SLFN11 expression in castration-resistant prostate cancer and response to platinum-based chemotherapy

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Background

The SLFN11 family of proteins includes a DNA/RNA helicase, first described for its role in normal thymocyte development, immune response, and cell proliferation. Later, SLFN11 expression was assessed in several cancer cell lines, including Ewing’s sarcoma, small cell lung, ovarian, and colon cancers. SLFN11 expression has been associated with response to DNA damaging chemotherapy agents. In addition, SLFN11 expression has been associated with sensitivity to PARP inhibitors.

Objective

We sought to identify SLFN11 expression in tissue and blood from advanced prostate cancer patients and to elucidate its potential predictive and prognostic role in platinum (PTL)-treated CRPC patients.

Methods

1. Patient cohort

Patients with metastatic CRPC treated with PTL were retrospectively identified. Patients had a metastatic biopsy of adenocarcinoma (CRPC-Adeno) or mixed or pure neuroendocrine prostate cancer (CRPC-NE). The protocol was approved by the Institutional Review Board. Clinical and demographic information was collected by medical record review. PCWG3 criteria was used to assess clinical, biochemical, and radiographic response to different therapies.

2. Tissue biopsies

In cases with adequate fresh/frozen tissue, RNA sequencing (RNA-Seq) data was evaluated to assess the expression of SLFN11. In addition, when available, metastatic tumor genomic status of select genes (i.e., AR, TP53, RB1, PTEN, BRCA2, BRCA1, ATM) was collected from review of whole-exome sequencing (WES) data from a CLIA/CAP-accredited clinical assay.

3. CTC collection and characterization

Whole blood samples (10 ml) from CRPC patients were collected in Streck tubes and shipped to Epic Sciences for processing. In the Epic Sciences platform, slides were stained for DNA (DAPI), whole blood cell image marker (CD45), epithelial cells marker (CK), and SLFN11. CTC enumeration was performed, the slides were evaluated by immunofluorescence (IF), and the images of nucleated cells were assessed using a multi-parameter digital cytology analysis.

4. In vitro studies

A dose response curve with PTL was performed in patient-derived organoids using CellTiter-Glo according to the manufacturer’s protocol.

Results

1) Patient cohort characteristics

- 41 patients with metastatic CRPC (21 CRPC-Adeno, 20 CRPC-NE) were identified between May 2012 and June 2018 with a median age of 67.1 years (range 50-90).
- All patients underwent PTL (38 in combination with etoposide (N=21) or taxanes (N=17), and 3 monotherapies with carboplatin).
- Specimens were collected with a median of 85 days (range 0-707 days) before PTL.
- All patients received prior ADT and a median of 2 therapeutic lines (range 1-7) for CRPC before PTL, including in 23 (56.1%) cases AR-directed therapies (abiraterone or enzalutamide).

2) SLFN11 expression by RNA-Seq

- We evaluated SLFN11 mRNA expression in prostate cancer cancer and compared with other tumor types (Fig 1) and disease states (Fig 2), and identified a subset of CRPC cases with SLFN11 overexpression (lower in CRPC-NE).

3) SLFN11 detection in circulating tumor cells

- SLFN11 expression in CTCs of patients was concordant with SLFN11 expression by RNA-Seq of matched metastatic tumor biopsies.

4) Association of SLFN11 expression and response to platinum therapy

- SLFN11 expression in PTL treated CRPC patients was significantly associated with radiographic PFS and PSA response, but not with OS.
- Multivariable analysis identified SLFN11 as an independent predictor of PFS in PTL-treated patients.

Conclusions

- SLFN11 overexpression may identify CRPC patients with a better response to platinum-based chemotherapy.
- Larger prospective studies are warranted to translate these findings into biomarker-informed clinical decision making for patients with advanced prostate cancer.