Locally advanced leiomyosarcoma of the urinary bladder: near-complete pathologic response to neoadjuvant gemcitabine and docetaxel

Rishi Sawhney[a], Nancy Curry[a], Tucker Burks[b] and Uzair B. Chaudhary[a]

Leiomyosarcoma of the urinary bladder is a rare mesenchymal tumor with distinct pathologic features. Although radical cystectomy is the standard therapy for locally invasive disease, available literature appears to support the benefit of perioperative chemotherapy, similar to that seen with the more conventional urothelial malignancies. We report on a 77-year-old gentleman with locally advanced leiomyosarcoma of the bladder achieving a near-complete pathologic response to neoadjuvant chemotherapy with a unique regimen: gemcitabine and docetaxel. Further study of this anthracycline-sparing regimen is warranted. ***Anti-Cancer Drugs*** **18:745–747**

Anti-Cancer Drugs 2007, **18**:745–747

Keywords: bladder, chemotherapy, docetaxel, gemcitabine, leiomyosarcoma, neoadjuvant

[a]Medical University of South Carolina, Charleston and [b]Spartanburg Regional Health System, Spartanburg, South Carolina, USA

Correspondence to Dr Uzair B. Chaudhary, MD, Medical University of South Carolina, 96 Jonathan Lucas Street, 903 CSB, Charleston, SC
Tel: +1 843 792 4271; fax: +1 843 792 0644;
e-mail: chaudu@musc.edu

Received 11 July 2006 **Revised form accepted** 22 December 2006

Introduction

Leiomyosarcomas of the urinary bladder are rare mesenchymal tumors, representing only 0.1% of bladder cancers [1]. Radical cystectomy remains the mainstay of therapy for organ-confined disease, For patients with locally advanced or 'high-risk' disease, however, the use of neoadjuvant chemotherapy has been reported, with moderate success utilizing anthracycline-based regimens [2]. We report on a patient with locally advanced bladder leiomyosarcoma achieving a near-complete pathologic response to a novel neoadjuvant regimen of gemcitabine and docetaxel – the first such documented response to this regimen in the literature to date.

Case presentation and management

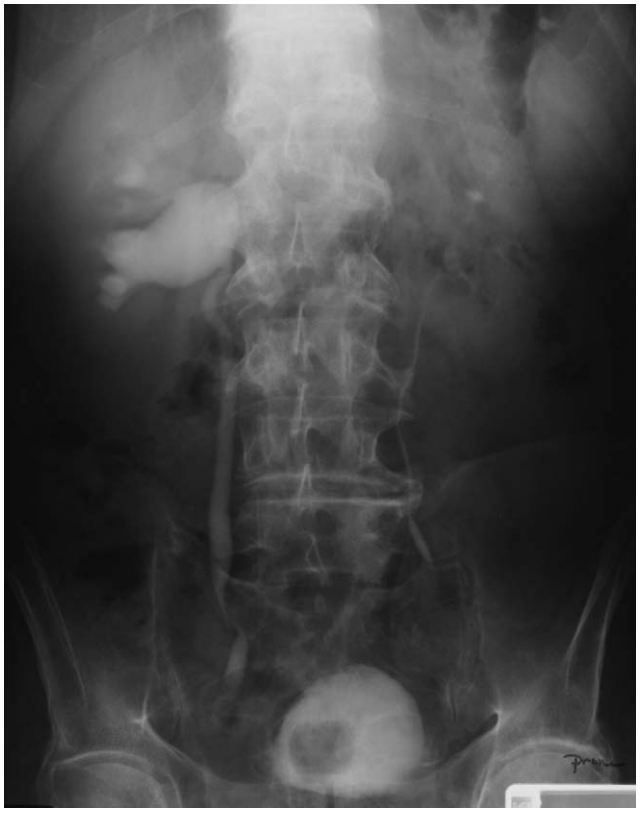
A 77-year-old white male presented with urge incontinence, gross hematuria and a 15-lb weight loss over 2–3 months. Past medical history included coronary artery disease, s/p three-vessel bypass graft. Cystoscopy revealed a large bladder tumor arising from the trigone. Two transurethral biopsy series disclosed similar findings. The malignant spindle cell neoplasm was characterized by fascicular growth, high cellularity, nuclear pleomorphism, brisk mitotic activity (greater than 10 mitoses/10 high-power field) and coagulative tumor necrosis. An excretory urogram was performed showing right partial ureteral obstruction associated with a mass in the urinary bladder (Fig. 1). Computed tomography scans of the abdomen and pelvis (following transurethral biopsy and resection) confirmed the presence of a large bladder tumor (5 cm), without associated lymphadenopathy. The remainder of metastatic workup, including chest radiograph and bone scan, was unremarkable. The patient received neoadjuvant chemotherapy, consisting of gemcitabine 900 mg/m^2 (days 1 and 8) and docetaxel 100 mg/m^2 (day 8), every 3 weeks, for four cycles. Growth factor support was utilized. Therapy was well tolerated, other than alopecia and moderate fatigue. No significant hematologic toxicities were noted. Restaging computed tomography scans demonstrated complete radiographic resolution of bladder tumor, with no evidence of extravesical disease. Radical cystoprostatectomy was then performed, with the subsequent specimen containing a small amount of residual tumor residing in the muscularis propria that recapitulated some but not all of the original features (Figs 2 and 3). All surgical resection margins were clear and all of a total of 13 pelvic lymph nodes (five from the left and eight from the right) were negative for metastatic sarcoma. The patient is now approximately 16 months out from surgery and continues to do well without evidence of disease recurrence.

Discussion

Cancer of the urinary bladder is the fifth most common malignancy in the US, with approximately 63 210 new diagnoses annually [3]. Most bladder cancers are epithelial in origin, with 95% of epithelial tumors demonstrating transitional cell histology. Bladder sarcomas, which are malignant mesenchymal tumors, are rare in adults, with only 192 cases reported in the English-language literature between 1954 and 1998 [4]. Leiomyosarcomas comprise the most common subtype of bladder sarcomas.

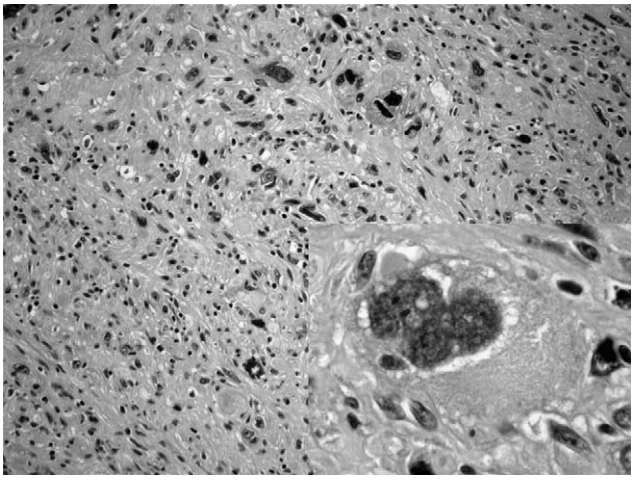
0959-4973

Fig. 1



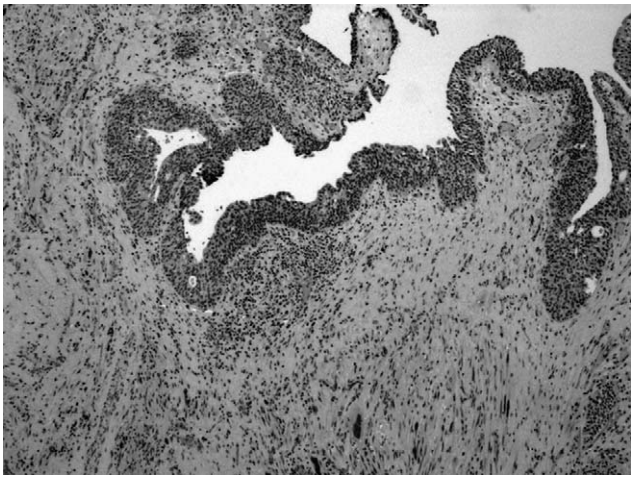
Fifteen-minutes posterior–anterior (prone) intravenous pyelography radiograph shows right hydroureteronephrosis and a filling defect in the right bladder.

Fig. 2



Pretreatment – transurethral biopsy: the tumor cells show nuclear hyperchromasia, occasional examples of multinucleation and marked pleomorphism (inset).

Fig. 3



Posttreatment – cystectomy specimen: subjacent to the urothelium are residual spindle cells arrayed in a disorderly fashion.

These tumors, which have been grossly described as sessile masses of the bladder wall, are often indistinguishable from transitional cell carcinomas (TCCs) macroscopically [5]. Grossly, these tumors are typically smooth and encapsulated. Under light microscopy, leiomyosarcoma is classically described as elongated, spindled cells with prominent fibrillar, eosinophilic cytoplasm. Prominent anaplastic features are typically seen, with pyknotic nuclei. The mitotic indexes of the tumors are usually elevated. Like sarcomas of other sites, immunohistochemistry analysis of these tumors reveals negative epithelial markers, though usually positive for muscle differentiation markers such as vimentin and actin [6].

The largest and most comprehensive series by Rosser *et al.* [2] reported on 36 cases of high-grade bladder leiomyosarcoma. Patients were predominantly male, with a median age of 63 years. Risk factors for this rare malignancy appear to largely coincide with those well documented for TCC of the bladder. Previous tobacco exposure was present in 78% of the patients in Rosser's series. Furthermore, at least nine cases of bladder leiomyosarcoma associated with prior cyclophosphamide exposure have been reported. Acrolein, the urinary metabolite of cyclophosphamide, appears to play a primary role in carcinogenesis. In terms of clinical presentation, most leiomyosarcomas of the bladder involve the dome of the bladder. Thus, patients most commonly present with gross hematuria, urinary frequency and dysuria. Furthermore, given the relatively large size of these tumors (mean 4.2 cm in Rosser's series), obstructive uropathy was seen in 20% of patients at initial presentation. Leiomyosarcomas have traditionally been associated with a high recurrence rate and poor prognosis [7]. Rosser's retrospective series of bladder

leiomyosarcoma demonstrated a 34% recurrence rate at a median follow-up of 38 months, with both local and distant disease sites affected. The disease-specific overall survival in this series was 62% at 5 years, with the Memorial Sloan-Kettering Cancer Center staging system noted to be the only significant prognostic factor for survival by multivariate analyses.

Definitive therapy for leiomyosarcoma of the bladder centers around radical cystectomy with wide margins. Similar to TCCs, radical cystectomy with lymph node dissection and creation of urinary diversion or reconstruction is typically performed. Wider surgical margins are generally recommended owing to the infiltrative nature of sarcomas [5]. Of the 36 patients, however, in Rosser's retrospective series, 10 (29%) presented with locally advanced disease and received neoadjuvant chemotherapy. The most commonly employed regimen consisted of doxorubicin and ifosfamide. Chemotherapeutic options for leiomyosarcomas are limited, with few active agents having been identified. Gemcitabine and docetaxel, through having different mechanisms of action, have been postulated to have synergistic antitumor activity, via DNA synthesis termination by gemcitabine and promotion of apoptosis by docetaxel [8]. Hensley *et al.* [9] examined 34 patients with advanced, unresectable leiomyosarcoma (primarily of uterine origin), treated with gemcitabine/docetaxel (similar dose and schedule as listed above), with growth factor support. An overall response rate of 53% was demonstrated, including complete responses in 9% (3/34 patients). Overall toxicities with this regimen were relatively modest, with up to 29% grade 3/4 hematologic toxicities and no grade 4 nonhematologic toxicities reported. More recently, a phase III trial reported on this gemcitabine/docetaxel combination vs. gemcitabine alone in previously treated patients with metastatic sarcoma (including leiomyosarcoma). With 119 evaluable patients, the combination proved superior with respect to progression-free (6.2 vs. 2.6 months) and overall survival (18.0 vs. 11.2 months), although at the expense of increased toxicity [10].

Neoadjuvant chemotherapy has been extensively studied in locally advanced, muscle-invasive TCC of the bladder. Recent meta-analyses have confirmed a statistically significant overall survival benefit in the range of 5–6.5% at 5 years, with the use of neoadjuvant chemotherapy [11,12]. Rosser's series has suggested the favorable outcome associated with neoadjuvant chemotherapy for high-risk leiomyosarcomas of the bladder as well, primarily utilizing anthracycline and ifosfamide-based regimens. In this patient, although initial surgical resection (i.e. radical cystectomy) may have been possible, we chose the above strategy utilizing neoadjuvant systemic therapy based on the following rationale: (1) data from Rosser's series suggesting improved outcomes with neoadjuvant systemic therapy for patients with *large* bladder sarcomas, (2) extrapolation from the data with TCC demonstrated a significant survival benefit with preoperative therapy and (3) promising activity of the gemcitabine/docetaxel regimen in this tumor histology. We report on, to the best of our knowledge, the first documented case of locally advanced leiomyosarcoma of the bladder achieving a complete radiographic response and near complete pathologic response to a neoadjuvant gemcitabine/docetaxel regimen. This regimen has potential advantages over the commonly used anthracine–ifosfamide regimen, as it is associated with less cardiotoxicity, improved tolerability and the convenience of outpatient administration. These features may prove especially useful in the typically elderly population afflicted with invasive bladder sarcomas. The potential activity and favorable toxicity profile of this approach can be capitalized on, and further study with this regimen is warranted.

References

1 Pedersen-Bjergaard J, Jonsson V, Pedersen M, Hou-Jensen K. Leiomyosarcoma of the urinary bladder after cyclophosphamide. *J Clin Oncol* 1995; **13**:532–533.

2 Rosser CJ, Slaton JW, Izawa JI, Levy LB, Dinney CP. Clinical presentation and outcome of high-grade urinary bladder leiomyosarcoma in adults. *Urology* 2003; **61**:1151–1155.

3 Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, et al. Cancer Statistics, 2005. *CA Cancer J Clin* 2005; **55**:10–30.

4 Vogelzang NJ, Scardino PT, Shipley WU, Debruyne F, Linehan WM. *Comprehensive textbook of genitourinary oncology*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2000. pp. 1105–1108.

5 Parekh DJ, Jung C, O'Conner J, Dutta S, Smith ER Jr. Leiomyosarcoma in urinary bladder after cyclophosphamide therapy for retinoblastoma and review of bladder sarcomas. *Urology* 2002; **60**:164xii–164xiv.

6 Martin SA, Sears DL, Sebo TJ, Lohse CM, Cheville JC. Smooth muscle neoplasms of the urinary bladder-A clinicopathologic comparison of leiomyoma and leiomyosarcoma. *Am J Surg Pathol* 2002; **26**:292–300.

7 Russo P, Brady MS, Conlon K, Hajdu SI, Fair WR, Herr HW, et al. Adult urological sarcoma. *J Urol* 1992; **147**:1032–1036.

8 Leu KM, Ostruszka LJ, Shewach D, Zalupski M, Sondak V, Biermann JS, et al. Laboratory and clinical evidence of synergistic cytotoxicity of sequential treatment with gemcitabine followed by docetaxel in the treatment of sarcoma. *J Clin Oncol* 2004; **22**:1706–1712.

9 Hensley ML, Maki R, Venkatraman E, Geller G, Lovegren M, Aghajanian C, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. *J Clin Oncol* 2002; **20**:2824–2831.

10 Maki RG, Hensley ML, Wathen JK, Patel SR, Priebat DA, Okuno S, et al. A SARC multicenter phase III study of gemcitabine vs. gemcitabine and docetaxel in patients with metastatic soft tissue sarcomas. *Proc Am Soc Clin Oncol* 2006; **24 (18S)**:9514.

11 Winquist E, Kirchner TS, Segal R, Chin J, Lukka H. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. *J Urol* 2004; **171**:561–569.

12 Advanced Bladder Cancer (ABC) Meta-Analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data. *Eur Urol* 2005; **48**:202–205.