HER3 and c-Met Co-Expression in Lung Cancers

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INTRODUCTION

Tyrosine kinase inhibitors (TKI) (e.g. gefitinib & erlotinib) which target the epidermal growth factor receptor (EGFR) pathway (Fig. 1A), are effective in the treatment of non-small cell lung cancers (NSCLC) harboring somatic mutations in EGFR. However, despite an initial response, most EGFR mutant NSCLCs ultimately become resistant to these agents. The T790M of EGFR, which leads to persistent phosphorylation of HER3 (Fig. 1C), and MET amplification (Fig. 1B) are important mechanisms of this acquired resistance, through the PI3K/Akt pathway. To overcome this, ongoing clinical trials are evaluating irreversible EGFR inhibitors alone or in combination with MET kinase inhibitors (Fig. 1D). Here we conducted the first large-scale study of HER3 and c-Met protein expression in EGFR TKI-naïve NSCLC and small cell lung cancer (SCLC).

RESULTS

- Both HER3 and c-Met showed a predominantly cytoplasmic staining pattern and were expressed in the majority of cases (see Table 1).
- HER3 expression was strongest in SCC and SCLC, and was weakest in LCLC (p<0.01, Kruskal-Wallis test).
- c-Met was strongest in AC and weakest in SCC (p<0.01).
- The two markers were frequently co-expressed with either weak or strong staining patterns (SCC 48%, AC 95%, SCLC 76%, LCLC 86%).
- There was no significant difference in the expression level between tumor center and advancing edge, or between primary tumor and metastatic lesion.

CONCLUSIONS

- HER3 and c-Met are co-expressed in the majority of EGFR TKI-naïve NSCLC and SCLC.
- Both HER3 and c-Met showed a predominantly cytoplasmic staining pattern and were expressed in the majority of cases.
- Our data supports the potential use of combined EGFR TKIs in naïve NSCLC to avoid inevitable drug resistance.
- This study is the first to show that both HER3 and c-Met are co-expressed in the majority of SCLC (76%), suggesting that SCLC patients with both HER3 and c-Met abnormalities may benefit from combined regimens targeting these two genes.

STUDY DESIGN

Tumor tissue microarrays of 25 squamous cell carcinomas (SCC), 42 adenocarcinomas (AC), 34 SCLC, and 35 large cell lung carcinomas (LCLC), with at least 2 cores from each case were immunohistochemically stained for HER3 and c-Met. Among them, 60 cases (23 SCC, 19 AC, 7 SCLC and 11 LCLC) had cores from both tumor center and advancing edge. In addition, a separate set of 16 metastatic tumors (4 SCC, 7 AC and 5 LCLC) with cores from both primary tumor and lymph node metastasis were studied. The staining intensity was scored as: 0 (negative), 1+ (weak), or 2+ (strong) (Figs. 2 & 3).

Table 1. Expression of HER3 and c-Met in Lung Cancers

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>HER3</th>
<th>c-Met</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Weak</td>
</tr>
<tr>
<td>SCC</td>
<td>4%</td>
<td>32%</td>
</tr>
<tr>
<td>AC</td>
<td>0%</td>
<td>50%</td>
</tr>
<tr>
<td>SCLC</td>
<td>6%</td>
<td>29%</td>
</tr>
<tr>
<td>LCLC</td>
<td>6%</td>
<td>74%</td>
</tr>
</tbody>
</table>

REFERENCES


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