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/ISH 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 (16.7%, 2/12), PTEN (83.3%, 1/1), EGFR (77%, 1/1), and PMS2 (72.7%, 1/1). 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%). Amplified genes found in SCBC included DDR2 (50%, 1/2) and EGFR (25%, 1/4). In SCPC, amplification was found in AKT2 (20%, 1/5), CCNE1 (20%, 1/5), FGFR3 (20%, 1/5), and MYC (20%, 1/5). The highest protein expression rates in SCBC involved MRPI (100%, 1/1), TOPO1 (94.4%, 17/18), and TUBB3 (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 RB2 mutations, common alterations in SCLC, were found in both SCBC and SCPC. Amplification in genes CCNE1 and FGFR2, frequently identified in SCLC, were also found in SCPC. The high protein expression in biomarkers like MRPP1, RRM1, and TUBB3 may explain the poor response to cytotoxic chemotherapy. Prospective studies are urgently needed.

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

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

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

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

References

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. By AR was higher in SCLC (29.4% vs. 7.7%, p=0.001, q=0.014) but PTEN expression by IHC was lower (50.0% vs. 78.1%, p=0.026, q=0.265) in SCPC compared 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. TMPRSS2-ERG fusions).
• 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 assays (MRPP1, RRM1) and biomarkers associated with tumors (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.