Can sensitivity to cytotoxic chemotherapy be predicted by biomarkers?

Enriqueta Felip
Vall d’Hebron University Hospital, Barcelona, Spain
Cytotoxic chemotherapy and biomarkers

Points to consider

• For the majority of NSCLC patients, standard of care is still cytotoxic CT

• Not all patients benefit from CT

• NSCLC, morphological and molecular heterogeneous entity
Cytotoxic chemotherapy and biomarkers

Outline

• Studies analyzing biomarkers and CT sensitivity

• Driver mutations/alterations and sensitivity to CT

• Current recommendations

• Potential new biomarkers for CT sensitivity
Cytotoxic chemotherapy and biomarkers

Studies analyzing biomarkers and CT sensitivity
Most often analyzed biomarkers for CT sensitivity
ERCC1 / RRM1 / BRCA1 / Class III β-tubulin / TS

- **ERCC1**, DNA damage-repair gene of NER pathway which removes cis-induced DNA adducts
- **RRM1**, component of ribonucleotide reductase, required for deoxynucleotide production and the molecular target of gem
- **BRCA1**, gene involved in DNA repair and in cell-cycle checkpoint control
- **Class III β-tubulin**, isotype with enhancing impact on microtubule dynamics that may lead to resistance to anti-microtubule agents
- **TS**, enzyme regulating production of nucleotide synthesis by catalyzing the conversion of deoxyuridylate to thymidylate and main target of pem
ERCC1 / GILT trial
First prospective pharmacogenomic study

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Control</th>
<th>Genotypic</th>
<th>Low levels (ERCC1)</th>
<th>High levels (ERCC1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>oRR</td>
<td>51.2%</td>
<td>57.5%</td>
<td>P = 0.02</td>
<td>53.2%</td>
<td>47.2%</td>
</tr>
<tr>
<td>ITT-RR</td>
<td>37.6%</td>
<td>47.5%</td>
<td>P = 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mTTP</td>
<td>5.8m</td>
<td>5.2</td>
<td>6.1</td>
<td>6.7</td>
<td>4.8</td>
</tr>
<tr>
<td>mOS</td>
<td>9.8</td>
<td>9.9</td>
<td></td>
<td>10.35</td>
<td>9.5</td>
</tr>
<tr>
<td>1y S</td>
<td>39%</td>
<td>40.4%</td>
<td></td>
<td>44%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Cobo, Rosell, JCO 2007
ERCC1 / RRM1

• P with low RRM1 expression respond better to carbo/gem (*Bepler, JCO 06*)

• Phase II trial in 60 p; double-agent CT (carbo, gem, doc, vin) on basis of ERCC1 / RRM1 expression (*Simon, JCO 07*)
  – RR 44%
  – PFS 6.6 mo
  – mOS 13.3 mo
ERCC1 and RRM1-tailored CT

- Stage IV NSCLC p and PS0-1 included in 4 phase II trials
  - Trial A, carbo/gem followed by doc
  - Trial B, doc/gefitinib in p ≥ 70 yrs
  - Trial C, carbo/pac/atrasentan
  - Trial D, personalized therapy based on ERCC1 and RRM1

- Better results in trial D when compared to trials A, B, C
  - RR, 44% vs 22%; P=.002
  - mPFS, 7.0 vs 4.3 mo; P=.03
  - mOS, 13.3 mo vs 8.9 mo; P=.016
International randomized phase III trial in stage IV based on ERCC1 / RRM1, completed

- P randomized 2:1 to
  - Experimental arm, CT doublet with carbo if ERCC1 low, gem if RRM1 low, doc if ERCC1 or RRM1 high, and doc/vin if both markers high
  - Control arm, gem/carbo

- Trial powered for 32% improvement in 6-month PFS

- Of 331 p registered, 275 were eligible
  - Median time from informed consent to completed gene analysis, 11 d

*PI, G Beppler*
BRCA1

- Pre-clinical evidence suggests that BRCA1 confers sensitivity to apoptosis induced by anti-microtubule drugs but resistance to DNA-damaging agents

- In locally advanced p treated with platinum/gem, longer survival for those with low BRCA1 levels *(Taron, Hum Mol Genet 04)*

- Advanced ADC p treated according to BRCA1 levels (low cis/gem, intermediate cis/doc, high doc alone) had good outcomes; survival influenced by RAP80 *(Rosell, PLoS One 09)*
International BREC
(BRCA1 & RAP 80 Expression Customization)

MULTICENTRIC, PHASE III, RANDOMIZED STUDY TO EVALUATE TREATMENT CUSTOMIZED ACCORDING TO RAP80 AND BRCA1 ASSESSMENT IN PATIENTS WITH ADVANCED NSCLC

- **Primary endpoint** PFS
- **Secondary endpoints** OS, RR, safety profile

216 patients per arm (N= 432)

*Courtesy of Dr Rosell and Dr Moran*
International BREC
BRCA1 & RAP 80 expression customization

Spain - 44 active centers
France - 14 centers
Belgium - 3 centers
Saudi Arabia - 1 centers
Luxemburg - 2 centers

<table>
<thead>
<tr>
<th>Total screened</th>
<th>Total included</th>
<th>Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>945</td>
<td>305</td>
<td>Spain</td>
</tr>
<tr>
<td>136</td>
<td>63</td>
<td>France</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>Belgium</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>Saudi Arabia</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>Luxemburg</td>
</tr>
<tr>
<td>1104</td>
<td>375</td>
<td>Total</td>
</tr>
</tbody>
</table>
Class III β-tubulin

• Pac-treated p with low class III β-tubulin, better survival, retrospective analysis *(Seve, Mol Cancer Ther 05)*

• Benefit with ADJ cis/vin greater in p with high class III β-tubulin in BR.10 *(Seve, CCR 07)*

• The predictive value of class III β-tubulin in advanced disease restricted to ADC in a randomized study *(Vilmar, CCR 11)*

• Meta-analysis of 10 studies (N=552 p), correlation between low class III β-tubulin and favorable outcome with pac/vin-based therapy *(Zhang, Lung Cancer 12)*
Consistent findings across phase III trials established favorable predictive effect of non-SCC histology on treatment with pem

- TS significantly higher in SCC compared with ADC in biopsy specimens (*Ceppi, Cancer 06*)

No clinical data clearly confirm predictive role of TS to pem (*Gronberg, ASCO 11*)

TS by IHC, great variability (*Wynes, JTO 12*)

ITACA trial, prospective ADJ study including mRNA TS levels
Blood samples: polymorphisms / DRC

• No evidence to support use of ERCC1 C118T/C8092A and ERCC2 Lys751Gln/Asp312Asn as predictors of platinum-based CT in meta-analysis (Yin, Lung Cancer 11)

• Genetic variation in CMKLR1 gene associated with decrease in OS in p receiving platinum-based CT / studies needed to elucidate CMKLR1 function (Wu, JNCI 11)

• Germline polymorphisms in the pem transport pathway associated to pem benefit / small sample size (Adjei, JCO 10)

• DRC in peripheral lymphocytes, a predictor of survival in 591 p receiving platinum-based CT/ heterogeneous group (Wang, JCO 11)
Blood samples: CTCs

- Genomic analysis of CTCs; “real-time” monitoring

- CTCs, prognostic factor in stage IV p \((\text{Krebs, JCO 11})\)

- ERCC1 expression in CTCs correlates with PFS in p receiving platinum-based CT \((\text{Das, Lung Cancer 12})\)

- IHC detection of biomarkers (TS) in CTCs is feasible \((\text{Christoph, JTO 12})\)
Cytotoxic chemotherapy and biomarkers

Driver mutations/alterations and sensitivity to CT
# EGFR mut and CT sensitivity

## CT response in 1st line randomized trials

<table>
<thead>
<tr>
<th>Studies</th>
<th>Design</th>
<th>RR in CT arm</th>
<th>PFS in CT arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS</td>
<td>Gefitinib vs carbo/pac</td>
<td>47%</td>
<td>6.3 mo</td>
</tr>
<tr>
<td>Mok, NEJM 09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North-East Japan</td>
<td>Gefitinib vs carbo/pac</td>
<td>31%</td>
<td>5.4 mo</td>
</tr>
<tr>
<td>Maemondo, NEJM 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WJTOG3405</td>
<td>Gefitinib vs cis/doc</td>
<td>32%</td>
<td>6.3 mo</td>
</tr>
<tr>
<td>Mitsudomi, Lancet 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>Erlotinib vs carbo/gem</td>
<td>36%</td>
<td>4.6 mo</td>
</tr>
<tr>
<td>Zhou, Lancet Oncol 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EURTAC</td>
<td>Erlotinib vs platinum/doublet</td>
<td>15%</td>
<td>5.4 mo</td>
</tr>
<tr>
<td>Rosell, Lancet Oncol 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lux-Lung 3</td>
<td>Afatinib vs cis/pem</td>
<td>22%</td>
<td>6.9 mo</td>
</tr>
<tr>
<td>Yang, ASCO 12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ALK and CT sensitivity

• Presidential Symposium, Sunday September 30; Phase III study of crizotinib vs pemetrexed or docetaxel chemotherapy in patients with advanced ALK-positive NSCLC (PROFILE 1007) *(Shaw et al)*

• Is pem more active in ALK+ tumors? *(Shaw, Ann Oncol 12)*
  – PFS using pem or non-platinum/pem combinations, similar in ALK+ and ALK- p
  – In never/light smoking p treated with 1st line platinum/pem, no differences in PFS between ALK+ and ALK- p
Cytotoxic chemotherapy and biomarkers

Current recommendations
Potential treatment algorithm for advanced-stage NSCLC (good PS)

Gandara, Clin Lung Cancer 09
www.esmo2012.org
Sensitivity to cytotoxic chemotherapy and biomarkers

• 1st ESMO Consensus Conference in Lung Cancer *(Ann Oncol 11)*
  – Routine testing for mRNA levels of ERCC1, RRM1, TS and BRCA1 is not currently recommended outside of clinical trials

• 2011 Focused Update of 2009 ASCO Clinical Practice Guideline Update on Chemotherapy for Stage IV NSCLC *(JCO 11)*
  – Evidence is insufficient to recommend routine use of molecular markers to select systemic treatment in patients with metastatic NSCLC

• NCCN guidelines do not include recommendations on the use of biomarkers to select patients for CT
Cytotoxic chemotherapy and biomarkers

Potential new biomarkers for CT sensitivity
Potential new biomarkers for CT sensitivity

- nab-pac/carbo improves RR vs pac/carbo (33 vs 25%, P=0.005) ([Socinski, JCO 12])
  - SPARC, proposed marker to predict the efficacy of nab-pac

- Classification of NSCLC subtypes based on gene expression profiles may be helpful to tailor pem therapy ([Hou, JTO 12])

- Temozolamide has activity in relapsed SCLC; response may correlate with MGMT methylation ([Pietanza, CCR 12])

- PARP1, increased levels in SCLCs; PARP inhibitors? ([Byers, Cancer Discovery 12])
Potential new biomarkers for CT sensitivity

• In k-ras mutant mouse models, concomitant loss of either p53 and Lkb1 impaired response to doc (Chen, Nature 12)

• Vitamin B6 metabolism found to be a central regulator of cis responses (Galluzzi Cell Rep12)
  – Treatment with vitamin B6 precursor enhanced the anti-tumor effects of cis and promoted cis-induced death, but only when PDXK (pyridoxal kinase, an enzyme that converts vitamin B6 precursor into their active form) was present
  – Low PDXK associated with poor outcome
  – PDXK, potential marker?
Challenges in the development and evaluation of marker-based clinical tests

• Methodological issues: IHC / automated scoring system (AQUA) on TMAs, mRNA expression?

• Tumor heterogeneity: ERCC1 status discordant in primary NSCLC and metastatic sites in 41% of cases, with trend toward overexpression in brain and adrenal met (Gomez-Roca, JTO 09)

• Are these tumor markers stable during disease? Need for re-biopsy? Blood, a better source?

• Studies, adequate sample size for statistical power
Cytotoxic chemotherapy and biomarkers

- No routine testing for biomarkers for CT benefit
  - Few prospective trials ongoing

- Limited interest in the development of new CT agents
  - Little support for this line of research

- Relevant area of investigation
  - The majority of stage IV patients receive CT, even those with molecular alterations

- Collaborative efforts needed