Abstract: P875

Title: EPIGENETIC LIQUID BIOPSY FOR THE DIFFERENTIATION OF BENIGN AND MALIGNANT FORMS OF PLASMA CELL DISORDERS.

Abstract Type: Poster Presentation

Topic: Myeloma and other monoclonal gammopathies - Biology & translational research

Background:

Plasma cell disorders (PCD) encompass a spectrum of monoclonal plasma cell proliferation disorders, including the premalignant conditions: Monoclonal gammopathy of undetermined significance (MGUS) and Smoldering Multiple Myeloma (SMM) which may progress along time to the highly malignant active multiple myeloma (MM). Predicting this progression has proven to be a challenging task in the everyday clinical practice. To date, there is no blood test that may differentiate among the PCD, and laborious as well as invasive procedures such as biopsies are the gold standard. Clinical models have limited ability to predict this transition. Cell-free DNA (cfDNA) methylation patterns are released into the blood stream and are hallmarks of cell turnover. Methylation disruption is a well-documented epigenetic alteration in various cancer types, affecting genome stability, gene expression, and chromatin structure.

Aims:

We hypothesized that plasma cell (PC) cfDNA methylation-based marker and cancer related disturbances in methylation can serve as a biomarker for surveillance and diagnosis of MGUS, SMM and MM.

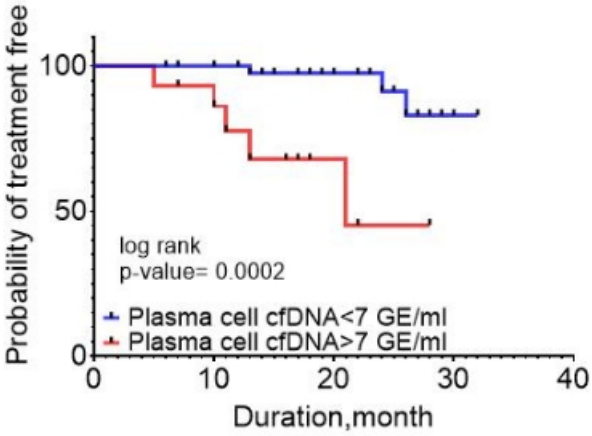
Methods:

PC from bone marrow of patients were isolated for deep whole-genome bisulfite sequencing and compared with healthy individuals. Subsequently. we developed a 17 loci simplified and specific PCR based assay for sensitive detection of PC and MM-specific methylation changes in cfDNA. We applied the assay to cfDNA samples from patients with MGUS (N=61), SMM (N=43) and MM (N=37) and compared findings to clinical progression.

Results:

The assay could significantly differentiate among the PCD disease states. MM patients have increased plasma cell cfDNA levels compared (Median=54.5 GE/ml) with healthy individuals (AUC=0.9, P-value<0.0001, Median=0.12 GE/ml), patients with MGUS (AUC=0.89, P-value=0.0001, median=0.84 GE/ml) and SMM (AUC=0.8, P-value=0.0001, Median=3.47 GE/ml). Furthermore, the assay could significantly predict the progression of premalignant PCD. Patients with MGUS and SMM that had higher levels of plasma cell cfDNA (>7 GE/ml) had an overall faster biochemical progression (log rank, p-value=0.0007) and a lower probability of being treatment free [figure 1] as compared with those that did not progress to treatment (log rank, p-value=0.0002). Targeted disordered methylation patterns in cfDNA were elevated in MM patients (Median=0.027 fraction) compared to MGUS (median=0.013 fraction) (AUC=0.84, P-value<0.0001), and SMM (median=0.014 fraction) (AUC=0.79, P-value<0.0001). Notably, disordered methylation patterns did not exhibit a gradual trend of elevation as observed with plasma cfDNA, suggesting that plasma cell cfDNA serves as a biomarker of plasma cell turnover, whereas disordered methylation indicates advanced and malignant disease.

Summary/Conclusion: normal and cancer-specific cfDNA methylation patterns are a promising biomarker for diagnosis and surveillance of plasma cell disorders. Furthermore, it has the potential to identify patients at risk of progressing to MM, and may be able to establish a practical essential tool to aid in the assessment of individual patient's risk**.**



Keywords: liquid biopsy, Epigenetic, DNA methylation, Multiple myeloma