A multiplatform biomarker analysis of small cell bladder cancers

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Abstract

Background: Small cell bladder cancer (SCBC), a malignancy indistinguishable from small cell lung cancer (SCLC), is a rare and aggressive subtype of bladder cancer. Response to chemotherapy in SCBC is poor, yet the standard therapy remains cisplatin and etoposide. Novel therapies based on a better understanding of the underlying mechanisms of transformation are needed. The purpose of this study is to identify potential targets and therapeutic options for this disease, using multiplatform tumor profiling.

Methods: In total, 19 small cell bladder cancer specimens were tested via a multiplatform profiling service (Caris Life Sciences, Phoenix, AZ) consisting of gene sequencing (Sanger or next generation sequencing (NGS), with NGS evaluating up to 47 genes via a multiplatform profiling service (Caris Life Sciences, Phoenix, AZ). NGS and Sanger sequencing were used to identify cell surface receptors and downstream molecules that could be targeted with chemotherapy and its aggressive course. NGS and Sanger sequencing were performed by either Sanger or NGS, with NGS evaluating up to 47 genes at a depth of 1500x.

Results: Loss of RRM1 (22.2%, 4/18), MGMT (83.3%, 15/18), and TP53 (26.3%, 5/19) by IHC are associated with potential benefit to traditional chemotherapy. High expression of ERBB2, associated with resistance to platinum-based therapy, was 37.5% (3/8). High expression of TOP2A (93.8%, 15/16) and TOPD1 (78.9%, 15/19) is associated with treatment benefit to anthracyclines and camptothecins, respectively. MRP1, a drug pump associated with resistance to various chemotherapies, was present in 100% (5/5) of specimens. PO-L1 (0%, 0/6) was not expressed.

Conclusion: A multiplatform approach may be valuable for identifying novel targets in this rare disease.

Background (cont.)

only 0.5-1.0% of bladder malignancies. In fact, up to 65% have metastases at, or soon after, diagnosis. The standard therapy for SCBC is cisplatin and etoposide, however, response to chemotherapy is poor. Novel therapies based on a better understanding of the underlying mechanisms of transformation are needed. The purpose of this study is to identify potential targets and therapeutic options for this disease, using multiplatform tumor profiling.

Methods

In total, 19 small cell bladder cancer specimens were tested using a CLIA-certified, multiplatform profiling service (Caris Life Sciences, Phoenix, AZ). Protein expression was assessed by immunohistochemistry (IHC). Gene amplification was determined using fluorescent in situ hybridization (FISH) or chromogenic in situ hybridization (CISH). Sequencing was performed by either Sanger or next generation sequencing (NGS), with NGS evaluating up to 47 genes at a depth of 1500x.

Presence of gene amplification (CISH or FISH).

Results

Nineteen SCBC specimens were tested. The average age of this cohort was 67.6 years old. Most patients were male (see Figure 1).

Most specimens (see Figure 2) were collected from the bladder using transurethral resection of the bladder (TURB). The second most common collection site was lymph nodes, either pelvic (n=2) or supravacular (n=1).

Results (cont.)

The bar chart (Figure 3) below shows distribution of IHC in SCBC.

The high expression of MRP1 may explain this cancer’s resistance to traditional therapy. In this disease, high expression of RRM1, TUBB3, and TP53 imply resistance to agents such as gemcitabine, paclitaxel, and fluorouracil. Regardless, high protein expression of TOP2A, TOPD1 indicate anthracyclines (i.e. doxorubicin) and camptothecins (i.e. irinotecan) may play a role in disease management. MGMT may identify those patients who derive benefit from temozolomide.

Mutations detected by NGS or Sanger sequencing revealed the following (see Figure 4):

Like small cell lung cancer, TP53 was the most common mutation (90.0%). The presence of PIK3CA, PTEN, and FBXW7 mutations warrants consideration of targeting the PIK3CA/Akt/mTOR pathway in a subset of patients. Targeting cMET may be an option in a small group of these patients as well, although the utility of cMET in a subset of patients is still under debate. The lack of mutations in this disease warrants further studies involving multi-omic modalities to better understand and target this disease.

Conclusions

To the best of our knowledge, this is the most comprehensive molecular analysis of SCBC, a malignancy accounting for 1% of all bladder cancers.

• High IHC expression of biomarkers such as MRP1, RRM1, TUBB3, and TP5 may contribute to this malignancy’s resistance to cytotoxic chemotherapy.

• Taking the combination of high ERBB2 and high TOP2A expression by IHC into account may identify those patients who derive the most benefit from upfront chemotherapy. Of note, in addition to high MGMT protein expression may identify these patients who derive benefit from temozolomide. Prospective trials are needed to test the potential value of these biomarkers for response.

• Similar to small cell lung cancer (SCLC), TP53 mutations are found in SCBC with high frequency.

• Based on sequencing results, other potential options in this disease include employing agents targeting the PIK3CA/Akt/mTOR pathway.

• A small group of SCBC have amplified EGFR or EGR2 mutations. Clinical trials testing efficacy of EGFR inhibition may be worthwhile.

• A multiplatform approach may be valuable for identifying novel targets in this rare disease. Larger analyses of this aggressive disease is warranted.

References

