Real-world experience managing unresectable or metastatic small cell carcinoma of the prostate

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Abstract

Introduction: Unresectable and metastatic small cell carcinoma of the prostate (SCPC) is a rare and aggressive disease that is under-represented in clinical trials. We carried out a retrospective chart review of metastatic or unresectable SCPC patients at British Columbia (BC) Cancer centers, studying diagnosis and treatment patterns.

Methods: Drug dispensing records from the six BC Cancer centers were obtained from 2002–2017. For each patient, information was collected on baseline information prior to therapy, and for each line of treatment. Treatments at each line were compared regarding time to progression and overall survival by Kaplan-Meier curves.

Results: Forty-one patients received treatment; 65.6% had metastatic disease and 61% had pure small cell carcinoma. Median time from treatment to death was 10 months (95% confidence interval [CI] 6–16). Patients with initially prostate-confined disease had a better median overall survival (mOS) of 21 months (95% CI 13–34) compared to those with initially locally advanced (mOS 19 months, 95% CI 5–37) and metastatic disease (mOS 8 months, 95% CI 6–10) (log-rank p=0.0364). All patients received either cisplatin- or carboplatin-based combination chemotherapy as the first-line treatment and 36.7% received second-line therapy. Time to

second-line therapy was eight months for those who presented with metastatic SCPC, compared to 13 months for those with initial non-metastatic SCPC.

Conclusions: This single-province, multi-institution cohort reports data on unresectable and metastatic SCPC and highlights the poor prognosis of this rare disease entity.

Introduction

Small cell prostate cancer (SCPC) is not only clinically, biologically, and histologically different from prostatic adenocarcinoma, but a more aggressive variant as well. SEER data suggests approximately 60% of men present with metastases, with a median survival of 18 months from diagnosis[1]. Metastatic small cell prostate cancer (mSCPC) typically emerges from patients with high-grade metastatic adenocarcinoma that have been treated with androgen deprivation therapy. This transformation to SCPC occurs approximately 18-25 months from time of diagnosis of prostatic adenocarcinoma, though this can be extremely variable[2,3]. When this transformation occurs, these cells are no longer responsive to hormonal manipulations to control the disease.

Metastatic SCPC is a rare entity, occurring in only 0.5 to 2% of men with prostate cancer[4,5], which has precluded many prospective trials. Data has historically been gathered from case series or single-arm clinical trials among which enrollment criteria have substantially differed, treatment regimens and sequences have not been standardized, and histological diagnoses have not been necessarily required to make a firm diagnosis. Prognosis and natural history of this disease have been similarly scant in literature[6]. A more in-depth analysis of "real-world" practice patterns from a Canadian perspective would be useful, given the paucity of guidelines on diagnosis and management of this rare entity. We therefore carried out a retrospective chart review of metastatic or unresectable SCPC patients at British Columbia (BC) Cancer centres, studying practice patterns around diagnosis and management.

Methods

We initially identified patients with SCPC by reviewing drug dispensing records for patients treated at the six BC Cancer centres with the following protocols available on the BC Cancer website: GUSCPE (created in August 2002): Palliative Therapy of Extensive Stage Genitourinary Small Cell Tumours with a Platinum and Etoposide; and GUSCPERT (created in September 2002): Therapy of Genitourinary Small Cell Tumors with a Platinum and Etoposide with Radiation. All consecutive patients who received these regimens between Jan 1, 2002 and Dec 31, 2017 and treated at the regional BC Cancer centres were included. Patients who received these regimens outside of the BC Cancer centres (i.e. Community Oncology Network clinics) were also included if they received them between Jan 1, 2013 and Dec 31, 2017. This inclusion criteria assumed that all patients who had non-resectable, locally advanced or metastatic prostate small cell carcinoma and were eligible for treatment would have received systemic therapy under

the two protocols. We then reviewed each case individually to identify and only include those who had histology-proven small cell carcinoma originating from prostate. The study was reviewed and approved by the BC Cancer Research Ethics Board (H18-00043).

Baseline demographic and laboratory information prior to therapy initiation for each patient was collected from electronic charts. The site of metastatic burden, if applicable, was documented. All information regarding first-line mSCPC treatment was recorded; the same was done for subsequent lines of treatment. The time interval between lines of therapy was recorded, and inclusion criteria included all patients who had completed and had progressed on at least one line of therapy in the unresectable or metastatic setting for SCPC at one of the six BCCA centres. Exclusion criteria included patients not treated at a BCCA centre, with non-metastatic disease, or disease not treated as SCPC (on clinical or pathologic grounds).

Pathology reports for each patient were used to determine the proportion of patients that had their diagnosis made on pathological grounds, versus clinical features alone. The percentage of patients diagnosed with *de novo* versus treatment-emergent (i.e. transdifferentiated from prostatic adenocarcinoma) disease was established. Where applicable, the disease setting at time of transformation was recorded.

All treatments were documented, including radiation to prostate/pelvis, prophylactic cranial irradiation, and systemic therapy. Information regarding the first-line and later line therapy was documented.

Treatments at each line were compared regarding time to progression and overall survival by Kaplan Meier curves. All statistical analyses were performed on SAS v.9.

Results

We identified, in total, 41 patients who received treatment for small cell carcinoma of prostate who met eligibility. The baseline characteristics are described in Table 1. Most patients had metastatic (65.9%) or locally advanced (26.8%) cancers. 61% had pure small cell carcinoma; the rest had mixed histology. A total of 24 patients had Gleason scores associated with their histology (58.5%). Many patients presented with bone or lymph node metastases, followed by liver and lung. Median PSA at the time of diagnosis was 2.3 (interquartile range 0.27, 11.7), relatively low compared with typical patients with an initial diagnosis of metastatic castrate sensitive prostate cancer (mCSPC). Median Gleason score, if the cancer had adenocarcinomatous pathology, was 9 (range 6-10). 20 patients (48.7%) had de-novo disease, while 21 patients (51.2%) had treatment-emergent disease.

In terms of survival outcomes, median time from treatment of mSCPC to death was 10 months (95% CI 6-16 months). Patients with initially prostate-confined disease had the best median overall survival (mOS) of 21 months (95% CI 13-34 months), whereas those with initially locally advanced disease (mOS 19 months, 95% CI 5-37 months) and metastatic disease (mOS 8 months, 95% CI 6-10 months) had significantly decreased mOS (log-rank p=0.0364, see

Figure 1). Patients with de novo mSCPC had OS of 16.5 months (95% CI 9-28 months), while those with treatment emergent mSCPC had 6 months (95% CI 5-10 months), log-rank p=0.0223.

Table 2 illustrates treatments administered for SCPC. All patients received either cisplatin- or carboplatin- based combination chemotherapy as the first-line treatment. 34.1% received either concurrent or sequential local radiation therapy to prostate, and 36.7% received second-line systemic therapy. Few patients received third-line systemic therapy or beyond. Median number of treatment lines was 1 (range 1-7). Only 1 patient had prophylactic cranial radiation therapy. Table 3 illustrates time to subsequent systemic therapies after the first-line treatment for SCPC. Patients with metastatic SCPC had 8 months before the patient progressed to the second-line treatment, while patients with initially non-metastatic SCPC had 13 months before the second-line treatment.

Discussion

To our knowledge, this study is the first to report on the clinical characteristics and outcomes of patients diagnosed with SCPC in BC, Canada. Although presumed to be rare[7,8], one study shows that treatment-emergent SCPC is present in nearly one fifth of patients with mCRPC[9]. Genomic analysis further shows that the transformation from adenocarcinoma to SCPC is likely one of the major mechanisms for resistance to hormonal manipulations[9], and may be a distinct subset from other types of mCRPC that develop DNA repair mutations[10,11]. Once diagnosed, patients with SCPC have invariably poor survival, and is associated with liver and other soft tissue metastases, also shown in our cohort[9,10]. A low PSA with even a relatively heavy burden of disease, and with new liver or visceral metastases, may be indicative of SCPC; similar to our study, other studies have shown that the median PSA is a2-4 mg/mL[2]. Recognition and diagnosis of SCPC transformed from adenocarcinoma can be challenging, however, and literature reports that approximately 40% present as mixed histology[12].

Our study adds to the existing case reports and cohort studies that have reported on outcomes from other parts of the world[1,13,14]. For example, Horne et al. presented on 800 patients with SCPC from the National Cancer Database, US, diagnosed between 2004 and 2015[15]. Although the data only exist in abstract form, it reports that only 45% patients received chemotherapy, in contrast to our cohort in which everyone received chemotherapy. Despite the disparities in treatment receipt, the OS outcomes were similar to those of our cohort when stratified by staging. Our study also expands upon the pre-existing Canadian data reported on outcomes for SCPC. One Canadian study by Ahmed et al. assessed the small cell cancers of bladder and prostate[16]. In their study, 14 patients with SCPC were included, all but one patient with metastatic disease. The outcomes from our cohort are consistent with Ahmed et al., with OS of approximately 10 months. Our study, however, includes a larger group of patients with initially prostate-confined disease and with a focus on SCPC.

Comparable to recommended systemic therapies for small cell lung cancer (SCLC), patients in our cohort have received platinum and etoposide as first-line treatment. No level I

evidence exists to guide clinicians on optimal treatment modalities of SCPC, due to the lack of relevant prospective studies. A phase II trial enrolled "anaplastic" CRPC in which SCPC was included, and administered first-line carboplatin and docetaxel and second-line etoposide and cisplatin to 120 patients, and showed a median survival of 16 months[17]. Given that over 70% patients in this study went on to receive second-line treatment, in comparison to 36% in our cohort, the numerically better OS in this study is likely due to inclusion of patients who are well enough to enrol in a prospective study. Response rates are thought to be short, in the order of 5-6 months, and lower than small cell cancer of lung, in the order of 30-60%, demonstrating the limitations in the current treatment options for SCPC[17,18]. If most treatments are extrapolated from SCLC, other treatment options such as an addition of programmed-death ligand-1 (PD-L1) inhibitors to chemotherapy may need to be considered and studied in a trial[19,20]; however, funding under a public payer and obtaining level 1 evidence to support their use remain a challenge.

Our study, as well as other studies, illustrates that clinical characteristics may be limited in prognosticating and predicting response to treatment for SCPC. In prior literature, factors such as age, N1 status, and receipt of radiation were associated with survival in patients with non-metastatic SCPC[15]. Factors such as treatment in a non-academic facility, stage 4, and Gleason 8-10 may also predict poorer outcomes[21]. Further studies to elucidate genomic landscape that may identify driver mutations and potential biomarkers are likely critical to improving outcomes. One study identified ONECUT2 as a candidate master transcriptional regulator of poorly differentiated SCPC, through regulating tumour hypoxia signaling[22]. Another study showed gene-signatures of SCPC that resemble SCLC, with at least a subset exhibiting preserved AR-signalling[23].

Our study is significantly limited by a small number of patients, retrospective cohort design, and a lack of information on the treatment decision making processes for each patient. While no conclusion can be drawn regarding optimal treatment algorithm based on our data, it reports on the Canadian single-province multi-institution cohort on an uncommon but aggressive subset of prostate cancer, SCPC, with outcomes following standards of care in heterogeneous stages and clinical settings.

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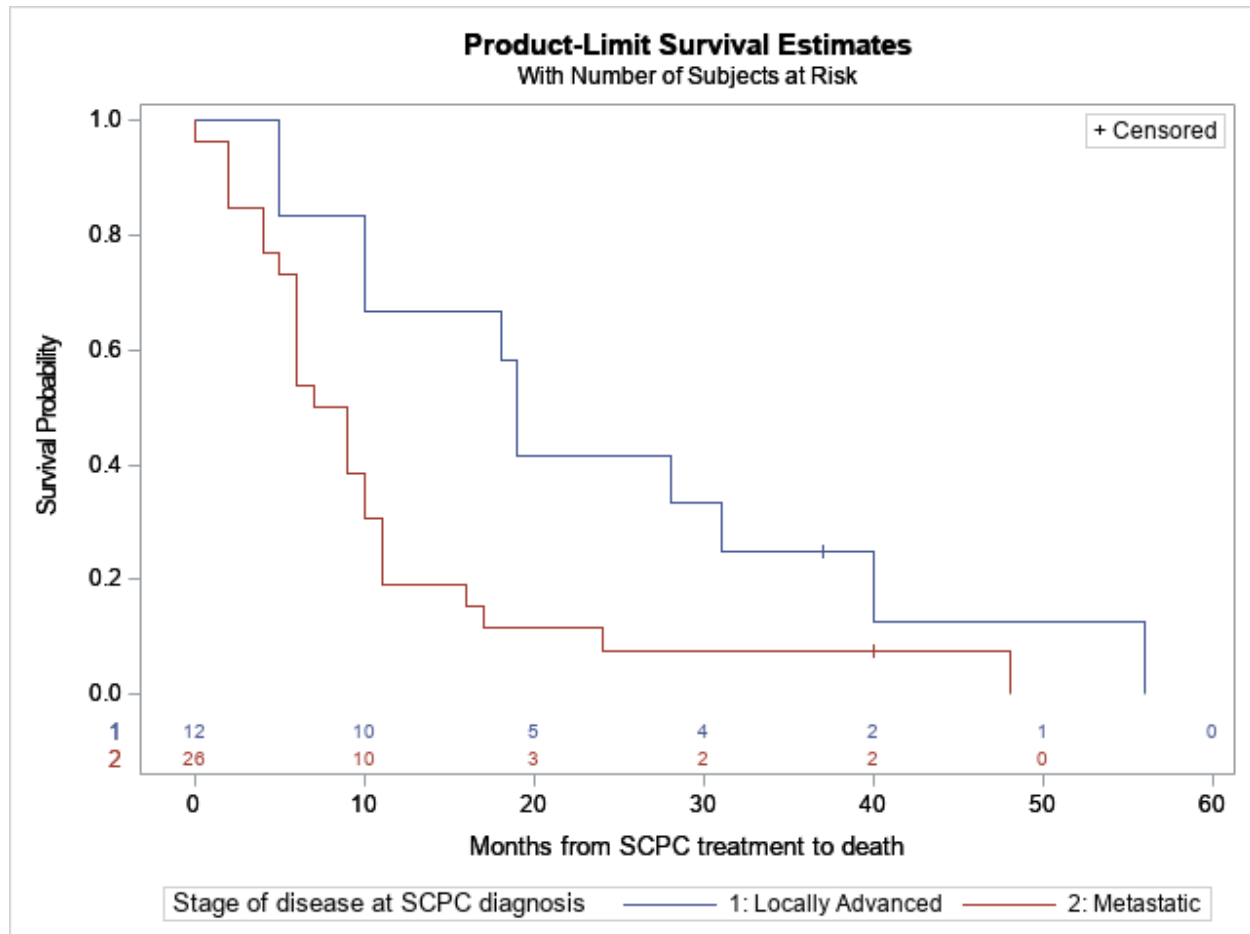
Figures and Tables

Figure 1. Overall survival probability of small cell prostate cancer (SCPC) by stage of disease.

Table 1. Baseline characteristics at time of diagnosis of unresectable or metastatic small cell prostate carcinoma (u/mSCPC)	
n=41	Value, n (%)
Age (median, interquartile range)	68 (62–72)
ECOG	
0	6 (18.8)
1	11 (34.4)
2	9 (28.1)
3	6 (18.8)
Unknown	9 (28.1)
Stage of disease	
Prostate-confined	3 (7.3)
Locally advanced	11 (26.8)
Metastatic	27 (65.9)
Diagnosis of pure small cell carcinoma	25 (61)
Diagnosis by pathology	37 (90.2)
Burden of disease at time of u/mSCPC diagnosis	
Bone	19 (46.3)
Visceral	12 (29.3)
Liver	7 (17.1)
Lymph nodes	20 (48.8)
Lung	5 (12.2)
Labs at time of u/mSCPC diagnosis	
PSA (median, interquartile range), ug/L	2.3 (0.27,11.7)
Hb (median, interquartile range), g/L	121 (112.5, 132)
LDH (median, interquartile range), U/L	323.5 (206, 562.5)
Albumin (median, interquartile range), g/L	37 (32, 40)
ALP (median, interquartile range), U/L	87.5 (71, 285)
Median Gleason score where applicable (i.e., of adenocarcinomatous portion of disease)	9 (6,10)
De novo vs. transformation	
De novo diagnosis of SCPC	20 (48.7%)
Transformation from adenocarcinoma to SCPC	21 (51.2%)
Recurrence after treatment of prostate-confined disease	4 (9.8%)
mCSPC	5 (12.1%)
nmCRPC	3 (7.3%)
mCRPC	9 (22.0%)

ALP: alkaline phosphatase; Hb: hemoglobin; LDH: lactate dehydrogenase; mCSPC: metastatic castrate-sensitive prostate cancer; mCRPC: metastatic castrate-resistant prostate cancer; nmCRPC: non-metastatic castrate-resistant prostate cancer; PSA: prostate specific antigen.

Table 2. Treatments employed for SCPC	
n=41	Value, n (%)
Radiation to prostate	14 (34.1) 8 concurrent, 6 post-chemotherapy consolidation
Prophylactic cranial irradiation (c=41)	1 (2.4)
Agent used in first line Platinum-based treatment	100%
Percentage of patients embarking on 2nd-line therapy (c=41)	15 (36.7)
Agent used in 2nd-line (c=15) Platinum re-challenge Irinotecan Topotecan CDV Etoposide	7 (46.7) 2 (13.3) 1 (6.7) 3 (20) 2 (13.3)
Percentage of patients embarking on 3rd-line therapy (c=41)	8 (19.5)
Agent used in 3rd-line (c=8) Platinum re-challenge Irinotecan Topotecan CDV Etoposide	3 (37.5) 1 (12.5) 1 (12.5) 0 (0) 3 (37.5)
Percentage of patients embarking on >3-line therapy (n=41)	3 (7.3)
Median number of small cell prostate cancer treatment lines, n (range)	1 (1,7)

SCPC: small cell prostate carcinoma.

Table 3. Time to subsequent therapy after first-line treatment for SCPC	
	Value, n (%)
Time to 2nd-line of treatment (months)	All: 12 Non-metastatic: 13 Metastatic: 8
Time to 3rd-line of treatment (months)	7
Time to 4th-line of treatment (months)	1 patient: 7 months

SCPC: small cell prostate carcinoma.