Impact of clonal hematopoiesis mutations in solid tumor patients with a future focus for men with castration-resistant prostate cancer

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Background: Genomic testing is commonly performed for both prognostication and application of targeted therapies for oncologic patients. Results from next-generation sequencing (NGS) assays should reflect the burden of somatic mutations of the sequenced tumor, yet challenges can arise from differentiation of germline mutations and from contamination of biopsies by non-tumor tissue. Clonal hematopoiesis (CH), defined by the presence of somatic mutations typically in leukemia-associated genes in hematopoietic cells, occurs in aging individuals, with an increased risk for hematologic cancers and cardiovascular mortality and shorter survival in solid tumor (ST) patients. CH is associated with prior radiation therapy and tobacco use. Here we examine the prevalence of CH in ST patients leading to possible misattribution on commercial NGS assays and we explore the impact of CH in prostate cancer.

Methods: This is a multi-institution, retrospective cohort study of ST patients undergoing NGS. All patients undergoing commercial NGS (FoundationMedicine) testing were examined (N=768 at UNC and 989 at MCC), including 24 prostate cancer patients. For a subset of patients (N=64 at UNC and 30 at MCC), NGS of paired blood samples was performed to examine the prevalence of true CH events, defined as a variant allele frequency (VAF) in the blood exceeding the VAF in the tumor tissue.

Results: Mutations in genes that are frequently altered in CH (*DNMT3A*, *TET2*, *ASXL1*, *TP53*, *ATM*, *CHEK2*, *SF3B1*, *CBL*, *JAK2*) were identified in 65% of patients; excluding *TP53*, these events were seen in 35% of patients. A bimodal distribution of VAFs was seen for CH genes, with low VAF events most suggestive of true CH events. Using paired blood samples, we confirmed such mutations as true CH events in 8% of patients. The majority of *DNMT3A* mutations (64%, 7/11) were CH; the minority of *TP53* mutations (4%, 2/50) were CH.

Conclusions and Future Directions: Mutations in CH genes are commonly reported on unpaired clinical NGS testing; some are true CH events as opposed to somatic tumor events. It is important to recognize CH as a possible confounder when interpreting NGS results. Future work will focus on examining the frequency and clinical significance of CH among patients with metastatic castration-resistant prostate cancer using specimens from a recently completed Phase 3 clinical trial (Alliance 031201, enzalutamide versus enzalutamide/abiraterone/prednisone). Prostate cancer is an ideal malignancy to examine the impact of CH on cancer-specific outcomes, as it is a highly prevalent cancer occurring in aging individuals, many of whom have had prior radiation therapy. We hypothesize that CH will lead to inferior prostate-cancer specific outcomes including overall survival, progression free survival, and PSA response. Exploratory outcomes will include hematologic and cardiovascular toxicity/events.

Conflicts of Interest: No conflicts of interest related to this work

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