A blood-based DNA methylation risk score (RS) for predicting the prognosis of EGFR mutation positive (EGFRm) advanced non-small cell lung cancer (NSCLC) after first line TKI treatment

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ABSTRACT

In our study, we aimed to develop the prognosis-associated DNA methylation markers based on the differentially expressed methylation patterns between EGFRm and EGFR negative patients (pts). We analyzed 61 blood samples from pts with advanced NSCLC. A total of 69 differentially methylated blocks (DMBs) in methylenome were common with Wilcoxon and limma methods, of which 13 upregulated and 56 downregulated by comparing EGFRm with wildtype. Univariate Cox hazard analysis for DMBs was used to identify potential prognostic blocks. By step-wise regression analysis, a four-DMB-based prognostic RS model for EGFRm pts was developed. The RS stratified pts into high-risk and low-risk groups for PFS, and achieved AUC values of 0.818. Pts in the HR group (median RS as cutoff) showed significantly poorer PFS than those in the LR group in survival analysis (p = 0.0015).

METHODS AND MATERIALS

Patients: Forty pts positive for EGFR Ex19del or L858R (EGFRm) and 21 pts negative for EGFR were included in this study. Blood was collected from pts prior to the treatment.

Methods: Methylation levels from all samples were profiled by targeted bisulfite sequencing using a bespoke NSCLC methylation panel covering 80,672 CpG sites, spanning 1.95 mega bases of the human genome. To improve the linkage of methylation sites, we further analyzed the methylation profile as methylation blocks. Methylenome represents the average methylation values within the methylation block.

RESULTS

The four DMBs involved in prognostic RS model were:

<table>
<thead>
<tr>
<th>Gene</th>
<th>DMB_Pvalue</th>
<th>Cox_Pvalue</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>15:89914882-90014968</td>
<td>0.03753128</td>
<td>0.00360899</td>
<td>Down</td>
</tr>
<tr>
<td>21:3553245-21306332</td>
<td>0.0064999</td>
<td>0.05707838</td>
<td>Down</td>
</tr>
<tr>
<td>6:16081313-16081469</td>
<td>0.00815421</td>
<td>0.0041621</td>
<td>Down</td>
</tr>
<tr>
<td>20:2084957-20901620</td>
<td>0.0436317</td>
<td>0.0257758</td>
<td>Down</td>
</tr>
</tbody>
</table>

The RS stratified pts into high-risk (HR) and low-risk (LR) groups for PFS, and achieved AUC values of 0.818. Pts in the HR group (median RS as cutoff) showed significantly poorer PFS than those in the LR group in survival analysis (p = 0.0015).

CONCLUSION

Our study constructed a DNA methylation-based RS that may potentially be used as the prognostic assay for predicting survival in EGFRm NSCLC pts after 1st line TKI treatment. Further validation is warranted.

Conflicts of interest: The authors have no conflicts or financial disclosures to make.

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