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PROGNOSTIC ASSOCIATION OF PLASMA CELL FREE DNA BASED ANDROGEN RECEPTOR AMPLIFICATION AND CIRCULATING TUMOR CELLS IN PRE-CHEMOTHERAPY METASTATIC CASTRATION RESISTANT PROSTATE CANCER PATIENTS TREATED WITH ABIRATERONE ACETATE

Manish Kohli
Mayo Clinic, USA

Background: The prognostic significance of plasma cell-free DNA (cfDNA) androgen receptor amplification (ARamp) in metastatic castration resistant prostate cancer (mCRPC) stage is not known.

Methods: As part of a prospective study in mCRPC stage, concurrent collection of plasma and circulating tumor cell (CTC) counts was evaluated for determining prognostic value of plasma cfDNA ARamp. Specimen collection was performed twice, after progression on androgen deprivation therapy (baseline) and then repeated after 12 weeks. QuantStudio3D digital PCR. system (dPCR) was used to determine plasma cfDNA AR copy number variations (CNVs) and Cell search assay for enumerating CTC counts. Association of baseline cfDNA ARamp status/CTC counts with overall survival (primary goal) was evaluated using Kaplan–Meier method and log-rank test ($p \leq 0.05$ for significance) and Receiver Operator Curves (ROC) for ARamp status and CTCs ≥ 5. A multivariate analysis was also performed using Cox regression models that included ARamp, CTC counts, volume of metastatic disease, cfDNA amount, Gleason score and PSA levels.

Results: ARamp was detected in 19/70 patients of baseline plasma specimens. At the time of analysis, 28/70 patients had died (median study follow-up 806 days (IQR: 535-966)). ARamp was associated with poor overall survival (2 year OS of 35% vs. 71% in non-ARamp; log-rank p-value= <0.0001). Baseline CTC count ≥ 5 (vs < 5) was also associated with poor survival (2 year OS of 44% vs 74%); log-rank p=0.001). ROC analysis demonstrated area under the curve (AUC) of 0.66 for ARamp and 0.68 for CTC counts based prognosis (p=0.84 for difference). The best two variables included for multivariable analysis were ARamp and CTC ≥ 5, however the two factor model was not significantly better than using ARamp alone for predicting survival (HR=5.25; p=0.0002).

Conclusions: Plasma cfDNA ARamp has clinical utility as an independent prognostic factor in mCRPC stage.

BIOGRAPHY

Manish Kohli holds an academic rank of Professor and Consultant in Oncology at Mayo Clinic. He has participated extensively in cancer clinical research for the past 15 years. During this time, he has initiated therapeutic trials, recruited several hundred patients for intervention and non-intervention cancer biomarker-based clinical trials and published results of several of these studies. During the course of this research effort, he interacted with multi-disciplinary teams which involved working with geneticists, laboratory scientists, bio-statistical and bio-informatic colleagues, study personnel among others. His early publications were focused on clinical research, mainly in prostate cancer therapeutics. These publications helped advanced therapeutic science in particular with the establishment of docetaxel chemotherapy in castrate resistant prostate cancer in 2004. Subsequently, he built upon these research experiences in developing genomic-based biomarker profiling in advanced prostate/kidney cancer therapeutics as a tool towards developing a precision medicine that is based on cancer's genetic landscape. In this regard, he initiated the building of prospective clinically annotated bio-repositories, which have uniform processing protocols for obtaining quality research specimens.

Kohli.Manish@mayo.edu