Spatial and temporal tumor heterogeneity representation in liquid biopsies of pediatric precision oncology patients

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Abstract

Background High-risk pediatric solid malignancies are often challenging to access for tissue biopsies, and even when obtained, they frequently provide limited information due to the spatial and temporal heterogeneity of the tumors. This heterogeneity complicates both diagnosis and therapy but also presents an opportunity for more personalized treatments. Liquid biopsies, in particular circulating cell-free DNA (cfDNA) analysis, could provide valuable complementary information to traditional biopsies by detecting multiple tumor subclones.

Objective

We investigated the potential of cfDNA as a liquid biopsy analyte to optimize cfDNA analysis in pediatric cancer detection and to demonstrate that cfDNA can provide a more comprehensive overview of the tumor mutational profile compared to traditional tissue biopsies.

Methods

As part of the prospective, multicenter pediatric precision oncology program, INFORM,

liquid biopsy samples were collected from 130 patients. Optimized cfDNA extraction protocols were utilized, with subsequent whole-genome, methylome, whole-exome, and targeted panel sequencing. Integration of cfDNA-derived molecular data with tissue-based analyses was performed for a comparative assessment to improve the characterization of tumor heterogeneity.

Results

Orthogonal validation and integration with tissue-derived molecular information confirmed low-coverage whole-genome sequencing (lcWGS) as a highly sensitive and reliable method for the detection of circulating tumor DNA (ctDNA). Furthermore, in silico fragment length analysis combined with copy number variation (CNV) analysis significantly improved the sensitivity and specificity of plasma-based tumor detection. In-depth analyses of illustrative patients highlighted the potential of liquid biopsies to decipher tumor heterogeneity. In a Wilms tumor patient, liquid biopsy revealed a molecular profile distinct from the corresponding tissue biopsy analyzed within the precision oncology program. In-depth molecular workup of multiple tumor sites could localize the ctDNA origin and refine patient stratification. The presence of previously undetected subclones was unique to liquid biopsy analyses highlighting its superiority in specific clinical scenarios.
Conclusion

Our findings underscore the clinical potential of cfDNA analysis in pediatric precision oncology. By capturing spatial and temporal tumor heterogeneity, liquid biopsies can improve diagnostic accuracy and facilitate the detection of previously unidentified subclones and metastases, potentially revealing effective therapy targets.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.