EGFR in Non-Small Cell Lung Cancer and its role as a targeted therapy

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Introduction

Until recently, all types of Non-Small Cell Lung Cancer (NSCLC), which account for 85-90% of lung cancers, were treated with cytotoxic chemotherapy which produces great toxicities owing to the lack of selectivity for tumor cells. Further understanding of molecular alterations was vital to introduce a new approach: the targeted therapy. Some of these mutations occur in the Epidermal Growth Factor Receptor (EGFR). EGFR signalling pathway has become an encouraged targeted therapy to improve outcomes in NSCLC patients. This review will provide a fresh insight into the major progress toward the understanding of EGFR so far.

EGFR in NSCLC

The discovery of somatic EGFR mutations was a very significant breakthrough in the understanding of NSCLC.

Oncogene addiction: EGFR-mutated cells require hyperactivated EGFR for its own survival → Key point for targeted therapy.

Acquired resistance to TKIs

The overwhelming majority of patients bearing EGFR mutations inevitably become resistant to TKIs mostly within 6-12 months.

Main acquired resistances:
- Bypass signalling
- Histologic transformation
- T790M
- The most frequent resistance (50%)
- Aa substitution in exon 20
- Mechanism of action:
  - Modify ATP cleft of TK domain
  - Enhance ATP molecules affinity

TKIs: overcome EGFR mutations

Mutations on TK domain are the most reliable predictive biomarkers for the sensibility and the efficacy to Tyrosine Kinase Inhibitors (TKIs).

TKIs had superior outcomes in Overall Response Rates (ORR) and Progression Free Survival (PFS) compared with chemotherapy in NSCLC patients.

TKIs: overcome T790M

Continuation of 1st-generation TKIs:

Table 1: 1st-generation EGFR-TKIs.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Drug</th>
<th>Target</th>
<th>Reversible or Irreversible</th>
<th>Stage of development</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st-generation TKI</td>
<td>Erlotinib</td>
<td>ATP cleft of TK domain</td>
<td>Reversible</td>
<td>FDA approved</td>
<td>Nausea, rash, diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Gefitinib</td>
<td>ATP cleft of TK domain</td>
<td>Reversible</td>
<td>EMA approved</td>
<td>Nausea, rash, diarrhoea</td>
</tr>
</tbody>
</table>

Table 2: 2nd and 3rd-generation EGFR-TKIs.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Drug</th>
<th>Target</th>
<th>Reversible or Irreversible</th>
<th>Stage of development</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd-generation TKI</td>
<td>Afatinib</td>
<td>Mutant EGFR, HER2</td>
<td>Irreversible</td>
<td>FDA approved</td>
<td>Rash, diarrhoea, acne, hoarse, dry skin</td>
</tr>
<tr>
<td></td>
<td>Dacomitinib</td>
<td>EGFR, HER2</td>
<td>Irreversible</td>
<td>Phase II</td>
<td>Stomatitis, rash, diarrhoea, acne, fatique</td>
</tr>
<tr>
<td></td>
<td>Neratinib</td>
<td>EGFR, HER2</td>
<td>Irreversible</td>
<td>Phase II</td>
<td>Severe diarrhoea toxicity</td>
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<tr>
<td>3rd-generation TKI</td>
<td>AZD9291</td>
<td>Mutant EGFR</td>
<td>Irreversible</td>
<td>Phase I</td>
<td>Rash, nausea, diarrhoea, poor appetite</td>
</tr>
<tr>
<td></td>
<td>CO-1686</td>
<td>Mutant EGFR</td>
<td>Irreversible</td>
<td>Phase II</td>
<td>Hyperglycemia, nausea, diarrhoea, fatigue</td>
</tr>
</tbody>
</table>

References

Over the last decade, there have been significant advances in the identification of targeted-EGFR therapy to overcome EGFR mutations. However, the emergence of T790M is still one of the hindrances of NSCLC. The prevailing situation is focused on the establishment of the most suitable therapy to maximize efficacy and minimize toxicity with the hope that, in a not so distant future, we will be able to overcome NSCLC.