

Multi-platform analysis of the heterogeneity of circulating melanoma cells and tumor DNA as useful tool to track disease evolution and targeted therapy response

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Background & objectives

Melanoma heterogeneity is one of the main obstacles for the management of metastatic melanoma. Although the advent of targeted therapy has significantly improved patient outcome, the occurrence of resistance makes the monitoring of tumor genetic landscape mandatory. Liquid biopsy, being a sum of the systemic disease, could be an important biomarker for the real-time tracing of disease evolution. Thus, we aimed to correlate liquid biopsy dynamics with treatment response and progression by devising a multiplatform approach applied to longitudinal melanoma patient monitoring.

Methods

In this pilot study, 17 stage IV melanoma patients, treated with BRAF/MEK inhibitors, have been enrolled, and followed for up to 24 months. A longitudinal screening at different time points (52 samples) has been applied to identify liquid biopsy dynamics during response to treatment and progression. Considering that resistance develops at a median time of 11-12 months, blood has been collected before starting the therapy, after 6 and 10 months to test the ability of our approach to detect early signs of tumor escape, and at relapse. We devised a multi-platform approach exploiting high-sensitivity techniques (NGS, ddPCR) and an FDA-cleared platform (CellSearch) to analyze circulating tumor DNA (ctDNA) trend, circulating melanoma cell (CMC) count, together with their customized genetic analysis and copy number variation assessment.

Results

BRAF mutations were detected in the plasma of 82% of patients. Single nucleotide variants known or suspected to confer resistance were identified in 60% of patients. Moreover, the amount of ctDNA, both at baseline and during response, correlated with the type and duration of the response itself. Finally, CMC number was confirmed to be a predictive/prognostic biomarker as a significant correlation between CMC count >0 at baseline and worse overall survival/progression free survival was identified.

Conclusion

This study provides the proof-of-principle of the power of this multi-platform analysis. Indeed, it can provide ctDNA tracking and profiling, together with CMC count variation, and genetic landscape, useful for capturing tumor evolution. Although a validation of this data in a larger cohort is mandatory, this kind of strategy opens new scenarios for the management and real time monitoring of melanoma patients.