Circulating cell-free DNA and circulating tumor cells as prognostic biomarkers in stage III melanoma

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Background & objectives

Stage III melanoma includes patients with positive lymph nodes or satellitosis. There is still no clear consensus on which patients with stage III melanoma should be treated with immunotherapy and which can safely avoid these treatments and their associated side effects. Currently, there are no clinically-useful biomarkers in melanoma, and identification of a liquid biopsy biomarker would be important for risk stratification and monitoring response to therapy.

The purpose of this study was to determine whether the identification of cell-free DNA (cfDNA) and/or circulating tumor cells (CTCs) in the blood of patients with stage III melanoma is associated with relapse and survival outcomes.

Methods

CTC assessment was performed using CellSearch (Menarini Silicon Biosystems). cfDNA was extracted from matching plasma samples using the MagMAX™ Total Nucleic Acid Isolation Kit (Applied Biosystems™) and quantified using the Qubit™ dsDNA HS Kit (Invitrogen™). Correlation analysis and linear regression models were used to determine association between cfDNA and CTC with outcomes. Survival analysis was performed by Kaplan-Meier estimator and cox regression models.

Results

We included 132 patients with stage III melanoma; 60% (79/132) experienced disease relapse while 40% (53/132) did not. Median cfDNA concentration for cases with disease-relapse was 7.1 ng/ml, while median level for non-relapse was 4.7 ng/ml. A positive correlation was found between cfDNA concentration and disease-relapse (95% CI: 1.32-4.43, P=0.0004). A threshold level of cfDNA concentration of ≥6.5 ng/ml was determined by optimizing the correlation with clinical outcome based on receiver operating characteristic (ROC) curve analysis. Threshold cfDNA cut-off was calculated to categorize the biomarker based on clinical event (relapse/non-relapse). In patients who relapsed, 82% (65/79) had CTCs identified while

32% (17/53) of patients without relapse had CTCs. Detection of CTCs and a cfDNA value ≥6.5 ng/ml were associated with significantly decreased relapse-free and overall survival (P=0.0001, 0.0201, respectively).

Conclusion

Presence of cfDNA in conjunction with CTCs was associated with relapse in patients with stage III melanoma. Use of cfDNA and CTCs might allow for risk stratification in clinical decision-making regarding use of immunotherapy.