Low-level variants present a challenge in the clinical interpretation of liquid-biopsy-based comprehensive genomic profiling for patients with solid tumors

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Abstract

Comprehensive genomic profiling (CGP) of circulating tumor DNA (ctDNA) from plasma holds great clinical potential for the identification of patient-specific actionable targets to guide targeted cancer treatments as it may better reflect the genetic landscape of a tumor compared to a single tissue biopsy. However, presence of low-level variants still presents a challenge for data interpretation.

We performed concordance analyses of paired genomic profiles assessed using the FoundationOne platform from tissue and plasma available from a multicenter phase II trial (SOUND trial), to evaluate the impact of low-level variants for clinical decision-making. From a total of 151 patients with advanced or metastasized solid tumors recruited to the trial, corresponding tissue samples were available from 52 patients (34%). Of those, the median tumor fraction assessed by aneuploidy or as the highest variant allele fractions (VAF) was 6.6% (range 0.02% to 72%), with 27 (52%) patients presenting elevated plasma tumor fractions of >1%. While 174/303 (57%) of pathogenic variants identified in tissue could also be detected in plasma, 165 variants were detected in plasma only. These variants had significantly lower VAF compared to the concordant ones suggesting subclonality, clonal hematopoiesis, or sequencing artifacts as their origin. The presence of such low-level variants affected the assessment of tumor mutational burden from blood (bTMB), highlighted by only an intermediate correlation between plasma and tissue TMB with an overestimation of the TMB in plasma. Furthermore, as the impact of such low-level variants on disease progression or treatment response is unclear, their presence posed a significant challenge for the molecular tumor board to make informed therapeutic decisions.

Taken together, despite advances in sequencing technologies, low-level variants still present a challenge for clinical interpretation of plasma-based CGP. Better computational tools and more comprehensive databases of known variants may help enhance the reliability and utility of detecting low-level variants in plasma DNA.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.