the treatment of recurrent uterine cancer. Although this study was based on a small number of selected patients with a variety of histologic sub-types, these findings are encouraging. In heavily pretreated patients, bevacizumab-combination therapy demonstrated anti-neoplastic activity and was accompanied by manageable toxicity. Bevacizumab warrants consideration for prospective evaluation for women with recurrent endometrial cancer and uterine leiomyosarcomas.

References

1 Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ and Thun MJ: Cancer statistics, 2005. CA Cancer J Clin *55(1)*: 10-30, 2005.

2 Aalders JG, Abeler V and Kolstad P: Recurrent adenocarcinoma of the endometrium: a clinical and histopathological study of 379 patients. Gynecol Oncol *17(1)*: 85-103, 1984.

3 Burke TW, Heller PB, Woodward JE, Davidson SA, Hoskins WJ and Park RC: Treatment failure in endometrial carcinoma. Obstet Gynecol *75(1)*: 96-101, 1990.

4 Yokoyama Y, Sato S, Futagami M, Fukushi Y, Sakamoto T, Umemoto M and Saito Y: Prognostic significance of vascular endothelial growth factor and its receptors in endometrial carcinoma. Gynecol Oncol *77(3)*: 413-418, 2000.

5 Obermair A, Tempfer C, Wasicky R, Kaider A, Hefler L and Kainz C: Prognostic significance of tumor angiogenesis in endometrial cancer. Obstet Gynecol *93(3)*: 367-371, 1999.

6 Lee CN, Cheng WF, Chen CA, Chu JS, Hsieh CY and Hsieh FJ: Angiogenesis of endometrial carcinomas assessed by measurement of intratumoral blood flow, microvessel density, and vascular endothelial growth factor levels. Obstet Gynecol *96(4)*: 615-621, 2000.

7 Salvesen HB, Iversen OE and Akslen LA: Prognostic significance of angiogenesis and Ki-67, p53, and p21 expression: a population-based endometrial carcinoma study. J Clin Oncol *17(5)*: 1382-1390, 1999.

8 Abulafia O, Triest WE, Sherer DM, Hansen CC and Ghezzi F: Angiogenesis in endometrial hyperplasia and stage I endometrial carcinoma. Obstet Gynecol *86(4 Pt 1)*: 479-485, 1995.

9 Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G *et al*: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med *350(23)*: 2335-2342, 2004.

10 Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, Steinberg SM, Chen HX and Rosenberg SA: A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med *349(5)*: 427-434, 2003.

11 Holland CM, Day K, Evans A and Smith SK: Expression of the VEGF and angiopoietin genes in endometrial atypical hyperplasia and endometrial cancer. Br J Cancer *89(5)*: 891-898, 2003.

12 Fleming GF, Brunetto VL, Cella D, Look KY, Reid GC, Munkarah AR, Kline R, Burger RA, Goodman A and Burks RT: Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol *22(11)*: 2159-2166, 2004.

13 Kanjeekal S, Chambers A, Fung MF and Verma S: Systemic therapy for advanced uterine sarcoma: a systematic review of the literature. Gynecol Oncol *97(2)*: 624-637, 2005.

14 Omura GA, Major FJ, Blessing JA, Sedlacek TV, Thigpen JT, Creasman WT and Zaino RJ: A randomized study of adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. Cancer *52(4)*: 626-632, 1983.

15 Hensley ML, Maki R, Venkatraman E, Geller G, Lovegren M, Aghajanian C, Sabbatini P, Tong W, Barakat R and Spriggs DR: Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol *20(12)*: 2824-2831, 2002.

Received July 30, 2007
Accepted August 13, 2007