Review Article

Changing trends in the management of small cell carcinoma of urinary bladder

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ABSTRACT

Small cell carcinoma (SCC) of the urinary bladder is a rare presentation, accounting for <1% of all bladder carcinomas. It has been considered as an aggressive variant of bladder carcinoma, with high incidence of distant relapse. Though cisplatin-based chemotherapy is considered the gold standard approach for this variety of bladder tumor, the role of radical cystectomy and radiotherapy cannot be neglected, due to its frequent association with transitional cell carcinoma. Different management strategies have been adopted by oncologists worldwide, in an effort to obtain survival benefits. Recently, neoadjuvant chemotherapy before surgery has been tried and the results are encouraging. This review article particularly focuses on the treatment evolution of SCC of bladder, various treatment options and their effects on the outcome, so that an optimal management can be planned for individual cases.

Key words: Management, small cell carcinoma, urinary bladder

INTRODUCTION

Small cell carcinoma (SCC) is one of the histopathological subtypes that demonstrates aggressive clinical behavior and most commonly arises in the lung. Though rare, it can occur at extrapulmonary sites also, such as the gastrointestinal tract, salivary gland, uterine cervix, and urinary tract. Extrapulmonary SCC comprises 4% of all SCCs.[1] Its incidence in the bladder is reported to be 0.3–0.7% of all primary carcinomas of the urinary bladder.[1] SCCs of urinary bladder (SCCB) share histopathological and immunohistochemical features with their pulmonary counterpart. The prognosis is poor due to local or distant metastases, and usually the muscle of the bladder is invaded. Definitive treatment strategy has not been defined yet, due to the availability of small case series or reports only. We carried out a literature search from January 1981 to February 2014, through the PubMed/Medline central database at National Center for Biotechnology Information website (http://www.ncbi.nlm.nih.gov/pmc) using the search terms "SCC," "urinary bladder," "management." This review article focuses on presentation, diagnostic workup, the treatment options for SCCB, and their effects on the disease outcome so that an optimal management can be planned for individual cases.

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DISCUSSION

Background

Small cell carcinoma of the bladder is a rare, poorly differentiated neuroendocrine epithelial tumor with a mean frequency of 0.7%.[1] It was first described in 1981 by Cramer *et al*.[2] Majority of the patients are male, with male:female ratio of 5:1. It is found in sixth to seventh decade of life. Like transitional cell carcinoma (TCC), SCCB is often associated with a smoking history in 65–79% of the cases. It is associated with a more aggressive behavior and poorer outcome than bladder TCC. It is frequently found combined with other histological forms: TCC, adenocarcinoma and squamous cell carcinoma.[3] It is mostly diagnosed at an advanced stage and has higher metastatic potential, still it is considered as less aggressive than its pulmonary counterpart.[4]

Pathogenesis

Risk factors are unknown, but there is a hypothesis for bladder localizations that these tumors are usually found in smokers, patients affected by longstanding cystitis,

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those with bladder lithiasis, and those with augmented cystoplasty.[5]

Several hypotheses have been proposed to explain the origin of SCC in the bladder. According to the first hypothesis, the malignant transformation of bladder neuroendocrine cells (which were previously found in the bladder) gives rise to bladder SCC. Second, SCCB arises from urothelial metaplastic changes. Third and most important theory suggests the origin of SCCB from a multipotential common stem cell that has the ability to differentiate into various cell types.[5] This may explain the coexistence of SCCB with TCC, and the heterogeneity of the immunohistochemical staining (cytokeratin [CK] and endocrine markers).

Presentation

Clinical features of SCCB are similar to bladder TCC. Gross hematuria is the most common presentation seen in 63–88% cases.[6] Dysuria is the second most common symptom. Urinary obstruction, abdominal pain, urinary tract infection, and weight loss are reported occasionally. Rare cases of paraneoplastic syndromes such as ectopic ACTH secretion and hypercalcemia have also been reported.

Confirmation of diagnosis

Diagnosis is obtained via histopathological examination of specimens obtained by cystoscopy and transurethral resection of bladder tumor. Light microscopy shows the tumor composed of nests of small round malignant cells with pyknotic round to oval nuclei and evenly dispersed "salt and pepper chromatin." Mitotic rate is high (>10 mitotic figures/10 high power fields) in 57% of the cases.[7] Tumor rosettes, tumor necrosis, vascular invasion are the other features that can be found in light microscopy.

Immunohistochemistry is extremely helpful in establishing the diagnosis.

Neuron-specific enolase, chromogranin, and synaptophysin are the markers found positive in 88.5%, 50%, and 72.4% cases, respectively.[8] Other markers are serotonin, CK, S-100 protein, TTF1, endothelial growth factor receptor (EGFR), and c-KIT. SCCB are also stained with the epithelial markers: CAM 5.2, CK7, and EMA, supporting the urothelial origin of SCCB.

Extent of disease

Pelvic and abdomen computed tomography helps in determining bladder mass and the locoregional extension of the disease, outside the bladder wall and in the pelvic lymph nodes. Bone scan is recommended in those with advanced disease to rule out distant bone metastasis.

Staging

More than 95% of patients are diagnosed at muscle invasive stage T2 or more. The most frequent sites of metastasis are pelvic and retroperitoneal lymph nodes (28.6–53%), liver (23.8–47%), bone (23.8–33%), brain (7.9%), and lung (9.5–13%).[9] As for bladder TCC, the tumor, node, metastasis staging system is commonly used for SCCB.

Differential diagnosis

Direct invasion of the bladder by SCC of the prostate can sometimes be confused with primary SCCB. But, prostatic SCC is typically negative for PSA. Metastatic SCCB from another primary, like small cell carcinoma lung cancer (SCLC), can be the other differential diagnosis. Metastatic SCLC may not be distinguishable histologically from a primary SCCB; however, the presence of TCC component (including TCC *in situ*) would support a diagnosis of bladder SCC. Primary lymphomas of the bladder can also sometimes have histological similarity to SCCB, but lymphomas are positive for leukocyte common antigen and negative for keratin and neuroendocrine markers.

Management

Because of the rarity of SCCB, there is no standard treatment of the disease. SCCB is an aggressive tumor. About 90% of patients are at stage II or more and 25% are at stage IV at diagnosis.[9] Many treatments have been tried, but the optimal management of these tumors has multimodality therapy, which includes surgery, chemotherapy, and radiation.[10] The treatment options include either the radical cystectomy followed by adjuvant treatment or the bladder preservation protocols.

ROLE OF SURGERY

It has been a debated issue whether receiving radical cystectomy provides a better overall survival (OS) for bladder SCC patients. In contrast to SCLC, radical resection is performed in 60–70% of the cases of SCCB. Surgery is favored because of the frequent combination of SCCB with TCC. Literature review[4,9,11] suggests that surgery is favorable, but the 5-year OS after radical resection alone in SCCB ranges from 20% to 36% only [Table 1], thereby concluding that surgery alone is not appropriate to achieve cure for patients with SCCB.

However, in a multi-institutional review of 64 patients with localized SCCB,[12] the efficacy of cystectomy has been questioned, as no survival difference was found between 38 patients undergoing radical cystectomy and those without surgery, receiving radical radiation (10 patients) or chemotherapy alone (23 patients). 5-year survival was 16% with surgery and 18% in the later group.

ROLE OF RADIOTHERAPY

Small cell lung cancer is treated with a combination of radiotherapy (RT) and chemotherapy. In analogy to SCLC, RT either alone or in combination with chemotherapy, has been tried to treat SCCB at a localized stage. The rationale for the use of radiation is that RT following radical surgery helps improve local control rates. Alone or in combination with chemotherapy, RT is used in bladder preservation protocols, or medically inoperable patients, or those not willing for surgery. As shown in Table 2, the 5-year survival of patients with SCCB treated with radiation ranges from 20% to 70% in various studies in literature.[4,13,14] However, most of these studies have utilized chemotherapy either in the neoadjuvant setting or as an adjuvant to radiation therapy. These results confirmed that RT can be curative, but significantly more curative when used in combination with chemotherapy.

Table 1: Outcome of small cell carcinoma bladder with surgery alone

Authors	Patient number	Treatment	Results
Holmäng *et al.* 1995[4]	25	RC->RT (18) CT (2) None (5)	5 years OS=20%
Siefker-Radtke *et al.* 2004 (MDACC)[11]	46	RC (25) CT->RC (21)	5 years OS=36% versus 78%
Choong *et al.* 2005 (Mayo Clinic)[9]	44	RC (20) RC->CT (12) NCT->RC (1) CT (5)	5 years OS=25%

CT: Chemotherapy, RT: Radiotherapy, RC: Rectal cancer, NCT: Neutron capture therapy, OS: Overall survival

Table 2: Outcome of small cell carcinoma bladder with RT in combination with surgery or chemotherapy

Authors	Patient number	Treatment	Results
Holmäng *et al.* 1995[4]	25	RC->RT (18) CT (2) None (5)	5 years OS=20%
Lohrisch *et al.* 1999[13]	14	CCT group CT->RT (8) CT->RC (1) CT-> CT (1) Non-CCT group RT (2) None (2)	OS in CCT group=41 months 5 years OS=70% I CCT group versus 0% in non-CCT group
Bex *et al.* 2005[14]	17	CT->RT (17) Salvage RC (3)	All patients have been treated with sequential chemoradiotherapy OS=32.5 months 2, 3, and 5 years OS=56%, 47%, and 36%, respectively

CT: Chemotherapy, RT: Radiotherapy, RC: Rectal cancer, OS: Overall survival, CCT: Combination chemotherapy

ROLE OF CHEMOTHERAPY

Chemotherapy is the major treatment modality for SCCB. On multivariate analysis,[15] cisplatin chemotherapy is the only predictive factor for survival of SCCB patients ($P < 0.0001$). In surgically resectable disease, chemotherapy has been tried as neoadjuvant therapy to shrink the tumor prior to local therapy or as adjuvant treatment after surgical resection. In metastatic patients, palliative chemotherapy remains the treatment of choice.

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy (NACT) before surgery in surgically resectable SCCB has been investigated in several retrospective studies. In addition, primary chemotherapy was used in sequence with radiation to increase the efficacy of RT.

The rationale for the use of NACT in SCCB is that SCCB is a highly chemosensitive disease. NACT allows downstaging, which facilitates the surgical techniques. Furthermore, it provides early treatment and control of micrometastatic disease. Besides, the systemic treatment is better tolerated by allowing the preoperative administration of chemotherapy drugs in optimal doses with less toxicity.

Siefker-Radtke *et al*. in 2004 analyzed a retrospective data[11] of 46 patients with SCCB and found that 5-year survival was significantly better in patients who received NACT prior to surgery, compared to the surgery alone group (76% vs. 36% [$P = 0.026$]). Same authors in 2009 conducted a prospective phase II trial[16] in 30 patients. Half of them were treated with NACT followed by surgery while others were given chemotherapy alone. The study concluded that the 5-year survival in the operable group was 80%, and the OS was 58 months versus 13.3 months in operable versus inoperable patients, respectively.

Ahsaini *et al*.[17] reported a rare case of a 54-year-old Arab male native of Moroccan, diagnosed as small cell neuroendocrine carcinomas of the ureter and the bladder with stage T2N0M0. Neoadjuvant alternating doublet chemotherapy with ifosfamide/doxorubicin and etoposide/cisplatin (EP) was given, and nephroureterectomy associated to a cystoprostatectomy was carried out. After 24 months of follow-up, no local or distant metastasis was detected. Based on these data, NACT should be considered as the treatment of choice for surgically resectable SCCB.

ADJUVANT CHEMOTHERAPY

No clear data define the role of adjuvant chemotherapy after primary surgery of invasive SCCB. The Mayo Clinic

recommendations propose cystectomy alone for patients with stage II disease, and adjuvant chemotherapy for patients with stages III and IV (M0) disease. However, many institutions who followed the Mayo recommendations of initial cystectomy, reported very poor outcomes and a high likelihood of upstaging. Some authors concluded that adjuvant chemotherapy may provide improved survival compared with cystectomy alone. Bex *et al*.[14] in his study reported a median survival period of 15 months in patients who received chemotherapy regardless of the tumor stage compared to 4 months median survival period in patients not on chemotherapy.

A recent study published reported that the mean survival of patients treated with local treatment (surgery and/or RT) plus chemotherapy and with chemotherapy alone to be 13.8 and 14.7 months respectively. This emphasizes the fact that chemotherapy is more significant than local treatment.[18]

CHOICE OF CHEMOTHERAPY REGIMEN

Owing to the rarity of this malignancy, no prospective study has been carried out to establish the efficacy and duration of chemotherapy or the relative efficacy of platinum-etoposide versus other chemotherapeutic regimens. The drugs and regimen of choice to be used in SCCB can be extrapolated from the successful use of these regimens in its pulmonary counterpart that is, in SCLC. In a Japanese phase III study,[19] conducted in patients with extensive stage SCLC, irinotecan/cisplatin (IP) significantly improved median progression free, as well as OS compared with standard EP therapy (median progression-free survival: 6.9 vs. 4.8 months, $P < 0.001$), (median OS: 12.8 vs. 9.4 months, $P = 0.0021$) respectively. However, a large North American trial[20] failed to confirm this, according to which both regimens produced comparable efficacy, with less hematologic and greater gastrointestinal toxicity with IP. However, for limited-stage SCLC, four cycles of EP, continue to be the standard of care.[21] Based on these results in SCLC, cisplatin – etoposide continues to be the most common chemotherapy being used in SCCB. Table 3 shows the list of various first and second line chemotherapy regimens used for the treatment of SCCB.

Table 3: Chemotherapy regimens used in the treatment of SCCB

Regimen	Drugs and doses; and their schedule
First line	
EP (IV)	Etoposide 120 mg/m^2 on day 1-3 Cisplatin 80-100 mg/m^2, on day 1 Repeated every 21 days
IA/EP (IV)	Ifosfamide 2 g/m^2, on day 1-3 Doxorubicin 25 mg/m^2, on day 1-3 Etoposide 80 mg/m^2, on day 22-26 Cisplatin 20 mg/m^2, on day 22-26 Repeated every 42 days
VIP (IV)	Ifosfamide 1.2 g/m^2, on day 1-4 Etoposide 75 mg/m^2 on day 1-4 Cisplatin 20 mg/m^2 on day 1-4 Repeated after 21 days
MVAC (IV)	Methotrexate 30 mg/m^2 on day 1, 15 and 22, vinblastine 3 mg/m^2 on day 2, 15, and 22 doxorubicin 30 mg/m^2 on day 2 cispatin 70 mg/m^2 on day 2 Repeated every 28 days
Second line	
Topotecan (IV)	Topotecan 1.5 mg/m^2 on day 1-5 Repeated every 21 days
CAV (IV)	Cyclophosphamide 800 mg/m^2 on day 1 Doxorubicin 50 mg/m^2 on day 1 Vincristine 1.4 mg/m^2 on day 1 Repeated every 21 days
Vinorelbine (IV)	Vinorelbine 25 mg/m^2 on day 1, 8, and 15 repeated every 21 days

SCCB: Small cell carcinoma of the bladder, EP: Etoposide, IA: Intra-arterially, VIP: Vasoactive intestinal polypeptide, MVAC: Methotrexate, vinblastine, doxorubicin, and cisplatin, CAV: Cyclophosphamide, adriamycin, vincristine, IV: Intravenous

BLADDER PRESERVATION (CHEMO-RADIATION) VERSUS CYSTECTOMY PLUS CHEMOTHERAPY

In a SEER database (the surveillance, epidemiology, and end results - Medicare database) of 106 patients, analyzed by Koay *et al*.[22] between 1995 and 2005, there was no difference in terms of OS (19% vs. 26%) ($P > 0.05$) b/w bladder-sparing approach, versus at least cystectomy with chemotherapy (of whom over 90% received radical cystectomy). A comparison of the bladder-sparing approach with cystectomy alone yielded similar results, and, therefore, the author concluded that cystectomy and bladder-sparing approaches represent two viable strategies.

However, this cannot be generalized and that the results of this study need to be interpreted with caution because bladder-sparing approach has not shown beneficial results in the recent phase two trial done at MD Anderson Cancer Centre.[16] In addition, it is important to note that the patients with localized disease analyzed by Koay *et al*.[22] had poor outcomes: Median OS in the chemotherapy and nonchemotherapy groups were 23 and 12 months, respectively.

TARGETED THERAPY

Despite the use of multimodality treatment, the outcomes of treating bladder SCC remain poor. Novel targeted agents have been tried to improve survival. The majority of SCCB express vascular EGFR on endothelial cells, the EGFR, the c-KIT, the platelet-derived growth factor receptor, and the fibroblast growth factor receptor. Antiangiogenesis agents and tyrosine kinase inhibitors can be tried in metastatic setting. However, the beneficial effect of these agents in terms of survival has not been proven yet.

Prognosis

The prognosis of SCCB is poor. The five-year survival rate of all stages combined is equal to 19% (16–25%).[10] The 5-year survival rates for patients with stages II, III, and IV were 63.6%, 15.4%, and 10.5%, respectively. Because of the rarity of this disease, no others prognostic factors were identified.

CONCLUSION

Small cell carcinoma of the urinary tract is a distinct histological and biologic disease entity with an aggressive clinical course. Therapeutic modalities vary from institution to institution. The prognosis in patients with SCCB tumors remains poor but the improvements in systemic multiagent chemotherapy, especially NACT with the aggressive surgical approach or radical RT, can improve the long-term survival. In surgically resectable disease (T1–T4aN0M0), management should include multimodal therapy with chemotherapy followed by radical cystectomy. In case, when surgery is performed first, adjuvant chemotherapy or adjuvant chemo-RT should be indicated. In advanced disease (T4b, N+ or M+), chemotherapy using a platinum agent (cisplatin in suitable patients) is the mainstay of treatment.

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