The winning liquid biopsy combination for prognostic information in patients with metastatic non-small cell lung cancer

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Background & objectives

Circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and extracellular vesicles (EVs) are minimally invasive liquid biopsy biomarkers/analytes that are particularly relevant in non-small cell lung cancer (NSCLC) where tumor assessment is often difficult. The aim of this study was to determine whether these biomarkers, alone and in combination, can predict prognosis in a heterogenous unbiased population of patients with NSCLC, regardless of the tumor type and treatment.

Methods

The clinical relevance of ctDNA and programmed cell death ligand 1-positive (PD-L1^{+}) small EVs (sEVs) was evaluated using plasma samples from 54 patients with advanced NSCLC from a prospective longitudinal clinical trial (NCT02866149).

MassARRAY® technology (Agena Bioscience©) was used to identify ctDNA mutations. After sEV isolation by ultracentrifugation, PD-L1 expression was assessed using an enzyme-linked immunosorbent assay. CTCs evaluation was previously performed in the same population using the CellSearch® system (Menarini©).

Results

At least one ctDNA mutation was detected in 37% of patients: in KRAS (14.8%) and in EGFR (24.1%). Mutations in ctDNA were not correlated with overall survival (OS) (HR = 1.1, 95%CI = 0.55; 1.83, P=0.980) and progression-free survival (PFS) (HR = 1.00, 95%CI = 0.57-1.76, P=0.991). High concentration of PD-L1$^+$ sEVs was correlated with OS (HR = 1.14, 95%CI = 1.03-1.26, P=0.016), but not with PFS (HR = 1.08, 95%CI = 0.99-1.18, P=0.095). However, the interaction analysis suggested that PD-L1$^+$ sEV correlation with PFS changed in function of CTC presence/absence (P interaction=0.036). Specifically, high PD-L1$^+$ sEV concentration was negatively correlated with PFS in patients without CTCs (HR=1.20, 95%CI 1.04-1.38, P=0.011), but not with CTCs (HR=0.98, 95%CI 0.87-1.11, P=0.809). The combination analysis highlighted a worse prognosis in the presence of both CTCs and high PD-L1+ sEV concentration (HR = 7.65, 95%CI = 3.11-18.83, P<0.001).

Conclusion

In this small cohort of patients with advanced NSCLC, CTCs, and high PD-L1$^+$ sEVs concentration correlated with PFS and OS, but not ctDNA mutations. Combining CTC and PD-L1$^+$ sEV analysis may help to identify patients with worse OS independently to ctDNA analysis.