National Cancer Policy Forum

Understanding Biological Activity to Inform Drug Development

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RECIST – Response evaluation criteria in solid tumors

- Tumor response defined by number and size of tumor lesions
- Criteria developed in the seventies (WHO criteria) for technologies available at this time (palpation and planar x-rays)
- Refined/simplified for broad use in clinical trials as RECIST 1.0 and RECIST 1.1 (decrease of the number of lesions measured, one-dimensional instead of bi-dimensional measurements)
- Correlation of RECIST response with patient outcome has been demonstrated by analyses of imaging data from multiple clinical trials
- Modified (but not fundamentally different) systems for response assessment are used in specific tumor types/treatments (e.g. immune-related response criteria)

RECIST and patient survival in metastatic breast cancer

Overall survival on patient level

- Control
- Experimental

P < 0.0001, N = 2126, 10 clinical trials

Correlation between response and survival on the trial level

Bruzzi et al. J Clin Oncol (2005) 5117-5125, Figure 3 (edited) and Figure 4
Prediction of survival by RECIST response


Thresholds of response difference of the needed to predict a survival gain at the 5% level
Limitations of RECIST

- Inability to differentiate between “viable tumor” and “treated disease (scar)"
- Not all metastatic sites are considered measurable (e.g. bone metastases)
- Criteria for response assessment are more or less arbitrary for current imaging technologies
- Parts of the RECIST assessment are subjective, e.g. selection of the “target lesion”, “unequivocal progression of non-target lesion”
- “Stable disease” is problematic in non-randomized clinical trials.
Tumor Control (SD) and Prognosis

Stable Disease in NSCLC Patients Treated with Placebo

ISEL Study

<table>
<thead>
<tr>
<th>Reason for failure of last chemotherapy</th>
<th>Gefitinib (n=1129)</th>
<th>Placebo (n=563)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory†</td>
<td>1011 (90%)</td>
<td>512 (91%)</td>
</tr>
<tr>
<td>Intolerant</td>
<td>114 (10%)</td>
<td>48 (9%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Gefitinib (n=959)</th>
<th>Placebo (n=480)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>77 (8%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>76 (8%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>304 (32%)</td>
<td>148 (31%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>360 (37%)</td>
<td>232 (48%)</td>
</tr>
</tbody>
</table>

Functional imaging to assess tumor response

• Differentiation between “treated disease” and viable tumor tissue
• Monitoring tumor response in body areas that cannot be assessed by RECIST, e.g. bone, esophageal wall
• Quantification of changes in physiologic/biochemical parameters
• Examples
  – DCE MRI to assess tumor vascularization and perfusion
  – FDG PET to assess tumor glucose metabolism
FDG-PET for monitoring tumor response

Hodgkin

Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin’s Lymphoma

Peter Johnson, M.D., Massimo Federico, M.D., Amy Kirkwood, M.Sc., Alexander Fossá, M.D., Leanne Berkhahn, M.D., Angelo Carella, M.D., Francesco d’Amore, M.D., Gunilla Enblad, M.D., Antonella Franceschetto, M.D., Michael Fulham, M.D., Stefano Luminari, M.D., Michael O’Doherty, M.D., Pip Patrick, Ph.D., Thomas Roberts, B.Sc., Gamal Sidra, M.D., Lindsey Stevens, Paul Smith, M.Sc., Judith Trotman, M.D., Zaid Viney, M.D., John Radford, M.D., and Sally Barrington, M.D.

A Progression-free Survival among Patients with Negative PET Findings

B Overall Survival among Patients with Negative PET Findings

Before Ctx  During Ctx
PET Response Criteria in Solid Tumors

**PERCIST 1.0**

- **CR** – Disappearance of all lesions
- **PR** – At least 30% decrease of SUV
- **SD** – Neither response or PD
- **PD** – At least 30% increase of SUV or increase in tumor size or new lesions

Repeatability of measurements of tumor FDG uptake

Meta-analysis of 5 studies on


de Langen et al. J Nucl Med (2012) 53:701-708, Figure 2, page 705
PET/CT imaging technology

- Widely available in the US due to the success of FDG PET/CT
- Established infrastructure for production and distribution of PET tracers
- Simple, robust image acquisition
- Inherently quantitative data
- Whole body imaging in ~ 15 min (with current scanners)

Scanners installed in 2009: ~ 2000
Capacity: 5-7 Million/year
(10-15 scans/day/scanner)

- Significant installed infrastructure that is only partially utilized by FDG imaging
- New imaging agents are of great clinical interest

Buck et al. J Nucl Med (2010) 51:401-412, Figure 1, edited
Using imaging to go beyond assessment of response

Biomarker Definitions Working Group
Clinical Pharmacology & Therapeutics (2001), modified
Imaging of biological activity

Key questions:
• Is the drug target present (at all disease sites, at high concentration)?
• What is the concentration of the drug at the site of the target?
• Does the drug interact with the target?
Genetic heterogeneity of metastatic cancer

B. Vogelstein. Science 339, 1546 (2013), figure 6
Assessing the expression/accessibility of a potential drug target

Imaging STEAP1 with Zr-89 DFO-MSTP2109A

- First member of the six-transmembrane epithelial antigen of prostate (STEAP) family
- New target for therapy of prostate cancer: use of antibody drug conjugates

Carrasquillo et al. AACR 2014
Imaging of tissue pharmacokinetics
Predicting the concentration of antibody drug conjugates

$^{89}$Zr-A33 antibody PET

Two days and seven days post-administration images.

Graph showing the percentage of administered A33 antibody per gram over time after administration.

Compartmental model

Prediction of tumor concentrations

“Theranostic” compounds

- Use of the same (or very similar) molecule for imaging and therapy
- Well established for radiiodine therapy of thyroid cancer (radioiodine imaging and therapy)
- The principle is to concentrate a radioactive isotope in the tumor for targeted radiotherapy
- Recently this concept has been expanded to several other malignancies

Iodine-131 SPECT/CT
NETTER-1 trial

- Randomized comparison of
  - $^{177}$Lu-DOTATATE
    (4 cycles of 7.4 GBq every 8 weeks)
  - Octreotide LAR
    (60 mg every 4 weeks)
- 230 patients with grade 1-2 metastatic midgut NETs
- Median PFS (primary endpoint)
  - Not reached for $^{177}$Lu-DOTATATE
  - 8.4 months for Octreotidte
- Deaths: 14 for $^{177}$Lu-DOTATATE vs. 26 for octreotide LAR
  ($p = 0.0043$, interim analysis)
Therapy of metastatic prostate cancer with a $^{177}$Lu labeled -PSMA ligand

71y/o patient, s/p Doc/Abi/Enza/Ra-223

Before therapy
PSA = 755 ng/mL

Cycle 1

Cycle 2

Cycle 3

Cycle 4
PSA < 0.2 ng/mL

$^{68}$Ga-PSMA-11 PET/CT

Heck et al. J Urol (2016) 196:382–391, Figure 4, edited
Importance of an in-vivo pharmacodynamics marker

• PARP1 is a DNA repair enzyme which is considered critical for the survival of cancer cells with deficiency in other repair mechanism (e.g. BRCA mutation).

• PARP inhibitors have been developed for treatment of various cancers, mostly ovarian, breast, and lung cancer.

• One of the first compound entering clinical trials was Iniparib.

PARP = poly ADP ribose polymerase

Iniparib is not a PARP1 inhibitor at clinically relevant dose levels in patients!
Radiolabeled PARP inhibitors for imaging PARP expression


Salinas, B. et al. *EJNMMI Res*. 2015


Imaging Interaction of Olaparib and Iniparib with $^{18}$F-FTT

Washington University; Michel et al. Radiology (2016) online
• Morphologic assessment by RECIST remains an important tool for drug development, but has well-known limitations
• Functional imaging techniques can overcome some of these limitations by using physiologic/biochemical parameters to monitor tumor response
• Molecular imaging allows for
  – Visualization and quantification of drug target expression in whole body imaging studies
  – Monitoring the interaction between drug and target
  -> Definition of the biologically relevant dose
• “Theranostic drugs”, combine imaging and therapy and have recently shown promise in neuroendocrine tumors and prostate cancer