ABSTRACT

Background: Prostate ductal carcinoma (PDC), prostatic acinar carcinoma (PAC), and prostate neuroendocrine carcinoma (PNC) are histologic subtypes of prostate cancer (PC). We queried whether these subsets would share similar genomic alterations (GA) reflecting their disease biology and clinical features.

Methods: CGP was performed using a hybrid capture-based assay on 61 PDC, 4,132 PAC, and 217 PNC. Tumor mutational burden (TMB) was determined on 0.83-1.14 Mbp of sequenced DNA and microsatellite instability (MSI) was determined on 214 loci.

Results: The age, GA per tumor and TP53 GA of PDC, PAC and PNC were similar (Table). RB1 GA were predominant in PNC. TMPRSS2:ERG fusions were most frequent in PNC, intermediate in PAC and lowest in PDC. AR GA were more often identified in PAC than PDC or PNC whereas PTEN GA were most frequent in PDC than PAC or PNC. Targetable GA were identified in all 3 groups when focused on BRCa2 (PARP inhibitors) and PIK3CA (MTOR inhibitors). ATM GA (PARP inhibitors) were more common in PAC than PNC or PDC. BRAF GA (BRAF/MEK inhibitors) were more frequent in PAC and PNC than PDC. CDK12 GA potentially associated with immunotherapy (IO) benefit were similar in PAC and PAC and low in PNC. Low frequencies of MSI-High and low median TMB levels were similar in all 3 groups.

Conclusions: The pathologic features of PDC, PAC and PNC have been classically maintained as representative of 3 different tumor types with potentially contrasting histogenesis. In the current CGP based study, all 3 tumor types did not display significant differences in genetic signatures other than the high RB1 GA. CGP may reveal biomarkers that could direct patients to targeted (PARP, MTOR and BRAF/MEK inhibitors) or immunotherapies (CDK12 GA, MSI-High or high TMB status) especially in PDC and PAC.

MATERIALS AND METHODS

- 250 ng DNA extracted from 40 µm of FFPE sections
- Sequencing performed for up to 315 cancer-related genes and introns from 28 genes commonly rearranged in cancer
- Hybrid capture-based sequencing using adaptor ligation-based libraries
- Mean coverage depth >600X
- Base substitutions, insertions and deletions (short variants; SV), rearrangements, and copy number changes were assessed
- Tumor mutational burden (TMB) calculated from 0.83-1.14 Mb sequenced DNA

RESULTS

- Ages, GA per tumor and TP53 GA of PDC, PAC and PNC were similar
- RB1 GA were predominant in PNC
- TMPRSS2:ERG fusions were most frequent in PNC, intermediate in PAC and lowest in PDC
- AR GA were more often identified in PAC than PDC or PNC whereas PTEN GA were most frequent in PDC than PAC or PNC
- Targetable GA were identified in all 3 groups when focused on BRCa2 (PARP inhibitors) and PIK3CA (MTOR inhibitors).
- ATM GA (PARP inhibitors) were more common in PAC than PNC or PDC
- BRAF GA (BRAF/MEK inhibitors) were more frequent in PAC and PNC than PDC
- CDK12 GA potentially associated with immunotherapy (IO) benefit were similar in PAC and PAC and low in PNC
- Low frequencies of MSI-High and low median TMB levels were similar in all 3 groups

CASES

Bone biopsy in a 68 year old Caucasian man with metastatic ductal adenocarcinoma of the prostate. CGP revealed short variant mutations in BRCa2, CDKN2A and BRCA2. Alterations that activate BRAF kinase activity, such as in the G618S BRAF mutation lead to hyperactivation of the downstream MEK-ERK signaling pathway and may confer sensitivity to BRAF and/or MEK inhibitors. BRAF mutations have been reported in 1% of prostate adenocarcinomas. For ductal prostate cancer, the frequency and significance of BRAF mutations has not been previously considered. BRCa2 mutations in prostate cancer such as were found in this patient are linked to defective DNA damage repair and have been widely associated with potential sensitivity to PARP inhibitors.

CONCLUSIONS

- In the current CGP based study, the PDC, PAC and PNC tumor types did not display significant differences in genomic signatures other than the high RB1 GA in PNC
- CGP may reveal biomarkers that could direct patients to targeted (PARP, MTOR and BRAF/MEK inhibitors) or immunotherapies (CDK12 GA, MSI-High or high TMB status) especially in PDC and PAC