The clinical impact of targeted next generation sequencing (tNGS) in the treatment of metastatic prostate cancer

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Background: Tumor profiling by tNGS is increasingly common in patients (pts) with metastatic solid tumors. It is unclear if this strategy leads to changes in treatment decision for mPCA pts.

Methods: A retrospective analysis of mPCA pts treated at Cleveland Clinic with available comprehensive genomic profiling using tumor tissue (FoundationOne, F1) or cell-free circulating tumor DNA (FoundationAct, Guardant360) was conducted. Targetable genomic alterations (tGA) were defined as a change in the copy number (amplification/duplication) or a mutation (deletion/rearrangement/truncation/fusion) in AR, DNA repair genes, mismatch repair (MMR) genes, cyclin-dependent kinases (CDK), ERBB2, BRAF, TSC and PIK3-mTOR pathway.

Results: Within 2013-2017, 66 pts, median age 68y (49-85), median ECOG PS1 (0-2), with mPCA, Gleason 9 (6-10), 86% castration-resistant (CRPC), received a median of 3 (0-7) systemic treatments for CRPC before tNGS panel. The most common tNGS platform used was F1 (91%) based on archival tumor tissue (45% primary, 55% metastatic). Overall, frequent alterations included TP53 (42%), PTEN (35%), AR (30%), DNA repair (30%), PI3KCA signaling pathway (21%), CDK (15%) and MSI-H/MMR (9%). Median tumor mutational burden was 7 (0.8-32) mutations/Mb. Among 45 with tGA+ pts, tNGS influenced treatment in 13 pts: PARP inhibitor (n = 7; olaparib 6, niraparib 1), mTOR inhibitor (n = 4; everolimus 3, temsirolimus 1), pembrolizumab 2, trastuzumab 1. PSA decline was observed in 54% and median (m) PFS was 4.1 months (95%CI, 2.8-5.4) with 9 pts (69%) progressing on therapy to date. Among tGA+ pts not treated with tGA-based therapy, first subsequent treatment (n = 17) included chemotherapy (71%), abiraterone (18%), cabozantinib (6%) and other (6%). PSA decline was observed in 24% and mPFS was 4.3 months (95%CI, 2.6-6.0); 12 pts (71%) progressed on therapy. There was no difference in mPFS between tGA+/tGA- pts (p = 0.652). The median OS was 60.4 months (95%CI, 51.9-68.9) compared with 17 months (95%CI, 10.3-23.3) after tNGS was ordered.

Conclusions: tNGS was ordered somewhat late in the course of the disease. tGA results only impacted therapy selection in 20% of pts but with modest clinic benefit.

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