ANALYSIS OF CELL-FREE DNA IN THE PLASMA OF PATIENTS WITH NON-RESECTABLE, PROGRESSIVE OR RELAPSED PEDIATRIC MALIGNANCIES

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Background & objectives

Circulating cell-free DNA released by tumor cells (ctDNA) provides the opportunity to minimally invasively survey clinically informative biomarkers and therapeutic targets. The INFORM registry aims to identify actionable targets on a personalized basis. Relapsed or refractory high-risk tumors, for which no further standard of care therapy is available, are characterized by next-generation sequencing (NGS) technologies. Our study aims at integrating liquid CtDNA was derived from plasma samples and isolated according to optimized protocols. Depending on the yield of ctDNA, data availability for the primary tumor, and tumor entity, we low-coverage whole-genome sequencing (lcWGS), whole exome sequencing (WES), targeted gene panel sequencing or combinations thereof were performed. Results were compared and integrated with data obtained from standard tumor biopsies and normal control tissues following adjustment of established bioinformatics pipelines to suit liquid biopsy-derived data.biopsies into the diagnostic INFORM pipeline and paving the way for clinical translation of these technologies.

Methods

CtDNA was derived from plasma samples and isolated according to optimized protocols. Depending on the yield of ctDNA, data availability for the primary tumor, and tumor entity, we low-coverage whole-genome sequencing (lcWGS), whole exome sequencing (WES), targeted gene panel sequencing or combinations thereof were performed. Results were compared and integrated with data obtained from standard tumor biopsies and normal control tissues following adjustment of established bioinformatics pipelines to suit liquid biopsy-derived data.

Results

Sensitivity and specificity of our approach is presented within a proof-of-concept study to compare the performance of different NGS platforms and their utility for analyzing ctDNA samples. We demonstrate robust tumor detection by lcWGS (n=115), mutation tracking by targeted approaches (n=74) and the advantages of the combinatorial use of various approaches (n=64). Despite reliable tumor monitoring, liquid biopsies aided in identifying druggable targets in metastatic disease (e.g., CDK4, CDK6, MDM2) that were absent in tumor biopsies.

Conclusion

Although limited sample volumes may impede analyses, we have demonstrated applicability of liquid biopsies in personalized pediatric oncology. Further development of a clinical decision support system for liquid biopsies may aid in optimally realizing in-depth spatial and temporal tumor resolution.

Our study is expected to guide and accelerate the implementation of liquid biopsies into prospective pediatric clinical trials.