Circulating tumor DNA (ctDNA) as sensitive and specific biomarker in stage I to III malignant melanoma

Marilena Heber[1]
Ann-Sophie Bohne[1], Franziska Axt[2], Peter Jülg[3], Tobias Hutzenlaub[3], Tru Truong[3], Michael Lehnert[3], Johanna Cordts[2], Eva Dazert[2], Ewan Langan[4], Patrick Terheyden[4], Christoffer Gebhardt[5], Katharina C Kähler[1] and Nikolas von Bubnoff[2]
[1] University Medical Center Schleswig-Holstein (UKSH), Campus Kiel, Department of Dermatology, Venerology and Allergology, Kiel, Germany
[2] University Medical Center Schleswig-Holstein (UKSH), Campus Lübeck, Department of Hematology and Oncology, Lübeck, Germany
[3] Hahn-Schickard, Georges-Koehler-Allee 103, 79110 Freiburg, Germany
[4] University Medical Center Schleswig-Holstein (UKSH), Campus Lübeck, Department of Dermatology, Allergology and Venerology, Lübeck, Germany
[5] University Medical Center Hamburg-Eppendorf, Department of Dermatology and Venereology, Hamburg, Germany

Background & objectives

The established malignant melanoma (MM) biomarkers S100B and LDH are of limited specificity and sensitivity to detect residual disease marking patients at risk for relapse and emerging tumor progression (PD). In this study, we retrospectively assessed the significance of free circulating tumor DNA (ctDNA) in predicting local and systemic PD. In the currently initiated prospective phase, we will evaluate the significance of ctDNA as marker for minimal residual disease identifying patients with stage IIB to III melanoma at risk for relapse.

Methods

In the retrospective part we included 61 patients with MM and known PD status, four had stage I, 20 stage II and 37 stage III at diagnosis (AJCC 2017). Baseline serum samples were taken four weeks after first diagnosis, and follow-up [FU] samples were obtained at regular clinical FU visits. cfDNA was isolated from 185 samples and considered positive for ctDNA if mutated fragments were detected for BRAF V600E/K, NRAS Q61K/L/R or TERT promotor mutations. The results were correlated with S100B (n <0.11µg/l) and LDH (n <250U/l).

Results

After baseline (BL), median time to PD was 21.1 months (range [r]:0-53). From all 185 samples, 65 (35.1%) were tested positive for ctDNA, 24 (14.0%) were positive for S100B and 16 (9,4%) for LDH. At BL 15/61 (24.6%) patients tested positive for ctDNA, 6/55 (10.9%) were positive for S100B and 2/51 (3.9%) for LDH. During FU, 50/124 samples (40.3%) were

ctDNA positive, while only 18/116 samples (15.5%) tested positive for S100B and 14/120 (11.7%) for LDH. Sensitivity of ctDNA was superior to LDH and S100B at PD, especially in localized PD with shift of stage II to stage III or within stage III, but also in patients progressing from stage III to IV.

Conclusion

Compared to established biomarkers LDH and S100B, the analysis of ctDNA levels in stage I to III MM displays superior sensitivity to detect residual disease and could potentially complement regular FU in predicting tumor progression. In the prospective part, 50 patients with stage IIB to III melanoma will be followed for two years every three month. Blood plasma samples will be investigated for mutations in BRAF, NRAS and TERT genes.. Primary endpoint is the proportion of ctDNA positive patients. Secondary objectives include correlation with outcome, comparison of singleplex versus multiplex and NGS analysis for cfDNA genotyping and predictive and prognostic significance of cfDNA analysis versus established biomarkers LDH and S100B.