Positive response to bevacizumab in a patient with metastatic, chemotherapy-refractory urothelial carcinoma

William E. Osai, Chaan S. Ng and Lance C. Pagliaro

We report the case of a 78-year-old man with metastatic transitional-cell carcinoma with squamous differentiation that responded dramatically to the monoclonal antibody agent, bevacizumab. The tumor originated in the bulbar urethra, with histology of poorly differentiated urothelial carcinoma. Metastasis to a right inguinal lymph node was biopsy-confirmed as transitional-cell carcinoma with areas of keratinization. At last follow-up, he had received 24 months of bevacizumab treatment with minimal toxicity and a positive response. Mediators of angiogenesis have been implicated in the clinical progression of bladder cancer, although the role of angiogenesis inhibitors as treatment has not yet been defined. The striking benefit achieved in this heavily treated patient suggests that bevacizumab could have clinically useful antitumor activity in advanced urothelial carcinoma. ***Anti-Cancer Drugs***

19:427–429 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2008, **19**:427–429

Keywords: angiogenesis, bevacizumab (Avastin), urethra, urethelial cancer, vascular endothelial growth factor

Departments of Genitourinary Medical Oncology and Diagnostic Radiology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

Correspondence to Lance C. Pagliaro, MD, Department of Genitourinary Medical Oncology, Unit 1374, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA
Tel: +1 713 792 2830; fax: +1 713 794 1446;
e-mail: lpagliar@mdanderson.org

Received 10 August 2007 **Revised form accepted** 6 December 2007

Introduction

Metastatic urothelial carcinoma is usually incurable, although complete responses to multiagent chemotherapy are sometimes durable. The median survival for patients with metastatic bladder cancer is 11–14 months [1]. Mediators of angiogenesis, such as vascular endothelial growth factor (VEGF), have been identified in tissue, serum, and urine of patients with bladder cancer, but treatment with angiogenesis inhibitors has been infrequently studied in these patients [2–4]. Bevacizumab single-agent therapy was used to treat a man with metastatic carcinoma of the urethra who had exhausted all conventional surgical and chemotherapy options. This case report was conceived after we observed the response to treatment.

Case report

A 78-year-old man presented with urethral carcinoma, transitional-cell with squamous differentiation, metastatic to inguinal and pelvic lymph nodes. He had undergone cystourethrectomy and penectomy with construction of an ileal conduit in 2003 and a right ilioinguinal lymph node dissection in 2005. Both surgeries were preceded by extensive multiagent chemotherapy, beginning with the standard methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) regimen in March 2002 (Table 1). Surgical pathology from the lymph node dissection done in February 2005 confirmed poorly differentiated carcinoma with areas of keratinization, consisting of a 4-cm metastasis in fibroadipose tissue and in one of six identified lymph nodes with extranodal extension.

Six- and 8-month postoperative computed tomography (CT) scans again showed progressive right external iliac lymphadenopathy (Fig. 1a and b) that increased from 1.5 cm on 12 May 2005 to 2.0 cm (9 August 2005) and 3.4 cm (14 October 2005). At that time, he was not considered a candidate for surgery, radiation, or additional chemotherapy, because the earlier attempts at local control had failed; there was a high risk of systemic progression, and the tumor was resistant to chemotherapy. After consideration of supportive care versus improvised treatment and with the patient's consent, he began treatment with 5 mg/kg bevacizumab (Avastin) intravenously every 2 weeks. This was done for treatment purposes only and was not a prospective effort to test the drug.

At the start of treatment, his weight was 92.7 kg; blood pressure was 116/66; serum creatinine was 1.8 mg/dl (calculated creatinine clearance was 44 ml/min), and hemoglobin was 12.5 g/dl. Lymph nodes were monitored with CT scanning. The right external iliac lymph node decreased to 2.0 cm on the follow-up CT scan at 2 months (14 December 2005) and 1.4 cm at 13 months (6 December 2006; Fig. 1c). The decrease was a 59% change from baseline and a partial response by the Response Evaluation Criteria in Solid Tumors (RECIST). At last follow-up (8 October 2007), the right external iliac lymph node measured 2.0 cm, and there were still no new sites of disease.

No skin, pulmonary, cardiac, gastrointestinal, or neurological toxicities were observed. After 21 months of therapy,

his weight was 90.6 kg; blood pressure was 128/73 without antihypertensive medication; creatinine was 1.9 mg/dl; and hemoglobin concentration was 13.5 g/dl. Urine collected from the ileal conduit showed a qualitative protein level of 1 + (grade 1 proteinuria). At 24 months, the urine qualitative protein increased to 2 + (grade 2 proteinuria). He developed a lower extremity deep vein thrombosis at 24 months (grade 3), but no other grade 3 or 4 adverse events were observed.

Table 1 Prior chemotherapy and surgery

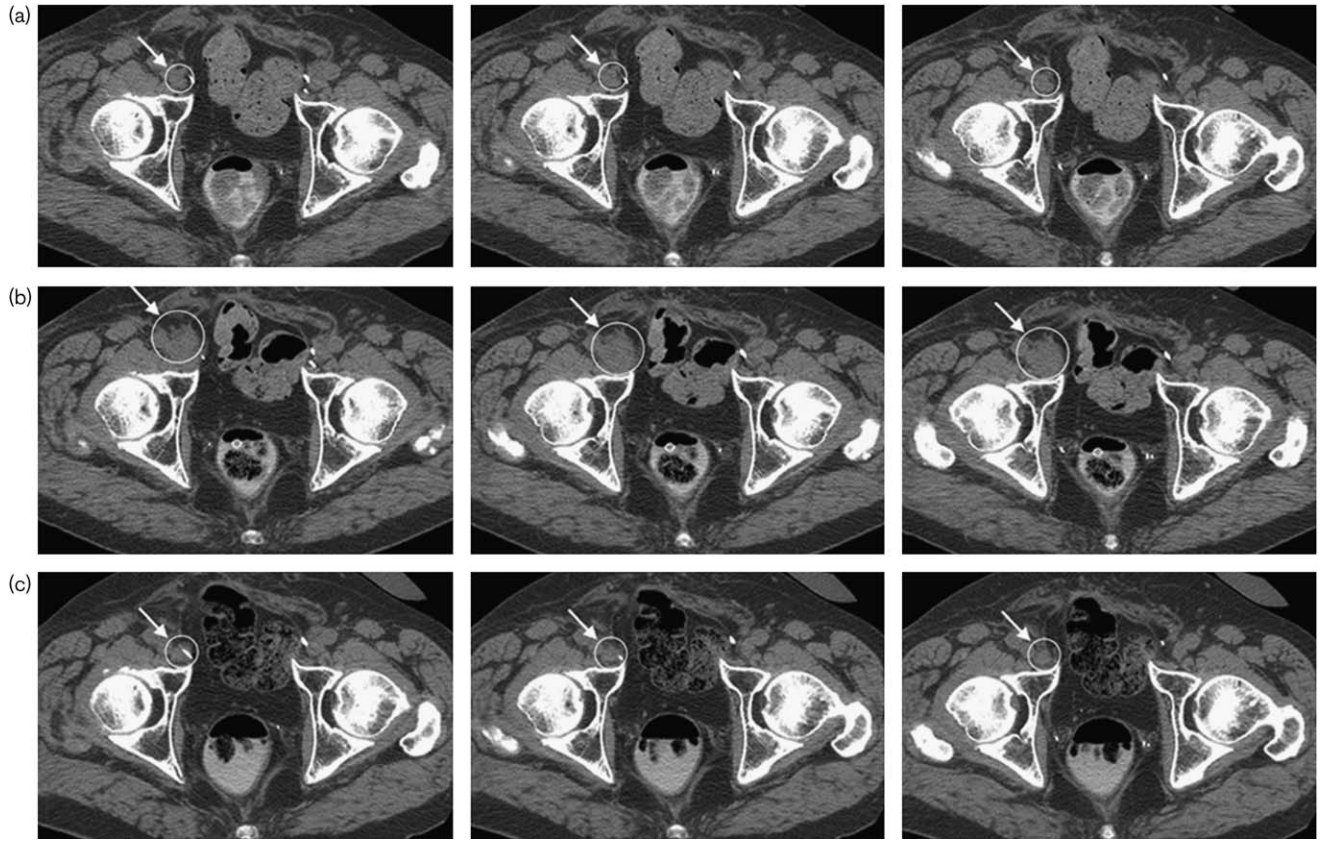
Treatment	Interval prior to bevacizumab (months)	Response
Chemotherapy		
MVAC	43	PR
Cisplatin, gemcitabine, ifosfamide	40	S
Cisplatin, gemcitabine, paclitaxel	38	S
Docetaxel, gemcitabine	33	S
Docetaxel, gemcitabine, doxorubicin	32	S
Vinblastine, ifosfamide, cisplatin	22	S
Cisplatin, gemcitabine	18	S
Cyclophosphamide, gemcitabine	14	P
Vinorelbine, gemcitabine	12	P
Surgery		
Cystourethretectomy and penectomy	30	
Ilioinguinal lymphadenectomy (right)	9	

MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; P, progressive disease; PR, partial response; S, stable disease.
Intervals are the time from the first day of chemotherapy (or date of surgery) to the first day of bevacizumab.

Comment

Our case involved a patient with extensively treated, progressive, metastatic urothelial carcinoma, who received bevacizumab treatment with positive response lasting 2 years. Bevacizumab is an anti-VEGF monoclonal antibody that has shown clinical efficacy in metastatic breast cancer [5], colorectal cancer [6], interleukin-2-pretreated metastatic renal cell carcinoma [7], and non-small-cell lung cancer [8]. The frequency of responses in urothelial carcinoma is unknown, and further study is warranted. A potential role for its use in the salvage setting, as illustrated by our case, and in combination with chemotherapy for earlier stages of the disease, is present.

Fig. 1



Computed tomography images of pelvis. (a) 12 May 2005, 5 months before bevacizumab treatment, showing a 1.5-cm mass. (b) 14 October 2005, at the start of bevacizumab treatment, showing a 3.4-cm tumor mass. (c) 6 December 2006, at 13 months follow-up showing improvement to 1.4 cm. Intravenous contrast was not used because of chronic renal insufficiency. The three images for each time point are at 2.5 mm intervals.

A phase II study to determine the efficacy of bevacizumab plus MVAC neoadjuvant chemotherapy for locally advanced bladder cancer is currently in progress at our institution. Other investigators are conducting phase II studies of bevacizumab, gemcitabine, and cisplatin in combination for neoadjuvant therapy and for treatment of metastatic transitional-cell carcinoma.

Angiogenesis is a logical target for the treatment of patients with urothelial carcinoma. Basic fibroblast growth factor and VEGF appear to be the primary inducers of angiogenesis in bladder cancer cell lines [2]. Moreover, preliminary studies suggested that high levels of these mediators in tumor tissue predict a shorter disease-free survival [3]. Bladder cancer cells also show reduced expression and secretion of thrombospondin-1, a physiological inhibitor of angiogenesis [2,4]. Low levels of thrombospondin-1 measured in tumor tissue have been correlated with shorter survival time and time to recurrence after cystectomy, regardless of the tumor stage, grade, and lymph node status [4]. The results of ongoing clinical trials will help define the role of angiogenesis inhibitors in the treatment of urothelial carcinoma.

References

1 von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, *et al*. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000; **18**:3068–3077.

2 Campbell SC, Volpert OV, Ivanovich M, Bouck NP. Molecular mediators of angiogenesis in bladder cancer. *Cancer Res* 1998; **58**:1298–1304.

3 Inoue K, Slaton JW, Karashima T, Yoshikawa C, Shuin T, Sweeney P, *et al*. The prognostic value of angiogenesis factor expression for predicting recurrence and metastasis of bladder cancer after neoadjuvant chemotherapy and radical cystectomy. *Clin Cancer Res* 2000; **6**:4866–4873.

4 Grossfeld GD, Ginsberg DA, Stein JP, Bochner BH, Esrig D, Groshen S, *et al*. Thrombospondin-1 expression in bladder cancer: association with p53 alterations, tumor angiogenesis, and tumor progression. *J Natl Cancer Inst* 1997; **89**:219–227.

5 Cobleigh MA, Langmuir VK, Sledge GW, Miller KD, Haney L, Novotny WF, *et al*. A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. *Semin Oncol* 2003; **30**:117–124.

6 Kabbinavar FF, Hambleton J, Mass RD, Hurwitz HI, Bergsland E, Sarkar S. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005; **23**:3706–3712.

7 Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, *et al*. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003; **349**:427–434.

8 Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, *et al*. Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006; **355**:2542–2550.