Molecular Profiling of Advanced Refractory Prostate Cancer

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Abstract

Prostate cancer is the second leading cause of cancer-related death among men in the US. Forty percent of men diagnosed will develop metastatic disease which has few treatment options. We aim to describe the molecular profile of prostate cancer tumors and potential for novel therapeutic options.

Methods: We reviewed profiling data of over 300 patients from a large referral laboratory (Caris Life Sciences, Phoenix, AZ) on biomarkers of drug response. Multiple methodologies were employed: sequencing (NGS, Sanger, pyrosequencing), in-situ hybridization (fluorescent and chromogenic) and immunohistochemistry (IHC).

Results: High expression was observed for AR, MMPI, TP53, TERT, TLE3 and EGFR, with positivity rates of 85%, 67%, 62%, 48%, and 47%, respectively. Low expression was observed for TP53, PTEN, p53, and MAPK, with negativity rates of 94%, 87%, 75%, 39%, and 45%, respectively. Same copy number increases for EGFR and AR were observed in 12% of patients. Sequencing data showed 48% mutation rate for TP53, 18% for PTEN, 5% for ETN5B3 and 5% for MMPI. In 4% of patients, PIK3CA mutation was inactivated by somatic deletions. Promising agents may be considered, including checkpoint inhibitors, based on TP53 of cut-off with TP53 activation or non-function. Several biomarkers have been identified as predictive factors for future treatments. Conclusion: Tumor profiling identified small subsets of patients that may benefit from targeted agents approved for other solid tumors (metastatic, breast), promising therapies in clinical trials (laboratory) or agents not routinely used for prostate cancer (genitourinary). By combining the biomarker results of IHC, SII and NGS, we identified subgroups that might benefit from combining traditional chemotherapy and hormonal agents with novel targeted agents.

Background

Prostate cancer remains to be a leading cause of cancer-related death in men. Although 65% of prostate cancer patients are considered indolent, 40% are aggressive and require multiple lines of treatment. The lack of distinguishing factors that differentiate indolent vs. aggressive subtypes of prostate cancer lead to unnecessary treatments and surgeries for some men.

Prostate cancer is largely driven by androgen receptor signaling, therefore, androgen deprivation therapy is a mainstay of treatment. Despite initial effectiveness, androgen deprivation therapy invariably leads to the emergence of castration resistant disease, which is highly aggressive and treatment refractory. Identifying the molecular mechanisms in all stages of prostate cancer, therefore, can direct therapy and may result in the introduction of new molecular alterations to target.

Molecular profiling using multiple platforms is a comprehensive approach in identifying molecular alterations that could be targeted by (1) agents considered standard of care for prostate cancer; (2) FDA-approved agents used in other solid tumors, (3) novel targeted therapies currently in clinical trial or (4) combination treatment strategies combining novel targeted agents with traditional therapies.

Methods

All 388 prostate cancer cases referred to Caris Life Sciences between 2009 thru 2013 from 50 states and 50 countries were evaluated; diagnoses were collected from referring physicians and classified at intake based on pathologic and clinical history. Specific testing was performed per physician request and included a combination of sequencing (Sanger or Next generation sequencing (NGS)), protein expression (immunohistochemistry), gene amplification (FISH) or IHC.

Protein or Gene Copy Number Changes

<table>
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<tr>
<th>Protein / Gene</th>
<th>Number Changes</th>
<th>Associated Single Agent Therapy</th>
<th>Potential Mediation of Response or Additional Alterations Identified by CM*</th>
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Figure 1 – Protein (IHC) expression rates and gene copy number (∆CN) changes. Expression rates correlate with therapeutic utility of associated drugs. Average number of samples tested by IHC was 264; average number of samples tested by SII was 50. Targeted therapies not commonly used in prostate cancer may be considered in patients demonstrating EGFR overexpression and gene amplification, e.g. trastuzumab; HER2 overexpression or gene amplification, e.g. trastuzumab; JAK1 and JAK2 overexpression, e.g. imatinib; MEK1 overexpression and gene amplification, e.g. cobimetinib. Conversely, low expression of MYC, JAK2 and TP53 correlate with better outcomes, respectively. Profiling also reveals potential clinical benefit of commonly used prostate cancer drugs including taxanes based on TP53 and TLE3, anti-androgens based on AR and platinum agents based on BRCA.

Results

Figure 2 – Mutational profile of prostate cancer using next-generation and single sequencing. Average number of samples tested by NGS and Sanger was 35. The most commonly mutated pathways in prostate cancer are the TP53, PTEN/PIK3CA and Wnt signaling pathways. Currently, agents targeting these pathways are under clinical investigation.

Figure 3 – Frequency of mutations in prostate cancer. Next generation sequencing data was available for 64 patients. Forty percent (n=25/64) of advanced prostate cancers lack actionable gene mutations; 96% of which have actionable targets identified by IHC and FISH platforms. Twenty three percent of prostate cancers exhibit multiple mutations, either double mutations in single genes, or single mutations in more than one gene. Eighty-nine percent (53/61) of patients with ≥2 mutations are derived from metastatic specimens.

Conclusions

388 prostate cancer samples, including advanced, localized and metastatic disease, were profiled with a multi-platform approach using immunohistochemistry, in-situ hybridization and mutational analysis tests. The most commonly mutated pathways in prostate cancer include TP53, PTEN/PIK3CA and Wnt signaling pathways. Forty four percent of prostate cancers lack actionable gene mutations. 96% of these patients have actionable targets identified by IHC and FISH platforms.

• Multiple agents are identified as having potential clinical benefit including agents considered standard of care, as well as FSA-approved agents for other solid tumors.

• Comprehensive molecular profiling of prostate cancer guides integration of traditional chemotherapies and anti-androgens with novel targeted agents.

• The Caris analysis includes measurement of the major molecular changes known to drive prostate cancer progression, providing the practicing physician with a robust, validated means of deciphering which of these changes are active in the patient under their care. As targeted drug development provides drugs capable of targeting these changes, the clinician can tailor treatment to their patient with steady increasing precision.

References