FDG PET status in the era of targeted therapy in lymphoma

Michel Meignan, France
Anas Younes, USA
Increased number of drugs targeting activated oncogenic pathways proposed in relapsed/refractory Lymphoma

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Drug</th>
<th>Target</th>
<th>% response rate in different histologies</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<td>DLBCL %</td>
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<tr>
<td>PI3K/AKT/mTOR</td>
<td>Everolimus</td>
<td>mTOR</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Temsirolimus</td>
<td>mTOR</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>CALI-101/</td>
<td>PI3K</td>
<td>0</td>
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<tr>
<td></td>
<td>GS-1101</td>
<td></td>
<td></td>
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<tr>
<td>B cell receptor (BCR)</td>
<td>Fostamatinib</td>
<td>Syk</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Ibrutinib</td>
<td>Btk</td>
<td>17</td>
</tr>
</tbody>
</table>

Younes, Lymphoma (Younes, Coiffier eds) 2013
Evaluation of targeted therapy

- Predictive biomarkers are critical
- Regression of lymphoma during therapy is an important end-point
  - Evaluation of response early in the course of therapy with biomarkers could
    - Optimize treatment modalities (combined targeting)
    - Avoid ineffective treatment
    - Reduce cost
Evaluation of targeted therapy 2 which biomarkers?

• Pharmacodynamic biomarkers
  – assess target inhibition
  – assess pathway downregulation
  ➢ This does not necessarily equate clinical benefit
• Many biomarkers assays not standardized
• Is there a place for metabolic imaging?
  – detect response and resistance before conventional Imaging
Use of Glucose analog FDG as a biomarker

- Intensity of FDG uptake
  - Membrane glucose transporters (GLTU1, GLUT3)
  - Hexokinase activity
- Activation oncogenic pathways in tumour cells
  - Increased glycolysis
  - Up-regulation and overexpresion of GLTU1, GLUT3
- Drug inhibition of these pathways alters the tumour cell glycolysis
Akt activation increases GLUT1 membrane localization in pancreatic adenocarcinoma cells resistant to Temsirolimus (AkT/mTOR pathway)

Ma et al. J Clin Oncol, 2009
AktT inhibition by gefitinib (EGRF inhibition) induces a GLUT3 translocation from membrane to cytosol

NSCLC cell lines

Su et al., Clin Cancer Res 2006
Many sources of complexity

To interpret imaging results with FDG after targeted therapy:

1. Interrelationship between oncogenic pathways and existence of resistance feed back loops

2. Time lag between effects on glucose transporter, effects on cell cycle, apoptosis and the effectiveness of receptor blockage

3. Differences between tumor types
Negative feed back loop:

Treatment of pancreatic adenocarcinoma cells by a TKI inhibitor Axitinib induced activation of Akt pathways and a GLUT1 translocation to the membrane.

Warrants combined therapy.

Hudson et al, Cell Death and Disease, 2014
Lag between withdrawal of the drug, target recovery (PI3K/mTOR) and metabolic recovery in an animal model of ovarian tumour

BEZ-235 withdrawal

A

Day 3    Day 4    Day 5

% change in SUV<sub>mean</sub>

D

<table>
<thead>
<tr>
<th></th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (untreated)</td>
<td>BEZ-235</td>
<td>Control (untreated)</td>
<td>BEZ-235</td>
</tr>
<tr>
<td>pAkt (Ser473)</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
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<tr>
<td>Akt total</td>
<td>![Image]</td>
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<tr>
<td>p4E-BP1</td>
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<tr>
<td>4E-BP1 total</td>
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<tr>
<td>Tubulin</td>
<td>![Image]</td>
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<tr>
<td>Actin</td>
<td>![Image]</td>
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Lheureux Translational Oncology, 2013
FDG as a prognostic biomarker: variable clinical results

Early prediction of response to Sunitinib
23 GIST patients after Imatinib failure

Prior J Clin Oncol 2009
FDG as a prognostic biomarker: variable clinical results

Ma et al. J Clin Oncol, 2009

34 patients, mTOR inhibition
Not predictive of response and TTP

Ma et al. J Clin Oncol, 2009
FDG PET in lymphoma patients treated with targeted therapy

• Data are scarce*
  – Complexity and diversity of the mechanisms involved in oncogenic pathways in lymphoma
  – Trend to treat with combined agents to avoid negative feedback
  – Optimal timing for response assessment undefined in the setting of a continuous daily long term treatment

Evaluation of a targeted therapy is more focused on appropriate definition of its CT variations

*Case report and one study including 11 patients (ALK+ NHL)
ALK+ ALCL animal model: 7 day treatment with a dual PI3K/mTOR inhibitor

• FDG PET
  – Discriminates very early sensitive from resistant lymphoma
  – Reduced metabolic activity correlates with
    – Decrease of proliferation marker Ki67
    – Increase of apoptotic marker (cleaved caspase-3)

Graf et al. OncoTargets and Therapy 2014
Is FLT thymidine analog as a biomarker > FDG?

ALK+ ALCL cell lines mTOR inhibitor

Granta 519 cells from human MCL Temsirolimus withdrawal

SU-DHL-1 xenograft

FLT>FDG in some experimental models. Different kinetics reported after drug withdrawal attributed to inflammatory reaction.

Li et al Cancer Res 2012
Advanced chemoresistant ALK+ Lymphoma patients treated by Crizotinib

- 11 refractory and relapsed patients
- 73% 2y OS and 64% 2y PFS
- FDG-PET performed before during and after therapy
- FDG-PET demonstrates sensitivity to inhibition within a few days of continuous administration
- FDG-PET predictive value in this short series cannot be assessed

July 27th 2010    August 12th 2010

Conclusions

• In theory FDG as a biomarker of targeted therapy
  – Gives high possibilities to investigate glycolysis linked to oncogenic pathways.
  – Detects sensitivity to the drug (is it target effect of real sensitivity to the inhibitor?)
  – Quantifies the metabolism via $\Delta$SUV$_{\text{max}}$

• Optimal timing of imaging unknown

• Prediction value for tumor regression and outcome is unknown
  – is FDG reduced uptake a false negative results relative to tumor regression and outcome?

• Well-organized ancillary trials based on preclinical results are warranted to define a possible role of FDG in response assessment to targeted therapy in lymphoma.
Back up slides
Dose related $SUV_{\text{max}}$ reduction

Ciunci et al. Cancer 2014