Caso Clinico n. 1 – A.P.

Beyond EGFR: a ‘molecular mosaic’

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Negrar, 12 Marzo 2014
Case Report - A.P.

- Female patient, 77 year-old
- Never smoker
- Performance Status 2
- Comorbidities [CLINICALLY SIGNIFICANT]
  - ischemic-hypertensive cardiopathy [NYHA class II]
  - diabetes mellitus
  - gastro-oesophageal reflux
- Persistent cough and dyspnea for about 1 month
Case Report - A.P.

- **Total-body CT-scan**: large left hilar pulmonary mass with infiltration of the mediastinum and extension to both lobes; ipsilateral parenchymal and pleural nodules associated with pleural effusion; right pulmonary thromboembolism.
Case Report - A.P.

- Total-body PET-CT: intense pathological uptake in correspondence of the known pulmonary lesions in the left hilar and para-hilar region, lingula and of the pleural thickening (parietal pleura before the arch back of the V coast and coast between XI and X)
Case Report - A.P.

- **Bronchoscopy**: hyperemia of the mucosa of the left main bronchus and enlargement of the spur between top and bottom, with no evidence of intraluminal disease; performed TBNA of the left main bronchus.

- **Histology**: lung adenocarcinoma.

- **Sequencing analysis of EGFR exons 18 to 21**: CTA-CAG point mutation in exon 21 [L861Q]
..going beyond ‘adenocarcinoma’..

Lung Cancer Mutation Consortium: Incidence of Driver Mutations

Modified By Paul A. Bunn, MD at 2013 ASCO Annual Meeting
Clinical Relevance of the ‘Oncogene Addiction’

- In patients with solid malignancies in which a **dominant mutation or gene amplification drives tumor growth**, targeted therapies are highly effective but rarely curative…
  - cKit mutations in GIST
  - HER2 amplification in breast cancer
  - **EGFR mutation in NSCLC**
  - ALK traslocation in NSCLC

**GENETICS** → **DEPENDENCY** → **PHARMACOLOGIC VULNERABILITY**
Medical Treatment for NSCLC – Molecular Selection

Validated Biomolecular Predictors

Evidences for Drugs’ Registration:

- **Randomized Studies:**
  - EGFR Sensitizing Mutations
    - Gefitinib [EMA, FDA?]
    - Erlotinib [EMA]

- Early Phases Studies → Randomized Studies:
  - EML4-Alk Traslocation
    - Crizotinib [EMA, FDA]
EGFR TKIs versus chemotherapy as first-line therapy in EGFR mutant

<table>
<thead>
<tr>
<th>Study [ref.]</th>
<th>Patients treated with TKI n</th>
<th>PFS</th>
<th>ORR %</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEJ002 [12, 23]</td>
<td>114</td>
<td>10.8 months versus 5.4 months; HR 0.32 [95% CI 0.24–0.44], p&lt;0.001</td>
<td>74 versus 31; p&lt;0.001</td>
<td>27.7 months versus 26.6 months; HR 0.89 [95% CI 0.63–1.24], p=0.483</td>
</tr>
<tr>
<td>WJTOG3405 [13, 25]</td>
<td>51 for PFS [stage IIIb/IV subgroup] 86 for overall survival</td>
<td>8.4 months versus 5.3 months; HR 0.33 [95% CI 0.21–0.54], p&lt;0.0001</td>
<td>62 versus 32**; p&lt;0.0001</td>
<td>36 months versus 39 months; HR 1.19 [95% CI 0.71–1.83], p=0.443</td>
</tr>
<tr>
<td>IPASS [8, 14]</td>
<td>132</td>
<td>9.5 months versus 6.3 months; HR 0.48 [95% CI 0.36–0.64], p&lt;0.001</td>
<td>71 versus 47; p&lt;0.001</td>
<td>21.6 months versus 21.9 months; HR 1.00 [95% CI 0.76–1.33], p=0.990</td>
</tr>
<tr>
<td>EURTAC [9, 19]</td>
<td>86</td>
<td>9.7 months versus 5.2 months; HR 0.37 [95% CI 0.25–0.54], p&lt;0.0001</td>
<td>58 versus 15; p-value not reported</td>
<td>19.3 months versus 19.5 months; HR 1.04 [95% CI 0.65–1.68], p=0.87</td>
</tr>
<tr>
<td>EURTAC [9, 19]</td>
<td>86</td>
<td>10.4 months versus 5.4 months; HR 0.47 [95% CI 0.28–0.78], p=0.0030</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LUX-Lung 3 [3]</td>
<td>230</td>
<td>11.1 months versus 6.9 months; HR 0.58 [95% CI 0.43–0.78]; p=0.001</td>
<td>56 versus 23; p=0.001</td>
<td>28.1 months versus 28.2 months; HR 0.91 [95% CI 0.66–1.25], p=0.55 (yet immature)</td>
</tr>
<tr>
<td>LUX-Lung 3 [15]</td>
<td>230</td>
<td>11.1 months versus 6.7 months; HR 0.49 [95% CI 0.37–0.65]; p=0.001</td>
<td>69 versus 44; p=0.001</td>
<td></td>
</tr>
<tr>
<td>OPTIMAL [10, 11]</td>
<td>82</td>
<td>13.1 months versus 4.6 months; HR 0.16 [95% CI 0.10–0.26], p&lt;0.0001</td>
<td>83 versus 36; p&lt;0.0001</td>
<td>22.7 months versus 28.9 months; HR 1.04 [95% CI 0.69–1.58], p=0.69 (yet immature)</td>
</tr>
<tr>
<td>LUX-Lung 6 [16]</td>
<td>242</td>
<td>11.0 months versus 5.6 months; HR 0.28 [95% CI 0.20–0.39], p&lt;0.0001</td>
<td>67 versus 23; p&lt;0.0001</td>
<td>Not reported; immature</td>
</tr>
<tr>
<td>LUX-Lung 6 [16]</td>
<td>242</td>
<td>13.7 months versus 5.6 months; HR 0.26 [95% CI 0.19–0.36], p&lt;0.0001</td>
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</tbody>
</table>
Mutations in the *EGFR* gene

**EGFR Transcript**

- Exons 1–16
- Exon 17
- Exons 18–24
- Exons 25–28

**Confer sensitivity/resistance to EGFR TKIs**

- G719A/S
- D761Y
- D770_N771 insNPG
- T790M
- L858R
- L861X

**Unclear effect on sensitivity to EGFR TKIs**

- P694X
- V700D
- E709X
- G735S
- V738F
- V742A
- T751I
- E746K
- S752Y
- T761N
- A763V
- N765A
- S768I
- L792F
- L798F
- G810S
- N826S
- L833V
- H835L
- T847I
- H850N
- V851X
- L855T
- A859T
- G863DA864T
- E809K

**Chromosome 7**

*TKI* = tyrosine-kinase inhibitor


Modified by Cappuzzo WCLC 2014
..but what about uncommon EGFR alterations?

<table>
<thead>
<tr>
<th>EGFR</th>
<th>Reversible EGFR-TKIs(^1)</th>
<th>Afatinib (^2,3,4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>RR (%)</td>
</tr>
<tr>
<td>Exon 19-21</td>
<td>278</td>
<td>74.1</td>
</tr>
<tr>
<td>Wild-type</td>
<td>272</td>
<td>16.5</td>
</tr>
<tr>
<td>Exon 20 insertion</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>G719</td>
<td>15</td>
<td>53.3</td>
</tr>
<tr>
<td>L861</td>
<td>15</td>
<td>60.0</td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
<td>20.0</td>
</tr>
</tbody>
</table>

\(^1\)Wu J et al. Clin Cancer Res 2011;17:3812-3821; \(^2\)Yang Y et al. WCLC 2013; \(^3\)Ahn et al, ESMO 2012; \(^4\)Sequist et al JCO 2013

Modified by Cappuzzo WCLC 2014
..but what about uncommon EGFR alterations?
..but what about uncommon EGFR alterations?

Entire population

Gefitinib arm

CBDCA-TXL arm

Watanabe JTO 2014
..and what about Gefitinib in EGFR mutant patients unsuitable for chemotherapy?

Inoue et al, JCO 2009
Case Report - A.P.

- **September 2012**: the patient started **Gefitinib** 250 mg/day
- **November 2012**: symptoms rapidly worsen in the 5\(^{th}\) – 7\(^{th}\) week and the CT-scan showed progressive pleural disease and two brain metastasis (7 and 3 mm)
November 2012: stereotactic radiosurgery on brain metastasis
FISH analysis for ALK: did not show any rearrangement, but an increased gene copy number was observed in 61% of cancer cells, with 2.6 mean signals per cell.
• FISH analysis for ROS1 and MET: did not show any rearrangement, but an increased gene copy number was observed in the 67% and 72% cancer cells, with 2.6 and 2.9 mean signals per cell, respectively
IHC analysis for ROS1 and ALK: did not show any expression.
PROFILing non-small-cell lung cancer patients for treatment with crizotinib according to anaplastic lymphoma kinase abnormalities: translating science into medicine

The ALK entity

5% of NSCLC (range 3-7)

- Median age of onset ~ 50 (20-80s)
- Mainly adenocarcinoma histology (signet-ring histology)
- Never/light smoking status
- Excess of
  - hepatic metastases,
  - pleural and pericardial effusions
  - and probably brain metastasis (35% in this trial)
- Minimal overlap with other driver mutations
- Neutral prognosis vis à vis EGFR and ALK WT control groups
Evidences for Drugs’ Registration:

- **Randomized Studies**:  
  - EGFR Sensitizing Mutations  
    - Gefitinib [EMA, FDA?]  
    - Erlotinib [EMA]

- **Early Phases Studies**  
  - EML4-Alk Trasllocation  
    - Crizotinib [EMA, FDA]
Clear and strong signal of activity

- Objective response is tripled
- PFS is improved by 4.7 months (HR of 0.49)
- Improvement of PFS in almost all subgroups
- Improvement of lung cancer-related symptoms and global QOL

The New England Journal of Medicine

Original Article

Crizotinib versus Chemotherapy in Advanced ALK-Positive Lung Cancer
November 2012: the patient started Crizotinib 250 mg/BID/day

After 4 weeks on crizotinib, a significant improvement of symptoms (cough and dyspnea) and Performance Status (0-1) was obtained. Treatment was well tolerated, except for a grade 1 skin rash and increase of transaminases.

July 2013: the last CT scan and clinical evaluation still confirm a stable disease after 8 months of crizotinib

August 2013: the patient suddenly died for arrhythmia and heart failure
Conclusions (Issues for Q&A)

• Emerging data about the potential predictive (and prognostic) role of the uncommon EGFR mutations
  – Very modest efficacy of currently available TKIs against T790M & exon 20 alterations
  – Similar efficacy in G719 and L861 mutations with reversible and irreversible TKIs
  – Waiting for new irreversible EGFR mutant selective agents (i.e. CO-1686)

• Who occurred first in the pathogenesis?
  – EGFR mutation as an ‘escape’ from ALK-driven addiction?
  – ALK (and ROS1/MET) high GCN as an ‘escape’ from EGFR-driven addiction?
  – Both clones resulting from distinct oncogenic events leading to the same phenotype?

• Is tumour heterogeneity a potential ‘confounder’?

• Which role as predictors of crizotinib for genetic abnormalities ‘other’ than traslocations?
  – Amplification
  – High GCN
    • In this case, what cut-offs?
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# Results: biomarkers assessment (n=9911)

![Pie chart showing the distribution of biomarkers: Double mutation (n=79), UKN, Mutant/Translocated.]

<table>
<thead>
<tr>
<th></th>
<th>EGFR</th>
<th>ALK</th>
<th>KRAS</th>
<th>BRAF</th>
<th>PI3K</th>
<th>HER2</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK</td>
<td>3</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>5</td>
<td>10</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI3K</td>
<td>16</td>
<td>1</td>
<td>33</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Supported by: [Institut National du Cancer] [IFCT]

Presented by Fabrice Barlesi, MD, PHD at 2013 ASCO Annual Meeting
The Issue of resistance to TKIs

anti-EGFR TKIs

Oxnard ASCO 2013

Doebele CCR 2012
Lung Cancers with Concomitant EGFR Mutations and ALK Rearrangements: Diverse Responses to EGFR-TKI and Crizotinib in Relation to Diverse Receptors Phosphorylation

Jin-Ji Yang¹, Xu-Chao Zhang¹,², Jian Su², Chong-Rui Xu¹, Qing Zhou¹, Hong-Xia Tian², Zhi Xie², Hua-Jun Chen¹, Yi-Sheng Huang¹, Ben-Yuan Jiang¹, Zhen Wang¹, Bin-Chao Wang¹, Xue-Ning Yang¹, Wen-Zhao Zhong¹, Qiang Nie¹, Ri-Qiang Liao¹, Tony S. Mok³, and Yi-Long Wu¹,²

A

Percentage change from baseline

B

C

PFS (mo)
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Long-Term Response to Gefitinib and Crizotinib in Lung Adenocarcinoma Harboring Both Epidermal Growth Factor Receptor Mutation and EML4-ALK Fusion Gene
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Acquired Resistance to Crizotinib from a Mutation in CD74-ROS1

A CT Scans of the Chest

B Acquired G2032R Mutation

C Detection of the G2032R ROS1 Mutation in Autopsy Specimens

Autopsy Site | G2032R
---|---
Liver (normal) | -
Chest wall tumor | +
Right lung tumor no. 1 | +
Right lung tumor no. 2 | +
Malignant pleural effusion | +
 Mediastinal lymph-node tumor | +
Left lung (microscopic disease) | +
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Prognostic value of ALK gene copy number (GCN) status for resected and metastatic Non-Small-Cell Lung Cancer (NSCLC): a retrospective analysis of 205 patients (pts)

Submitted (ASCO 2014)