MINI-REVIEW

Primary Small Cell Carcinoma of the Urinary Bladder - Mini-review of the Literature

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Abstract

Primary small cell carcinoma of urinary bladder is a rare but aggressive disease with poor prognosis and a high mortality rate. It accounts for less than 1 % of all the primary cancers seen in the urinary bladder. Diagnosis and management of this entity poses a challenge to the clinician due to the lack of a standardized protocol for its treatment. Herein we discuss primary small cell carcinoma of the urinary bladder in its entirety.

Keywords: Small cell carcinoma - urinary bladder - bladder tumor - etiology - diagnosis - treatment

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Introduction

Small cell carcinoma of the lung is a well known occurrence accounting to one fifth of all the lung cancers reported but the presence of primary small cell carcinoma in extrapulmonary sites is rare (Ibrahim et al., 1984). Apart from lungs, it is also seen to localize in the urinary bladder, ureters, prostate, kidneys, esophagus, stomach, small intestine, colon and rectum, pancreas, salivary glands, breast, cervix, vagina, pharynx, larynx and skin (Abbas et al., 1995).

The urinary bladder is known to be the most common genitourinary extrapulmonary site for small cell carcinoma to occur. Small cell carcinoma of the urinary bladder [SCCB] was first reported by Cramer et al. in 1981, accounts for less than 1% of all the primary cancers arising from the bladder (Blomjous et al., 1989; Holmäng et al., 1995; Mackey et al., 1998; Trias et al., 2001; Cheng at al., 2004; Choong et al., 2005). According to recent literature, 882 cases of SCCB have been reported till date (Ismaili et al., 2009). Small cell carcinoma also known as oat-cell carcinoma or small cell neuroendocrine carcinoma is a distinct histological and biological disease entity and is characterized by an aggressive clinical course, early metastatic spread and systemic dissemination, poor prognosis with an average life expectancy of only a few months, probably attributed to the fact that they are mostly diagnosed at an advanced stage (Mills et al., 1987; Grignon et al., 1992; Cheng at al., 2004). Diagnosis of SCCB is based on an identical criteria established by WHO classification system which is also used to diagnose small cell carcinoma of the lung (Eble et al., 2004). SCCB on histopathology, immunohistochemical tests and light microscopy evaluation shows features similar as of small cell carcinoma of the lung with comparable immunoreactivity and electron microscopy showing the presence of neurosecretory granules (Cramer et al., 1981; Christopher et al., 1991; Cheng et al., 1992; Van Hoeven and Artymyshyn, 1996). Immunochemical staining using chromogranin A, synaptophysin or neurone-specific enolase also aid in establishing the diagnosis of SCCB.

However, it is seen that often the bladder tumor is a mixture of small cell carcinoma with transitional cell carcinoma, adenocarcinoma, or both (Mills et al., 1987; Christopher et al., 1991; Grignon et al., 1992). Accurate diagnosis is essential from therapeutic and prognostic point of view. Although various modalities of treatment for SCCB have been proposed in the medical literature over years, there is no data concluding to a standard line of management.

Characteristics of SCCB

Although ample cases being reported till date since its first mention in the literature, primary small cell carcinoma of urinary bladder is still considered to be a rare disease with an incidence of 0.5-0.7 % of all bladder tumors (Blomjous et al., 1989; Trias et al., 2001; Holmäng et al., 1995; Holmäng et al., 2000; Sved et al., 2004). SCCB similar to its lung counterpart [small cell carcinoma of lung] is a disease making its appearance in advancing age with a male preponderance and is strongly related to cigarette smoking. Contrary to other carcinomas seen in the urinary bladder like transitional cell carcinoma, adenocarcinoma and squamous cell carcinoma, SCCB is characterized by an aggressive behavior, early metastatic incidence (56%), high disease related mortality rate (68.7% within 2 years from the time of diagnosis) with survival rates at the end of second and fifth year being 25% and 8% respectively, rare long term disease free intervals (post treatment) and a median survival of 9.3 months (post treatment) (Blomjous et al., 1989; Oesterling et al., 1990;

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Lopez et al., 1994; Abbas et al., 1995; Trias et al., 2001; Helpap, 2002).

Treatment Strategies for SCCB

Treatment strategies available for SCCB consist of a multidisciplinary and aggressive approach, being acquainted with the poor prognosis and early metastatic dissemination of this carcinoma. Different modalities of treatment have been suggested over the years which include a combination of surgery such as radical or partial cystectomy or transurethral resection of the tumor, chemotherapy and occasional radiotherapy. However a standard therapy for patients with SCCB is still uncertain attributed to the rarity of the disease and paucity of clinical studies. Treatment rendered depends on the staging of the disease i.e. limited or extensive stage.

Nonetheless, the gold standard for the treatment of SCCB remains platinum based chemotherapy with a major preference to cisplatin-etoposide regimen used both in limited or extensive stage (Sidhu, 1979; Blomjous et al., 1989; Oesterling et al., 1990; Cheng et al., 1992; Lopez et al., 1994; Syed et al., 1997; Mackey et al., 1998; Lohrisch et al., 1999; Trias et al., 2001; Helpap, 2002; Siefker-Radtke et al., 2004; Choong et al., 2005) Other chemotherapy regimens available is etoposide-cisplatine alternating protocol either with ifosfamide-doxorubicin or with cyclophosphamide, doxorubicin and vincristine. The use of single agents such as paclitaxel, irinotecan, topotecan, and doxorubicin, has also been documented (Siefker-Radtke et al., 2004; Choong et al., 2005). Previous studies have mentioned the benefit of cisplatin-based chemotherapy in the treatment of SCCB (Mills et al., 1987; Blomjous et al., 1989; Christopher et al., 1991; Grignon et al., 1992). Mackey et al. (1998) stated that regimens not including cisplatin were not associated with prolonged survival. However this should be interpreted with caution as the good performance status needed for cisplatin based chemotherapy may bias the results associating cisplatin with improved survival. Bex et al. 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 (Bex et al., 2005).

While considering treatment options for mixed SCCB i.e. small cell carcinoma associated with transitional cell carcinoma, adenocarcinoma and squamous cell carcinoma components, the prognostic influence of small cell counterpart should be kept in mind. Therefore, mixed SCCB mandates the classic cisplatin based chemotherapy. (Grignon et al., 1992; Holmäng et al., 1995; Angulo et al., 1996; Mackey et al., 1998). There is also documentation in previous literature concluding successful eradication in pure and mixed SCCBs following preoperative chemotherapy with a neuroendocrine regimen containing etoposide and cisplatin or ifosfamide and doxorubicin (Siefker-Radtke et al., 2004). However, methotrexate, vinblastine, doxorubicin and cisplatin regimen is favored if the transitional cell component obtained at trans urethral resection is greater than 50% as mentioned in earlier studies (Grignon et al., 1992). A recent study published reported that the mean survival of patients treated with local treatment (surgery and/or radiotherapy) plus chemotherapy and with chemotherapy alone to be 13.8 and 14.7 months respectively. This emphasizes on the fact that chemotherapy is more significant than local treatment (Ismaili et al., 2009).

Surgical approach in a case of SCCB is occasional and consists of cystectomy [radical or partial] aided by chemotherapy and/or radiation therapy. Surgical resection of urinary bladder in such setting has a dubious curative implication as majority of the patients present with metastasis either through bladder wall or pelvic lymph nodes at the time of the diagnosis even if not clinically evident. Hence, cystectomy is recommended only in patients with early stage disease where the tumor is localized to the bladder (Podesta et al., 1989; Lopez et al., 1994); Neoadjuvant or adjuvant combination chemotherapy with cystectomy is increasingly being practiced owing to high incidence of distant relapse following surgery for organ confined disease and due to good survival efficacy.

Several instances have been documented where cystectomy along with neoadjuvant or adjuvant chemotherapy has shown successful outcomes thereby increasing the survival period (Oesterling et al., 1990; Grignon et al., 1992; Cheng et al., 1995; Nejat et al., 2001; Quek et al., 2005). A study done at M.D. Anderson Cancer Centre reported a 78 v/s 36% 5 year survival rate in patients following cystectomy but on neoadjuvant chemotherapy and cystectomy alone respectively (Siefker-Radtke et al., 2004). Cheng et al. (2004) in their literature reported 1-year and 5-year disease-specific survival rates among patients who underwent cystectomy to be 57% and 16%, respectively and 55% and 18%, respectively, among patients who did not undergo cystectomy thus outweighing the role of surgery. Other surgical modality acknowledged is partial cystectomy in combination with chemotherapy and/or radiation therapy. Podesta and True reported two cases of pT3 tumors that underwent partial cystectomy with adjuvant radiation therapy offered to one of the patient reported disease free at 78 months (Podesta et al., 1989). There is also mention of bladder sparing strategy of transurethral resection [TURBT] followed by chemo-RT being practiced but as reported in previous cases, the outcome following TURBT is very poor (Trias et al., 2001; Helpap et al., 2002).

Radiation therapy for SCCB is always used concomitantly with chemotherapy. Oblon et al. was the first to describe the use of sequential chemotherapy and radiation therapy for SCCB (Oblon et al., 1993). Later on, Bastus et al. (1999), Lohrisch et al. (1999), Bex et al. (1999), Lester et al. (2006) reported favorable results with long term survival period hence supporting the chemo-RT treatment strategy. The only downside seen with chemo-RT therapy with bladder preservation is the development of uroepithelial tumors in almost 60% of the patients necessitating salvage cystectomy (Lohrisch et al., 1999). There is also mention of retroperitoneal lymph node irradiation following radical cystectomy, as most relapses (50%) are known to occur in retroperitoneal lymph nodes (Ismaili et al., 2008). Radiotherapy can also be beneficial

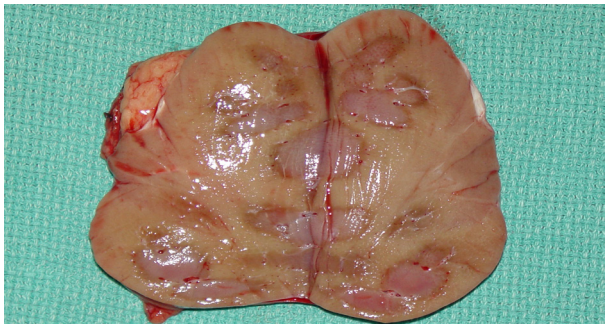

Figure 1. Multiple SCCB Lesions in a Urinary Bladder

in palliative treatment of brain metastases, symptomatic bone metastases and cord compression (Jackman and Johnson, 2005). Prophylactic pelvic irradiation is not included in routine management.

A few recent treatment options proposed in the literature include STI-571 [small molecule inhibitor of C-KIT kinase activity] in patients with c-kit positive tumors, imanitib mesylate and EGFR 225 IgG1 and 528 IgG2a [acts on tyrosine kinase receptors], although it should be remembered that the confirmatory beneficial effect has not been reported yet (Pan et al., 2005).

Familiar with the aggressive behavior of small cell carcinoma of the urinary bladder, 5 year survival rate associated with this disease ranges between 16 and 25% (Cheng et al., 2004; Choong et al., 2005). Holmang et al. and Lopez et al. reported a 5 year survival of 28% and 29% respectively (Lopez et al., 1994; Holmäng et al., 1995). Cheng et al. (2004) stated that organ-confined SCCB was associated with marginally better survival as compared to more widespread disease with a 1-year disease-specific survival rates of 58% and 25% respectively for organ-confined tumors (T1 and T2) and widespread disease (T3 and T4). On the contrary, long term survival has been reported in many patients subsequent multimodality treatment4, 17, 20, 25, 53 (Oesterling et al., 1990; Rollins and Schumann, 1991; Grignon et al., 1992; Holmäng et al., 1995; Lohrisch et al., 1999).

Conclusions

Treatment strategies available for SCCB consist of a multidisciplinary and aggressive approach, being acquainted with the poor prognosis and early metastatic dissemination of this carcinoma. Different modalities of treatment have been suggested over the years which include a combination of surgery such as radical or partial cystectomy or transurethral resection of the tumor, chemotherapy and occasional radiotherapy. However a standard therapy for patients with SCCB is still uncertain attributed to the rarity of the disease and paucity of clinical studies. Treatment rendered depends on the staging of the disease i.e. limited or extensive stage. Nonetheless, the gold standard for the treatment of SCCB remains platinum based chemotherapy with a major preference to cisplatin-etoposide regimen used both in limited or extensive stage (Sidhu, 1979; Blomjous et al., 1989; Oesterling et al., 1990; Cheng et al., 1992; Lopez et al., 1994; Syed et al., 1997; Mackey et al., 1998; Lohrisch et al., 1999; Trias et al., 2001; Helpap, 2002; Siefker-Radtke et al., 2004, Choong et al., 2005); Other chemotherapy regimens available is etoposide-cisplatine alternating protocol either with ifosfamide-doxorubicin or with cyclophosphamide, doxorubicin and vincristine. The use of single agents such as paclitaxel, irinotecan, topotecan, and doxorubicin, has also been documented (Siefker-Radtke et al., 2004; Choong et al., 2005). Previous studies have mentioned the benefit of cisplatin-based chemotherapy in the treatment of SCCB (Mills et al., 1987; Blomjous et al., 1989; Christopher et al., 1991; Grignon et al., 1992); Mackey et al. (1998) stated that regimens not including cisplatin were not associated with prolonged survival. However this should be interpreted with caution as the good performance status needed for cisplatin based chemotherapy may bias the results associating cisplatin with improved survival. Bex et al. 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 (Bex et al., 2005). While considering treatment options for mixed SCCB i.e. small cell carcinoma associated with transitional cell carcinoma, adenocarcinoma and squamous cell carcinoma components, the prognostic influence of small cell counterpart should be kept in mind. Therefore, mixed SCCB mandates the classic cisplatin based chemotherapy (Grignon et al., 1992; Holmäng et al., 1995; Angulo et al., 1996; Mackey et al., 1998). There is also documentation in previous literature concluding successful eradication in pure and mixed SCCBs following preoperative chemotherapy with a neuroendocrine regimen containing etoposide and cisplatin or ifosfamide and doxorubicin (Siefker-Radtke et al., 2004). However, methotrexate, vinblastine, doxorubicin and cisplatin regimen is favored if the transitional cell component obtained at trans urethral resection is greater than 50% as mentioned in earlier studies (Grignon et al., 1992). A recent study published reported that the mean survival of patients treated with local treatment (surgery and/or radiotherapy) plus chemotherapy and with chemotherapy alone to be 13.8 and 14.7 months respectively. This emphasizes on the fact that chemotherapy is more significant than local treatment (Ismaili et al., 2009).

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