Molecular profiles of small cell bladder and prostate cancer, comparisons with small cell lung cancer

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Abstract #264

Background: Small cell bladder cancer (SCBC) and small cell prostate cancer (SCPC), two malignancies histologically identical to small cell lung cancer (SCLC), are rare and aggressive subtypes of bladder and prostate cancer. Standard therapy remains a platinum agent combined with etoposide, with few options after recurrence. Advances in molecular genomics and drug development have altered our approach to cancer. These same novel approaches may alter how we approach SCBC and SCPC. The purpose of this study is to identify potential targets and compare molecular profiles of SCBC and SCPC with SCLC.

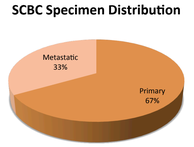
Methods: Retrospectively, 21 SCBC and 19 SCPC were identified from a de-identified database (Caris Life Sciences). Specimens were evaluated for genetic aberrations (Sanger sequencing or next generation sequencing [NGS] using either a hot-spot or whole exome platform, FISH/CISH) and/or protein expression (immunohistochemistry [IHC]). Comparisons were made against a de-identified cohort of SCLC (n=428).

Results: Pathogenic/presumed pathogenic mutations in SCBC were found in *TP53* (91.7%, 11/12), *RB1* (18.2%, 2/11), *PTEN* (8.3%, 1/12), *EGFR* (7.7%, 1/13), and *PIK3CA* (7.1%, 1/14). SCPC genetic aberrations were detected in *TP53* (72.7%, 8/11) and *RB1* (25.0%, 2/8). No carcinomas in this cohort had a high mutational burden or MSI-high status (0%, 0/7). Amplified genes found in SCBC included *DDR2* (50%, 1/2) and *EGFR* (25.0%, 1/4). In SCPC, gene amplification was found in *AKT2* (20%, 1/5), *CCNE1* (20%, 1/5), *FGFR1* (20%, 1/5), and *MYC* (20%, 1/5). The highest protein expression rates in SCBC involved MRP1 (100%, 5/5), TOP2A (94.1%, 16/17), RRM1 (81.3%, 13/16), and TOPO1 (73.7%, 14/19). The highest protein expression rates in SCPC were MRP1 (100%, 6/6), TUBB3 (100%, 9/9), TOP2A (94.4%, 17/18), and TOPO1 (75.0%, 9/12). Comparisons between SCBC and SCPC with SCLC revealed more similarities than differences. Statistically significant differences were found between SCPC and SCLC in AR (p< 0.001) and PTEN (p=0.026) by IHC.

Conclusion: Comparisons of GU small cell carcinomas reveal similarities to SCLC. Both *TP53* and *RB1* mutations, common alterations in SCLC, were found in both SCBC and SCPC. Amplification in genes *CCNE1* and *FGFR1*, frequently identified in SCLC, were also found in SCPC. The high protein expression in biomarkers like MRP1, RRM1, and TUBB3 may explain the poor response to cytotoxic chemotherapy. Prospective studies are urgently needed.

Results

Malignancy	n	Median Age	Age Range	Gender
SCBC	21	67	41-88	67% M; 33% F
SCPC	19	68	48-82	100% M



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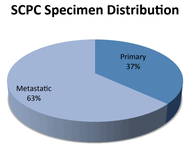
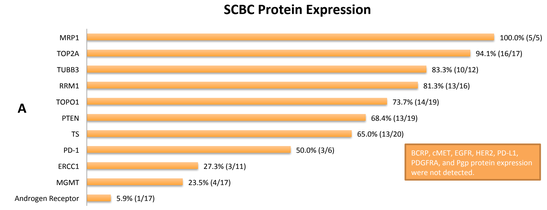


B

Table 1 and Figure 1 (A) and (B) – Demographics for SCBC, SCPC specimens. Age, gender, and specimen characteristics are shown above for both malignancies.



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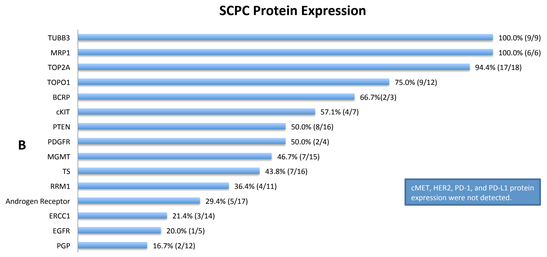

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Figure 2 (A) and (B) – Percent protein expression assessed by IHC in SCBC, SCPC. Protein expression sorted from highest to lowest in SCBC and SCPC. Boxes next to bar charts report under-expressed/absent protein biomarkers.

Results

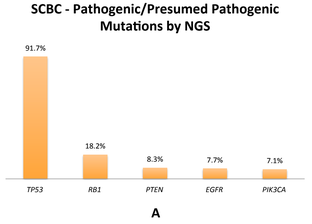
SCBC - amplification detected using NGS		
CLP1 (50%, 1/2)	*DDR2* (50%, 1/2)	*GPR124* (50%, 1/2)
SDC4 (50%, 1/2)	*ZNF217* (50%, 1/2)	*ZNF703* (50%, 1/2)
SCBC – amplification detected using FISH		
EGFR (25%, 1/4)		

A

SCPC - amplification detected using NGS		
AKT2 (20%, 1/5)	*CCNE1* (20%, 1/5)	*FGFR1* (20%, 1/5)
MYC (20%, 1/5)	*WHSC1L1* (25%, 1/4)	*ZNF703* (25%, 1/4)

B

Table 2 (A) and (B) – Gene amplification assessed by NGS or *in situ* hybridization. NGS CNV (copy number variance) results shown were based on two SCBC profiles and five SCPC profiles. Other biomarkers (*ERBB2*, *MET*) evaluated by FISH or CISH were unremarkable.



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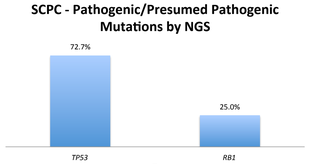

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Figure 3 (A) and (B) – Pathogenic and presumed pathogenic mutations assessed by either Sanger, hot-spot or whole exome NGS. The percentages shown combined both hot-spot and whole exon NGS results. Variants of unknown significance, presumed benign and benign variants were not included.

GU CA	MSI by NGS	Mean TMB score by NGS
SCBC (n=2)	0.0%	12.5
SCPC (n=5)	0.0%	6.4

Table 3 – TMB and MSI (by NGS) in small cell bladder and prostate CA. Like the gene amplification results, these numbers are based on two SCBC and five SCPC specimens. For reference, TMB was reported as mutations per megabase.

Results

SCPC – fusions detected using ArcherDx
TMPRSS2:ERG

Table 4 – Fusions in SCBC, SCPC. No fusions were detected in SCBC specimens evaluated (0.0%, 0/1). One fusion was detected in an SCPC, non-metastatic specimen (33.3%, 1/3).

Calculation	Statistical test	Three-way comparison	SCPC v SCLC	SCPC v. SCLC
p-value	chi-square	AR (IHC) PTEN (IHC)	None	AR (IHC) PTEN (IHC)
q-value	chi-square	AR (IHC)	None	AR (IHC)

Figure 4 – Statistically significant differences in SCBC and SCPC versus SCLC. Biomarkers with statistically significant p- and/or q-values (a FDR [false discovery rate] adjusted p-value) are shown. AR by IHC was higher in SCPC (29.4% v. 3.7%, p<0.001, q=0.014) but PTEN expression by IHC was lower (50.0% v. 78.1%, p=0.026, q=0.265) in SCPC when comparing to SCLC. No significant differences were detected in comparisons of hot-spot NGS biomarkers.

Conclusions

- Like SCLC, both SCBC and SCPC exhibit high alteration rates in *TP53* and *RB1*. SCPC also shows molecular features of prostate adenocarcinoma (e.g. *TMPRESS2:ERG* fusion).
- Increased number(s) of alterations are realized when utilizing larger panels, which may be advised given the dearth of targets in SCBC and SCPC.
- Few significant alterations/abnormalities were detected in biomarkers typically associated with potential benefit to checkpoint blockade therapy. However, given the favorable evidence of immune-based therapy in SCLC, these agents may still be of interest in these rare genitourinary malignancies.
- In both small cell malignancies, the high protein expression observed in drug pumps (e.g. MRP1) and biomarker overexpression associated with resistance (e.g. TUBB3) may explain the poor responses over time to cytotoxic chemotherapy.
- Future studies incorporating molecular profiling with outcomes in these rare diseases are urgently needed.

References

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