The role of molecular imaging in early drug development

Kristoff Muylle, MD
Department of Nuclear Medicine
Jules Bordet institute, Brussels
Disclosure slide

• I have no conflicts of interest to declare
Increased use of imaging biomarkers to evaluate:
- metabolism,
- cell proliferation
- cell migration
- receptor expression
- gene expression
- signal transduction
- hypoxia
- apoptosis
- angiogenesis
- Vascular function

**Figure 6 – Biomarker imaging.**
Molecular cancer biology revealed an ever-increasing number of disease regulating intracellular and extracellular tumour targets, which lead to the development of a broad range of targeted therapeutic agents.

Few targets have been identified that cover all types of cancer from a given site of origin. However, the common phenotype of elevated glucose consumption is considered as a hallmark for cancer.


www.esmo2012.org
1. To evaluate early metabolic changes in primary tumor after anti-HER2 therapies in patients with invasive operable breast cancer (biological therapy window: weeks 2 and 6)

2. To test whether FDG-PET metabolic response with anti-HER2 therapies alone predicts Pathological Complete Response (pCR) at the time of surgery
Metabolic responder

Metabolic non-responder
Results Neo-ALTTO PET substudy

Boxplots of the changes in SUVmax

- pCR is associated with greater SUVmax reductions at week 2 and week 6 ($p = 0.02$ for both).

G. Gebhart et al., SNM 2012

www.esmo2012.org
Correlation between metabolic response and pCR (EORTC criteria)

- pCR rates are twice as high in patients who are FDG-PET/CT responders compared to non-responders according to EORTC criteria (41% versus 21% at week 2 (p= 0.12) and 43% versus 19% at week 6 (p= 0.05)).
### Table 1. Cancer Therapies That Target Oncogenic Proteins. *

<table>
<thead>
<tr>
<th>Anticancer Drug</th>
<th>Target</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoclonal antibodies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab (Herceptin, Genentech)</td>
<td>ERBB2</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Cetuximab (Erbitux, ImClone)</td>
<td>EGFR</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Bevacizumab (Avastin, Genentech)</td>
<td>VEGF</td>
<td>Colorectal cancer, non–small-cell lung cancer</td>
</tr>
<tr>
<td><strong>Small molecules</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib (Gleevec, Novartis)</td>
<td>ABL, PDGFR, KIT</td>
<td>Chronic myelogenous leukemia, gastrointestinal stromal tumors, chordoma</td>
</tr>
<tr>
<td>Gefitinib (Iressa, AstraZeneca)</td>
<td>EGFR</td>
<td>Non–small-cell lung cancer</td>
</tr>
<tr>
<td>Erlotinib (Taceva, Genentech)</td>
<td>EGFR</td>
<td>Non–small-cell lung cancer</td>
</tr>
<tr>
<td>Sorafenib (Nexavar, Bayer/Onyx)</td>
<td>VEGFR, PDGFR, FLT3</td>
<td>Renal-cell carcinoma</td>
</tr>
<tr>
<td>Sunitinib (Sutent, Pfizer)</td>
<td>VEGFR, PDGFR, FLT3</td>
<td>Gastrointestinal stromal tumors, renal-cell carcinoma</td>
</tr>
</tbody>
</table>

* EGFR denotes epidermal growth factor receptor, FLT3 FMS-like tyrosine kinase 3, PDGFR platelet-derived growth factor receptor, and VEGF vascular endothelial growth factor.
• $^{89}\text{Zr}$-immuno-PET/CT combines the high sensitivity of PET/CT with the specificity of the chimeric monoclonal antibody (mAb) for the antigen expressed on the surface of cancer cells.
• Zirconium-89 ($^{89}\text{Zr}$) is a positron emitter with a half-life of 78.4 hours, which is compatible with the time needed for intact mAb to achieve optimal tumour-to-background ratios.

$^{89}\text{Zr}$-rituximab Immuno-PET/CT
Intra-abdominal relapse of a follicular lymphoma.

1 hour p.i.  1 day p.i.  3 days p.i.  6 days p.i.
Immuno-PET/CT
Prediction of toxicity (Zr89-rituximab)

- Toxicity observed with radioimmunotherapy is primarily hematological and difficult to predict.
- The aim of this study was to evaluate whether bone marrow (BM) activity on immuno-PET/CT with $^{89}$Zr-rituximab was correlated to hematological toxicity in 25 lymphoma patients treated with $^{90}$Y-rituximab.

**Therapeutic Regimen**

- **First preload + Zr89-rituximab**
  - Cold anti-CD20 antibody* (Rituximab 250 mg/m$^2$)
  - Followed by $^{89}$Zr-Rituximab (111-148 MBq)

- **Preload + Y90-rituximab**
  - Cold anti-CD20 antibody* (Rituximab 250 mg/m$^2$)
  - Followed by $^{90}$Y-Rituximab (14.8 MBq/kg BW)

Significant differences were observed in BM activity concentration between patients with < grade 3, grade 3 and grade 4 toxicities ($p=0.0009$ Kruskal-Wallis test).

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Immuno-PET/CT

Tumour heterogeneity (Zr89-trastuzumab)

• ability to quantify cellular targets for the entire disease burden
• Identify heterogeneous receptor expression > avoid the sampling error

FDG 1 h p.i.

Zr89-trastuzumab 4 days p.i.
Immuno-PET/CT
Prediction of response (Zr89-rituximab)

NHL
Biopsy proven CD20+

subcutaneous lesions
&
lymph node involvement

FDG-PET/CT Pre-treatment
Immuno-PET/CT Pre-treatment
FDG-PET/CT Post-treatment

Difference in accessibility: preferential sites of receptor-binding

Less accessible receptors:
No mAb-uptake
No response &
High accessible receptors:
high mAb-uptake
complete response

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Evaluate and adapt therapeutic regimens in function of patient characteristics (Zr89-rituximab)

Zr89-rituximab Immuno-PET/CT 6d p.i.

- Patient 1
- Patient 5

Bone marrow dosimetry

- Without cold Ab
- With cold Ab

Spleen dosimetry

- With cold AB
- Without cold AB

- Influence of a preload of rituximab on the distribution of the radioconjugate, especially the uptake in the spleen, highly depends on the amount of circulating CD20+ lymphocytes.
- Preload: minor influence on the radiation dose to the spleen in patients with B-cell depletion.
- Without preload: moderate increase of the bone marrow dose by 4-36%
Lesion uptake / tumor targeting is consistently higher **without** a preload, at least in patients with B-cell depletion…

3 lesions show less or no uptake without preload, all 3 in patients without B-cell depletion.
Evaluate and adapt therapeutic regimens in function of patient characteristics (Zr89-rituximab)

In this patient without B-cell depletion:

- Preload impairs uptake in involved lymph nodes < (partial) saturation with cold mAbs.
- Preload enhances uptake in the 2 visceral lesions < reducing the uptake in the spleen > higher residence time of the radioconjugate in blood > binding in less accessible regions.
Role of molecular imaging in early drug development

Implementation of molecular imaging in clinical trials has high potential in terms of:

• non-invasiveness
• the potential for serial studies for evaluation of the in vivo effects of a drug on the target
• ability to quantify cellular targets for the entire disease burden
• Identification of heterogeneous receptor expression
  > avoid sampling errors
• prediction of treatment outcome
  > avoid unnecessary toxicity
• enriching patient selection by assessing drug targeting and/or early-on response prediction > reduction of costs
• evaluation and adaptation of therapeutic regimens > reduction of costs
• development of patient tailored image guided therapy
THANKS