Liquid Biopsy: Measuring Circulating H3K27Me3-Nucleosomes In Lung Cancer Patients Is A Strong Prognostic Biomarker And A Potential Aid In Treatment Selection

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Abstract

Background:

Early detection and treatment save lives, but people are often diagnosed with advanced disease when treatment options are limited. Once the disease is diagnosed, molecular profiling of circulating tumor DNA (ctDNA) is often used to select treatment and monitor disease. But these techniques can lack of sensitivity. This could lead to delays in starting more aggressive treatment. The histone post-translational modification H3K27Me3 have been reported to play an important role in the development and progression of lung cancer.

Objectives:

To evaluate if circulating H3K27Me3-nucleosome levels could offer additional insight in patient with negative molecular profiling and could improve patient management

Methods:

H3K27Me3-nucleosomes levels were analyzed in plasma samples from two independent cohorts including 831 LC at diagnosis and 304 LC patients under treatment using Nu.Q® immunoassay. ctDNA analysis by NGS on the same samples was performed using a comprehensive custom NGS assay (78 genes, 1% sensitivity, cohort 1 (n=255) and 2), a targeted ultra-deep technique (33 genes, 0,2% sensitivity, cohort 1 (n=254)) or Plasma SeqSensei (4 genes, 0,2% sensitivity, cohort 1 (n=322)). The contribution of H3K27Me3-nucleosomes to molecular profiling and its prognostic value for overall survival (OS) were assessed.

Results:

LC patients had a higher level of H3K27Me3-nucleosomes compared to healthy controls at diagnosis (median 22ng/ml vs 8ng/ml; p-value<0.0001). Patients who died have twice more H3K27Me3 at baseline compared to survivors (median 35,5ng/ml vs 17ng/ml; p-value<0.0001). Survival analysis showed that patients with low H3K27me3 levels have a better OS (HR 3,54; 95%CI 2,79-4,48; cutoff 53,7ng/ml). Moreover, ctDNA negative patients but with a high H3K27Me3 levels have a worse OS; with high HR compared to those with low H3K27Me3 levels (HR 4,35; 95%CI 2,95-5,82; cut-off 44,7ng/ml). Using H3K27Me3-nucleosomes in combination with NGS revealed that 27% of the ctDNA negative patients under treatment were however H3K27Me3-positive.

Conclusion:

When combined with NGS, Nu.Q® H3K27Me3 levels improve the prognostics value for OS. It may also help to identify patients with a minimal residual disease. These patients could then be treated with a different line of treatment. Further clinical studies are ongoing to confirm the aid in disease monitoring and treatment decision of H3K27Me3-nucleosomes.

Do you have any conflicts of interest?

Yes, I have a conflict of interest.

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