

RESEARCH ARTICLE

Early Detection and Gemcitabine/Cisplatin Combination Positively Effect Survival in Sarcomatoid Carcinoma of the Urinary Bladder

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Abstract

Background and Objectives: This study aimed to present the clinicopathological characteristics and treatment of patients with bladder carcinoma with sarcomatoid differentiation at our institution. **Methods:** Between 1995-2009, 950 patients were followed-up for bladder carcinoma. Among them, 14 patients with sarcomatoid carcinoma were retrospectively reviewed, and their clinical, pathological features and treatment were recorded. **Results:** Median age of the patients was 65 years (range: 41-86 years), 12 (86%) being male and 2 (14%) female. All the patients presented with hematuria and 11 (88%) had a history of smoking. The tumor growth pattern was solid in 10 patients, papillary in 2, and mixed in 2. In all, 5 of the patients had urothelial carcinoma with sarcomatoid differentiation and 9 were diagnosed with sarcomatoid carcinoma. Five patients underwent radical cystectomy with ileal conduit surgery, 2 patients refused cystectomy, and 8 patients underwent re-TUR. Following diagnosis, 12 of the patients died in mean 10.7 months (range: 1-48 months). **Conclusion:** Urothelial carcinomas with sarcomatoid features are aggressive and are usually at advanced stage at the time of diagnosis. The outcomes of multimodal treatment are not satisfactory. Significant findings of the present study are that early diagnosis positively affect survival and that gemcitabine and cisplatin in combination can positively affect survival.

Keywords: Sarcomatoid carcinoma - urinary bladder - cancer - gemcitabine - cisplatin

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Introduction

Bladder cancer is the fourth most common cancer in the USA and is three times more common in man than women (Jemal et al., 2009). Bladder cancer constitutes 7% and 3% of all newly diagnosed cancers in males and females respectively (total number: 67,000) in the USA (Eble et al., 2004). The sarcomatoid variant of urothelial carcinoma is a rare subtype and constitutes 0.3% of all bladder carcinomas. The term sarcomatoid variant of urothelial carcinoma is used for all biphasic malignant neoplasms that show morphologic and/or immunohistochemical evidence of epithelial and mesenchymal differentiation (Torenbeek et al., 1994). It is associated with a rapid growth rate and an advanced stage at presentation (Young et al., 1987). Significant controversy exists in the literature regarding the nomenclature and histogenesis of these tumors. In some studies carcinosarcomas and sarcomatoid carcinomas are both covered under the heading of sarcomatoid carcinoma, whereas in others they are regarded as different entities.

There are limited information regarding treatment and outcome for this disease. The present study aimed

to present and discuss the clinical and histopathological features of 14 patients diagnosed with sarcomatoid carcinoma of the bladder and bladder cancer with sarcomatoid differentiation in the light of the emerging literature.

Materials and Methods

Patients group

This study included 14 patients diagnosed with sarcomatoid carcinoma among 950 patients that had been followed-up for bladder carcinoma between 1995 and 2009. Patients were considered to have sarcomatoid disease if the pathology report revealed any sarcomatoid component in their tumor. Patient medical records were retrospectively reviewed for demographic characteristics, clinical stage and outcome. All the patients were evaluated with physical examination, standard laboratory investigations, chest X-ray, and when required, urinary ultrasonography and intravenous pyelography prior to cystoscopy.

Staging was performed postoperatively based on the

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pathology report and appropriated imaging modalities including computerized tomography evaluation. Radiology, pathology and surgical reports were reviewed to determine the pathological staging at the time of pathological diagnosis using the 2010 TNM (tumor, lymph node, metastasis) classification for genitourinary tumors. The patients with performance score of ECOG 0-2, having objectively measurable disease, sufficient bone marrow reserve and normal hepatic and renal function have been involved in the study. Those patients with 3 or higher ECOG score and unsufficient bone marrow reserve and anormal hepatic and renal function have been excluded from the study. Patients files have been scanned backward and the information related to the phase of the disease and treatments received have been obtained.

Appropriate patients underwent cystectomy and received chemotherapy as primary treatment. Chemotherapy combination protocols consisting Gemcitabine 1 gr/m² on day 1 and 8, cisplatin 75 mg/m² on day 1 combination was used. The latest information regarding patient survival status was acquired from hospital records and telephone interviews.

Statistical analysis

Descriptive statistics medians and ranges, were used to characterize the patient sample. Overall survival was calculated from the date of diagnosis to the date of death or the date of last follow-up. Survival rates were examined with Kaplan Meier survival analysis. Those cases having type 1 failure level of less than 5% were interpreted as statistically significant.

Results

Characteristics of patients with sarcomatoid bladder cancer

Median age of the patients was 65 years (range: 41-86 years), and 12 (86%) were male and 2 (14%) were female. All the patients presented with hematuria and 11 (88%) had a positive history of smoking. Eleven of 14 (78,6%) patients presented with muscle invasive disease. The tumor growth pattern was solid in 10 patients, papillary in 2, and mixed in 2. (Table 1). The average tumor size was 5.5 cm (3-16 cm). All the tumors presented with high grade histology.

Five patients underwent radical cystectomy with ileal conduit surgery, 2 patients refused cystectomy, and 8 patients underwent re-TUR.

Survival

At a median follow-up of 7 months (range 1-48, five) (35.7%) 12 patients have died in last follow-up. Overall survival is illustrated in Figure 1. Mean survival time in the patients that underwent cystectomy was 6.7 months; one cystectomized patient died due to comorbidities on postoperative day 21, one patient died due to colonic perforation 8 months post-surgery, one patient died of chronic renal failure postoperative month 6, and one metastatic patient that was lost to follow-up died at home 11 months post surgery. Re-TUR was performed in 2 patients diagnosed to have stage T1 sarcomatoid

carcinoma; one patient was tumor negative at the time of re-TUR and died at home 11 months after diagnosis. The most important feature of this patient was stage T1 disease and an 8 cm solid tumor. Two patients that refused cystectomy and were lost to follow-up died at home. The patient with stage T2 sarcomatoid carcinoma at was tumor-free at the time of re-TUR and follow-up cystoscopy, although lung metastasis was detected during the follow-up.

Discussion

Sarcomatoid carcinomas comprise nearly 0.3% of all bladder cancers (Torenbeek et al., 1994). In our series it was 1.47%. Several terms, including carcinosarcoma, sarcomatoid carcinoma, pseudosarcomatous transitional cell carcinoma, and spindle cell carcinoma, are used for these neoplasms. Some researchers use the term carcinosarcoma for cases in which heterologous elements are observed in H&E-stained sections and specific mesenchymal differentiation markers are positive in immunohistochemical analysis. It is thought that both diagnostic categories are variations of the same neoplastic transformation. Recently performed molecular investigations suggest that epithelial and mesenchymal components seen in these tumors are of monoclonal origin (Sung et al., 2007). According to the latest classification of the World Health Organization (WHO), sarcomatoid carcinomas and carcinosarcomas are regarded as the same entity, and these heterogenous biphasic tumors are classified as sarcomatoid carcinomas (Table 2) (Eble et al., 2004).

Sarcomatoid carcinomas occur more commonly in males. In the presented series 12 of the 14 patients were male. The most common symptoms observed at presentation in patients with sarcomatoid carcinoma are hematuria, dysuria, nocturia, acute urinary retention, and lower abdominal pain. In the presented series macroscopic hematuria was observed in all the patients at presentation. A history of radiation therapy and cyclophosphamide therapy was reported in some patients (Jue et al., 2011). While none of the patients in the present study had such a history, the most significant common history was that of smoking. Although it is not known why aggressive tumors developed after smoking in these patients, it might be because of genetic predisposition responsible for cellular

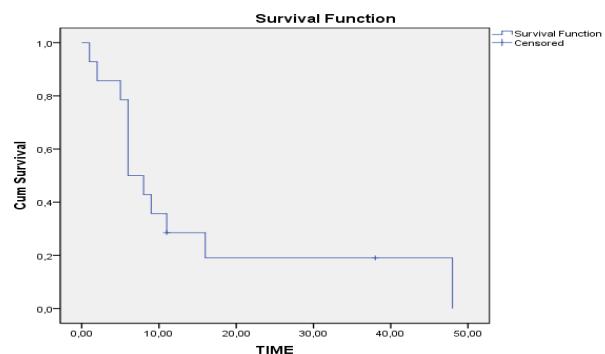


Figure 1. Overall Survival of 14 Patients with Sarcomatoid Bladder Cancer

Table 1. Clinicopathological Characteristics of the Patients

Patient No.	Age (years)	Gender	Location, size, and growth pattern	TUR-B pathology and stage	Treatment modality and pathology	Results (outcomes)
1	79	M	Multiple, papillary	T2, (superficial muscle layer was infiltrated)**	Underwent radiotherapy. re-TUR was performed	Re-TUR pathology: pT1 urothelial carcinoma with sarcomatoid differentiation
2	65	M	On the right lateral wall, 5 ´ 5 cm, mixed type	T1**	Re-TUR, no tumor observed.	Died 11 months post surgery
3	54	M	Multiple, solid type	T2**	Cystectomy, pathology: TCC showing diffuse sarcomatoid differentiation T3aN1M0 3 cycles of gemcitabine + cisplatin	Died 6 months post surgery due to chronic renal failure and metastasis
4	58	M	Multiple, solid type	T2**	Re-TUR pathology: no malignancy.	Died 11 months post surgery (lost to follow-up)
5	41	M	On the bladder dome, 4 ´ 3 cm, mixed type	T2**	Cystectomy, T3aN0 M0, grade 3, sarcomatoid differentiation (+) 3 cycles of gemcitabine + cisplatin	Died 9 months post surgery due to colonic perforation
6	69	F	On the base of the bladder, 10 ´ 15 cm, solid type	T2**	Cystectomy, pathology: T4N2M0 sarcomatoid carcinoma	Died 21 days post surgery
7	86	M	On the dome of the bladder, 5 ´ 4 cm, solid type	T2**	Re-TUR, no tumor detected with follow-up cystoscopy 4 cycles of gemcitabine + cisplatin	Lung metastasis, Died 16 months post surgery
8	77	F	Tumor invaded the right ureter orifice, 4 ´ 3 cm, papillary type	T2**	Refused cystectomy 1 cycle of gemcitabine + cisplatin	Died 6 months post diagnosis
9	66	M	On the base of the bladder, 8 ´ 6 cm, solid type	T1**	Re-TUR, sarcomatoid carcinoma	Tumor-free according to follow-up cystoscopy (performed during 6 months of follow-up)
10	62	M	Tumor extended to the anterior wall and base of the bladder from the right lateral wall, 3 ´ 3.5 cm, lobulated solid type	T3**	Re-TUR, sarcomatoid carcinoma (T2), 8 doses of intravesical therapy 1 cycle of gemcitabine + cisplatin	Died 48 months post surgery
11	72	M	Tumor extended to the base, 9 ≈ 10 cm, solid type	T2**	Radical cystectomy ileal conduit	Died 5 months post surgery
12	60	M	Tumor filled the base of the bladder and extended to the lumen from the right posterolateral wall, 33 ´ 27 ´ 25 mm, mixed type	T1**	Re-TUR, bilateral PCN Urothelial carcinoma with focal sarcomatoid differentiation (T1) 2 cycles of gemcitabine + cisplatin Acute renal failure	Died 8 months post surgery
13	72	M	Located on the posterior wall of the bladder, papillary type, 9 ´ 6 ´ 2 cm CIS	**	Radical cystectomy ileal conduit, sarcomatoid carcinoma T2N2M1 Lung metastasis 4 months later 3 cycles of gemcitabine + cisplatin Progressive disease later on	Died 6 months post surgery
14	54	M	Tumor located on the right lateral wall and filled the base, 3 ´ 2 cm, solid type	T2**	Re-TUR, (T2) bladder perforation, bladder wall reconstruction, sarcomatoid carcinoma	Died within 2 months of surgery

*Complaint (Patient No. 1-11, 14): Macroscopic hematuria. Complaint (Patient No. 12): Macroscopic hematuria, Dysuria.

**Sarcomatoid carcinoma

Table 2. Infiltrative Urothelial Carcinoma

Infiltrative urothelial carcinoma:	with squamous differentiation with glandular differentiation with trophoblastic differentiation nested microcystic micropapillary lymphoepithelioma-like lymphoma-like plasmacytoid sarcomatoid giant cell undifferentiated
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response; however, as the literature contains no report to support this, it should be confirmed in further research.

The gross appearance of sarcomatoid carcinomas is sarcoma-like with infiltrative margins. These tumors are generally polypoid masses and form gross intraluminal masses. In the presented series a papillary pattern was predominant whereas a solid component was dominant in the others. Microscopically, sarcomatoid carcinomas are composed of urothelial, glandular or small cell components that exhibit varying degrees of differentiation. Mesenchymal components are frequently undifferentiated, high-grade spindle cell neoplasms. The most common heterologous element is osteosarcoma, followed by chondrosarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, and angiosarcoma. Immunohistochemically, epithelial elements react with cytokeratin, and stromal elements react with vimentin or specific markers of mesenchymal differentiation. Carcinoma in situ is present in 30% of cases and sometimes the epithelial component is composed only of carcinoma in situ (Lopez-Beltran et al., 1998).

Non-neoplastic lesions, such as postoperative spindle cell nodule and inflammatory pseudotumor and carcinomas, which contain metaplastic bone or cartilage in their stroma, and malignant mesenchymal tumors are considered in the histopathological differential diagnosis of sarcomatoid carcinomas (Ikegami et al., 2000). Additionally, the existence of cleft-like vessels and the absence of significant cytologic atypia support the diagnosis of benign lesions. In the differentiation of malignant mesenchymal tumors, especially leiomyosarcoma, from sarcomatoid carcinomas composed entirely of spindle cells, cytokeratin positivity and desmin negativity are important. The diagnosis of sarcomatoid carcinoma must be considered in all adult patients with malignant spindle cell tumor of the bladder, unless proven otherwise. The recognition of sarcomatoid carcinomas has great therapeutic and prognostic significance (Wang et al., 2010).

Sarcomatoid carcinomas are high-grade, biologically aggressive tumors with a poor prognosis (Jue et al., 2011). At the time of diagnosis nodal and distant metastases are common and 70% of patients die within 1-48 months (mean: 17 months). The most important parameter for predicting survival is pathologic stage. In the series reported by Lopez-Beltran et al. only 1 of the 26 patients with sarcomatoid carcinoma was stage pT2; the others (96%) were stage pT3/4. Among the 21 patients with a

sufficient length of follow-up, 17 died from the disease within a mean 9.8 months (Lopez-Beltran et al., 1998). Doghri et al. (2012) reported a 75 year-old case diagnosed sarcomatoid carcinomas of the urinary bladder with no evidence of disease 12 months after transurethral resection under observation who diagnosed at an early stage. Two cases were reported by Singh et al. The first patient who had a large soft tissue mass of about 6 cm in diameter in the left lateral wall of the urinary bladder extending into the perivesicular fat, died 2 years after the transurethral resection of the tumor. The second patient with sarcomatoid urothelial carcinoma, (pT4a, pN2, Mx) was at follow up with no evidence of disease 12 months after radical cystoprostatectomy (Singh et al., 2011). Nishikawa et al. reported carcinosarcoma of the urinary bladder at nine months following surgery showed no evidence of recurrence. Thirteen months after the operation, Bulky intrapelvic tumor and right hydronephrosis were detected. This patient died 14 months after the operation (Nishikawa et al., 2011). Another patient who was reported by Zachariadis et al. in stage cT3N0M0. Radical cystectomy was deemed too high risk due to severe heart failure of the patient and the local extension of the disease. The patient was treated with 50 Gy of 3D conformal radiotherapy but did not complete the protocol due to progression of the disease. Their patient died five months later (Zachariadis et al., 2011).

Cystectomy following chemotherapy or radiotherapy is the preferred treatment protocol. Conservative treatment is rarely associated with long-term survival (Nimeh et al., 2002). Recently, combination therapies, such as cystoprostatectomy with lymphadenectomy in combination with neoadjuvant or systemic chemotherapy and/or radiotherapy, have been advocated by some researchers; however, prognoses are inconsistent. Cisplatin, Methotrexate, Vinblastine (CMV) was used in one patient in the series that was reported by Stamatiou et al. Four cases with bladder sarcomatoid carcinoma were reported, first patient who treated with adjuvant CMV regimen and radiation therapy died 21 months after diagnosis. The patient treated with only radiation therapy died 10 months after diagnosis. The other patient who treated with radical cystectomy died 14 months after diagnosis. One patient refused any intervention and discharged home. He died within 1 year of the diagnosis in the study that was reported by Stamatiou et al. (2010). In the present study 1 patient benefited from deep transurethral resection and radiotherapy. Although the combination of gemcitabine and cisplatin is a well-tolerated combination in advanced-stage urothelial carcinoma patients, the literature contains few cases regarding its use in carcinosarcoma. Some researchers reported that they obtained good results with ovarian- or sarcoma-type chemotherapy regimens (Wang et al., 2010). We used a systemically administered combination of gemcitabine and cisplatin regimen in the presented cases. Due to the rapid progression of the disease, most of the patients died before completing the chemotherapy protocol. Because the surviving patients were those that did not receive chemotherapy we cannot comment on chemotherapy. Additional multi-centered, broad-based randomized studies are required in order

to determine the best treatment protocol, but it seems unlikely in this group.

In conclusions, sarcomatoid carcinoma of the bladder is a cancer with high malignant potential and a poor prognosis, which is frequently seen in elderly males and is associated with short survival. Gemcitabine and cisplatin combination therapy is among the possible treatment options (Froehner et al., 2001). Significant findings of the present study are that early diagnosis positively affect survival and that the gemcitabine and cisplatin combination positively affect survival. Urothelial carcinomas of the bladder express molecules of the HIF and mTOR pathways, providing a rationale for clinical trials evaluating agents targeting these pathways (Mansure et al., 2009; Tickoo et al., 2010). As these tumors are associated with a poor prognosis and limited treatment options, additional systemic treatment options such as targeted therapy agents i.e antiVEGF and mTOR inhibitors are needed so these pathways must be searched in these tumors. Like renal sarcomatoid carcinoma; Everolimus is only the active agent for renal sarcomatoid carcinoma and that is different from clear cell renal carcinoma. Bladder sarcomatoid carcinoma can differ from urethelial carcinoma in treatment approachs like renal sarcomatoid carcinoma versus clear cell carcinoma (Escudier et al., 2007). The low incidence of this variant renders the conduct of randomized trials rather impossible and drawing clear guidelines for its management is subsequently difficult. We need further studies to answer this question.

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