Abstract: Circulating Tumor Cells (CTCs) With Small-Cell Like Features are Prevalent in Metastatic Castration Resistant Prostate Cancer (mCRPC) and Show Selective Pharmacodynamic Reductions in Patients Treated With Platinum Therapy but not an ARSi or Taxane

BACKGROUND

- The increasing availability and earlier use of life prolonging drugs targeting the androgen receptor signaling axis (ARsi) has resulted in an increase in the frequency of late stage tumors with "small cell/neuroendocrine like (NESC like or NESC) features" similar to small cell lung cancer (SCLC).
- Pathologic criteria to diagnose the prostate cancer "entity" are not definitive.
- Clinical trial eligibility criteria/requirements include a range of clinical, histologic and/or biologic measures but are not consistent, limiting the ability to relate outcomes between studies.
- We hypothesize that an analytically valid assay for a rigorously defined "small cell CTC" phenotype might serve as a unifying biomarker for the presence of NESC-like tumors in an individual for use in clinical trials.

METHODS

Hypothesis: The features that defined small-cell carcinoma of the lung can be used to reliably and reproducibly detect NESC like CTCs for use as a non-invasive real-time diagnostic.

Single-cell features for small cell carcinoma according to WHO:
1. Small cells with scant cytoplasm
2. High nuclear-to-cytoplasmic ratio
3. Absent or inconspicuous nucleoli
4. Salt and pepper chromatin

Translating Single-cell WHO Small Cell Morphologic Criteria to an Image Based CTC Detection Algorithm Using the EPIC Platform

Proposed Features to Define Neuroendocrine/Small-Cell (NESC) like CTC phenotypes

Defining Neuroendocrine Small-Cell (NESC) Features in CTCs

Features #1 & 2: Small CTCs With High N/C Ratios Are Observed In SCLC, mCRPC, And Cell Line Controls

- Single-cell feature for small cell carcinoma according to WHO:
  1. Small cells with scant cytoplasm
  2. High nuclear-to-cytoplasmic ratio

Feature #3: The Presence or Absence of Nucleoli Readily Determined From DAPI Staining That Are Expected to be Absent in Small-Cell Neuroendocrine

- Proposed CTC neuroendocrine/small-cell features:
  1. Small cells with scant cytoplasm
  2. High nuclear-to-cytoplasmic ratio
  3. Absent or inconspicuous nucleoli
  4. Salt and pepper chromatin

Feature #4: Salt-and-Pepper Chromatin are Observed In Small CTCs with High N/C Ratios

- Single-cell feature for small cell carcinoma according to WHO:
  4. Salt-and-pepper chromatin

Feature #5: (Not Accessible By H/E): Dot-like Cytokeratin Staining Patterns Are Often Observed In Small Cell CTCs

- Single-cell feature for small cell carcinoma according to WHO:
  1. Small cells with scant cytoplasm

CONCLUSIONS

- Single Circulating Tumor Cells (CTCs) that are consistent with the WHO pathologic criteria for a neuroendocrine / small-cell diagnosis can be detected in patients with mCRPC.
- The frequency of CTCs with small cell features were higher in patients who had failed one or more therapies.
- Reductions in the number of NESC-like CTCs subtype characterized by 3 of the 5 features after treatment vary by drug class and suggest the higher sensitivity to a platinum-based regimen.
- A rapid, reproducible, and non-invasive method for identifying neuroendocrine / small-cell disease could serve as a unifying biomarker in clinical trials

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