Mutations in CTC may predict outcomes in some castrate-resistant prostate cancer patients

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Various genetic alterations in circulating tumor cells (CTCs) were associated with clinical outcomes and resistance to hormone therapy in patients with metastatic castrate-resistant prostate cancer (mCRPC), according to results published in *Molecular Cancer Research*, a journal of the American Association for Cancer Research.

While only a minority of men with mCRPC have primary resistance to the androgen receptor (AR) inhibitors enzalutamide (Xtandi) or abiraterone acetate (Yonsa or Zytiga), most men will develop acquired resistance within several years, explained senior author Andrew Armstrong, MD, MSc, a medical oncologist at the Duke Cancer Institute Center for Prostate and Urologic Cancers at Duke University.

In the previously published PROPHECY study, Armstrong and colleagues found that the presence of the AR-V7 splice variant in CTCs from patients with mCRPC was associated with fewer responses and shorter progression-free and overall survival after treatment with enzalutamide or abiraterone. Based on these results, the National Comprehensive Cancer Network incorporated suggested AR-V7 testing into the clinical practice guidelines for patients with mCRPC who have progressed after one hormonal therapy, Armstrong noted.

"While these findings were encouraging, only about 5 to 40 percent of patients with mCRPC have CTCs that are positive for AR-V7,

depending on the disease context, suggesting that other genetic alterations may play a role in drug resistance," he added.

The latest study is a retrospective secondary analysis of the PROPHECY study. In this new analysis, Armstrong and colleagues identified genomic alterations in AR-V7-negative CTCs of patients with mCRPC and examined associations between these alterations and clinical outcomes.

Armstrong and colleagues analyzed individual patient pooled CTC DNA vs. germline DNA for whole genomic copy number alterations—indicating the gain or loss of genetic material—in 73 liquid biopsy samples collected over time from 48 men with mCRPC treated with AR inhibitors in the PROPHECY Study. They also looked for novel genomic alterations associated with acquired resistance over time by performing individual patient pooled CTC vs. matched germline whole-exome sequencing on 22 samples taken before and after progression on enzalutamide or abiraterone.

In addition to confirming previous work that suggested that poor outcomes to AR inhibition were associated with PTEN loss, MYCN gain, AR gain, and TP53 mutations in CTCs, the investigators identified several novel alterations associated with response to AR inhibitors. Gains of ATM, NCOR2, and HSD17B4 were associated with sensitivity to AR inhibitors, while gains of BRCA2, APC, KDM5D, CYP11B1, and SPARC, and losses of CHD1, PHLPP1, ERG, ZFHX3, and NCOR2 were associated with primary resistance to AR inhibitors.

"We were surprised to observe that a gain of BRCA2 was associated with worse outcomes in mCRPC resistant to AR inhibitors, as that has not been described before. Typically, loss of BRCA2 has been associated with poorer outcomes," said Armstrong. "Our finding may explain some resistance to DNA damaging agents and AR therapies that has not been well understood and requires further mechanistic investigation." The

present study is also the first to confirm that the loss of CHD1 in CTCs is associated with worse outcomes for patients with mCRPC in a clinical setting, Armstrong added. Loss or mutations in CHD1 were previously shown to promote lineage plasticity in prostate cancer.

Patients who benefited from AR inhibitors (defined as having a progression-free survival of at least six months) were more likely to have CTCs with alterations in genes involved in DNA repair, steroid metabolism, lineage plasticity, and PI3K and WNT signaling. In addition, chromatin and epigenetic gains linked to a loss of CHD1 and a gain of KDM5D were also observed in patients who benefited from AR inhibition. In contrast, patients who progressed on AR inhibitors showed clonal evolution of CTCs with gains of the ATM, FOXA1, UGT2B17, KDM6A, CYP11B1, and MYC genes, and acquired losses of NCOR1, ZFHX3, and ERG.

"Our study reinforces that analyzing CTC genomics has potential for identifying and tracking disease resistance or efficacy with AR inhibitors over time," Armstrong said. "The novel alterations we identified will need to be validated by further research but may represent priority candidates for new drug targets."

Limitations of this study include the small sample size, which limited researchers' ability to perform statistical testing between individual alterations and clinical outcomes. Disease burden and differences in the sensitivity of genomic assays at different time points due to changes in CTCs in response to therapy and at progression may have biased genomic findings. Finally, some alterations identified may represent low-level passenger change related to disease burden or genomic instability, rather than cancer drivers. The identified genomic alterations require mechanistic studies to determine their biologic and clinical relevance for treatment, Armstrong noted.

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