International Course on Theranostics and Molecular Radiotherapy

ImmunoPET in Breast Cancer

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Jules Bordet Institute
5/10/2017
PLAN OF THE TALK

• Increasing role of antibodies in anti-cancer treatment
• Target identification: the added value of immunoPET
• ImmunoPET: experience in HER2 positive Breast Cancer
Increasing role of antibodies in anti-cancer treatment

- Monoclonal antibodies
- Antibody-drug conjugates
- Radioimmunotherapy

Selective drugs

Chemotherapy

Lamberts et al. JCO 2015
Monoclonal antibodies: effects on tumors

Modulation of downstream cell signaling

Immune-related cell destruction by ADCC

Mode of action of antibody-drug conjugate

Lamberts et al. JCO 2015
### Mabs and ADC approved for cancer treatment in solid tumors

<table>
<thead>
<tr>
<th><strong>Generic name</strong></th>
<th><strong>Indications</strong></th>
<th><strong>Target</strong></th>
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<tbody>
<tr>
<td>Trastuzumab, Pertuzumab, Trastuzumab emtansine</td>
<td>Breast cancer</td>
<td>HER2 (tumor cell membrane)</td>
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<tr>
<td>Panitumumab</td>
<td>Colorectal cancer</td>
<td>EGFR (tumor cell membrane)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Colorectal cancer, Head and neck cancer</td>
<td>EGFR (tumor cell membrane)</td>
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<tr>
<td>Ipilimumab</td>
<td>Melanoma</td>
<td>CTLA-4 (T-cells)</td>
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<tr>
<td>Pembrolizumab</td>
<td>Melanoma</td>
<td>PD-1 (T cells)</td>
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<td>Atezolizumab</td>
<td>Non-small cell lung cancer</td>
<td>PD-L1</td>
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<td>Nivolumab</td>
<td>Non small cell lung cancer, Melanoma, Renal cell Carcinoma, Head and neck</td>
<td>PD-1</td>
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<td>Durvalumab</td>
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<td>PDL1</td>
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<td>MPDL3280A</td>
<td>Bladder cancer</td>
<td>PDL1 (tumor cell membrane)</td>
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<td>Ramucirumab</td>
<td>Gastric cancer</td>
<td>VEGFR2 (microenvironment)</td>
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<tr>
<td>Bevacizumab</td>
<td>Colorectal cancer, Renal cell cancer, Non small cell lung cancer</td>
<td>VEGF (microenvironment)</td>
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BREAST CANCER

Luminal breast cancer

HER2 positive breast cancer

Triple negative breast cancer

RO: oestrogen receptor
RP: progesterone receptor
HER2 POSITIVE BREAST CANCER
CURRENT ANTI-HER2 THERAPIES

- **Trastuzumab**
  - Inhibition through direct antibody binding
  - Tyrosine kinase

- **Pertuzumab**
  - Inhibition through dimerization inhibition
  - Pertuzumab
  - Dimerization domain
  - Tyrosine kinase

- **T-DM1**
  - Targeting for intracellular drug delivery
  - Internalization through endocytosis and intracellular release of DM1
  - Tyrosine kinase

- **TK inhibitors**
  - Small-molecule tyrosine kinase inhibitor
The medical treatment of HER2 positive Breast Cancer: a historical perspective

**1999**
- Single HER2 blockade saves lives
  - with a MAb
  - Prolongs survival in advanced B.C.
  - Saves lives in early B.C.
  - Is active... but less than a MAb in advanced and early disease

**2005**
- Dual HER2 blockade superior to single HER2 blockade
  - Eradicates twice as many tumors when given prior to Sx
  - Prolongs survival in advanced B.C.
  - Offers the hope for CTX-free regimens

**2010**
- An antibody-drug conjugate - TDM1- prolongs survival and improves quality of life in advanced B.C.

**2012-2016**
- Single HER2 blockade saves lives
  - with TKi

**Definitions**
- Mab: monoclonal antibody
- Tkii: Tyrosine kinase inhibitor
- Sx: standard therapy
- CTX: chemotherapy
The context of trastuzumab resistance: early disease

**HERA Trial**

- **DFS (%)**
  - Months from randomisation
  - No. at risk
    - CHEMOTHERAPY: 1703, 1591, 1434, 1127, 742, 383, 140
    - CHEMOTHERAPY + TRASTUZUMAB: 1698, 1533, 1301, 930, 606, 322, 114

- **Events**
- **HR**
- **95% CI**
- **p value**

<table>
<thead>
<tr>
<th>Events</th>
<th>3-year DFS</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
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<tr>
<td>218</td>
<td>80.6</td>
<td>0.63</td>
<td>0.53, 0.75</td>
<td>&lt;0.0001</td>
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<tr>
<td>316</td>
<td>74.0</td>
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*Smith IE et al., Lancet 2007*
TARGET EXPRESSION – Example HER2: IHC/FISH

IHC images courtesy of MJ Kornstein, MD, Medical College of Virginia.
TARGET EXPRESSION

IHC

FISH

Target identification ...but what about:

Heterogeneity of target expression

Relevance of an analysis done on the primary tumor many years before

Loss of target with long storage of tumor tissue

Early stage

Advanced stage

Courtesy of Susan Lester, MD, PhD and Andrea Richardson, MD, PhD

Obtained from E. Winer, with permission
TARGET EXPRESSION

IHC  FISH

Target identification ...but what about:

- Heterogeneity of target expression
- Relevance of an analysis done on the primary tumor many years before
- Loss of target with long storage of tumor tissue

IMMUNOPET

- Presence of an accessible target demonstrated non-invasively
- Whole body imaging: monitoring target expression across all lesions
IMMUNOPET in HER2+BC PATIENTS

Monoclonal antibodies
- Trastuzumab
  - $^{111}\text{In}$
  - $^{89}\text{Zr}$
  - $^{64}\text{Cu}$
  - SPECT
  - PET

Affibodies
- ABY-002
  - $^{111}\text{In}$
  - SPECT
  - PET

- ABY-025
  - $^{68}\text{Ga}$
  - SPECT
  - PET

Nanobodies
- HER2 nanobody
  - $^{68}\text{Ga}$
  - PET

VHH or Nanobody

INSTITUT JULES BORDET INSTITUUT

ULB iris
Overall results: Newly discovered tumor lesions in 13/15 patients
Perik et al, J Clin Oncol 2006
Labelled nanobodies with Gallium 68

Courtesy of Marleen Keyaerts, UZ Brussel, Brussels, Belgium
Nanobodies versus monoclonal antibodies

**68Ga-NOTA-anti-HER2 Nanobody**
- HER2+ breast cancer + axillary node.
- Fast biokinetics
  - fast blood clearance & tumor targeting
  - Renal clearance ++
  - Mean effective dose: 0.042 ± 0.005 mSv/MBq
  - Dose for 105 MBq: 4.6 mSv
  - Better suited for diagnosis / receptor assessment

**89Zr-trastuzumab**
- HER2+ bone and liver metastasis
- Slow biokinetics
  - slow blood clearance & tumor targeting
  - No renal clearance
  - Mean effective dose: 0.41 ± 0.02 mSv/MBq
  - Dose for 37 MBq: 18-25 mSv
  - Better suited for treatment simulation / dosimetry
ImmunoPET as a guide for therapy

ImmunoPET radiotracer vs Targeted therapy molecule

share a molecular pathway

have the same target

« Hot/Cold » theranostics

Zr-T PET - Hsp90 therapy

Zr-T PET – T-DM1: ZEPHIR STUDY
EXAMPLE 1: Zr-Trastuzumab PET - HSP90 inhibitor

Before HSP90 inhibitor therapy

3 weeks under HSP90 inhibitor therapy

Average decrease in SUVmax of 18% ↔ associated with change in lesion size

EXAMPLE 2:

**Molecular Imaging as a tool to investigate heterogeneity of advanced HER2 positive Breast Cancer and to predict response to Trastuzumab Emtansine (T-DM1)**

**THE ZEPHIR TRIAL**
T-DM1 selectively delivers a highly toxic payload to HER2-positive tumour cells.

**T-DM1**: 1st-in-class HER2 antibody-drug conjugate (ADC)

**Monoclonal antibody**: trastuzumab

**Cytotoxic agent**: DM1

**Systemically stable**: Breaks down in target cancer cell

**Linker**

**Receptor-T-DM1 complex is internalised into HER2-positive cancer cell**

**Potent antimicrotubule agent is released once inside the HER2-positive tumour cell**

**T-DM1 binds to the HER2 protein on cancer cells**
ZEPHIR TRIAL DESIGN

HER2 IMAGING

89Zr-trastuzumab injection
89Zr-trastuzumab PET/CT

D₀
D₄

SCREENING

Baseline FDG PET/CT
Diagnostic CT

TREATMENT

T-DM1
C₁
C₂
C₃

FU until PD

LATE ASSESSMENT

Diagnostic CT
Prediction of morphological response

$^{89}$Zr-Trastuzumab PET/CT

Diagnostic CT

TDM 1

TDM 1

TDM 1

Diagnostic CT
ZEPHIR: two different ways to image the disease
Patterns of $^{89}$Zr-trastuzumab PET/CT confronted with FDG-PET/CT

**A**
All lesions: high $^{89}$Zr-T uptake

**B**
Majority of the tumour load: high $^{89}$Zr-T

**C**
Majority of the tumour load: low/no $^{89}$Zr-T uptake

**D**
All lesions: low/no $^{89}$Zr-T uptake

**HER2 IMAGING METHODOLOGY**
PATTERNS OF HER2 EXPRESSION REVEALED BY HER2 PET/CT IMAGING

All or most of the tumor load is seen on $^{89}$Zr-Trastuzumab PET/CT

Minority of tumor load or no lesions are seen on $^{89}$Zr-Trastuzumab PET/CT
### Correlation between molecular imaging and morphological Response

<table>
<thead>
<tr>
<th>HER2 PET</th>
<th>RECIST 1.1</th>
<th>R</th>
<th>NR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>R</td>
<td>28</td>
<td>11</td>
<td>39</td>
</tr>
<tr>
<td>-</td>
<td>NR</td>
<td>2</td>
<td>14</td>
<td>16</td>
</tr>
</tbody>
</table>

- **PPV:** 72%
- **NPV:** 88%
Time to treatment failure

TTF: Time from start of T-DM1 until its discontinuation

\[ {}^{89}\text{Zr}-\text{trastuzumab} \text{ PET/CT} \]

Graph showing survival rates with key time points:
- 3.5 months
- 11.2 months

HR 4.5 95% CI 2.1-9.4 p < 0.0001
Baseline FDG
Biopsied lesion

Biopsied lesion

HER2

IHC

Post 3 T-DM1
Future perspectives

ImmunoPET radiotracer vs Targeted therapy molecule

- share a molecular pathway
- have the same target

« Hot/Cold » theranostics
« Hot/Hot » theranostic

HER2 imaging for Lu-177-trastuzumab therapy selection
Lu-177-trastuzumab

- Tracer dose (not therapeutic dose)
- 10 metastatic patients: 6 HER2 positive, 4 HER2 negative
- No serious AE
- Primary tumor seen on SPECT images in 5/6 HER2+ patients
- No uptake of Lu177 T in IHC proven HER2 negative patients
- Biodistribution: liver (intense-limiting factor for therapeutic dose?), spleen, heart, nasopahrynx

Bhusari et al. International Journal of Cancer
CONCLUSIONS

• ImmunoPET, especially with $^{89}\text{Zr}$ is showing real promise as a biomarker for the efficacy of antibody drug conjugates

• ImmunoPET may reveal target presence/internalization and demonstrate antibody uptake in tumor just before or during treatment

• Whole body exam: highlights the « between and within-lesion » tumor heterogeneity

• More work is needed to prove the clinical utility of immunoPET: immunoPET should influence treatment choice and this should result in improved patient’s outcomes
Thank you for your attention