Imaging in Clinical Trials

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Acknowledgements


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Clinical Trials in Perspective

16,000 cancer related trials listed in Clinical Trials.gov (2009)

Aggarwal S. NATURE REVIEWS | DRUG DISCOVERY | VOLUME 9 | JUNE 2010 | 427
Challenges for Imaging in Cancer

Tumour Phenotyping

Can we improve tumour phenotyping?
- Important biological characteristics may not be depicted by conventional imaging

Assessment of treatment response

Can we improve imaging response assessment?
- Better responsive/predictive biomarkers?
- Detect response at an earlier stage?
# Types of Clinical Trials

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
</table>
| ▪ Small no. of patients  
▪ Safety/Toxicity/Dosage | ▪ Small no. of patients  
▪ Drug effectiveness  
▪ Safety | ▪ Large no. of patients  
▪ Randomisation  
▪ Tested vs standard treatment |

**Question:** Is the agent safe & is there biological activity?  
**Question:** Does the drug work sufficiently well?  
**Question:** How well does the drug work compared to what we have?
# Role of Imaging?

## Phase I
- Small no. of patients
- Safety/Toxicity/Dosage

## Phase II
- Small no. of patients
- Drug effectiveness
- Safety

## Phase III
- Large no. of patients
- Randomisation
- Tested vs standard treatment

- Prospective end-point to estimate the benefit of treatment

- Objective treatment response (RR)
- Classification of response:
  - Complete remission
  - Partial remission
  - Stable disease
  - Progressive disease
Role of Imaging?

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<td></td>
<td></td>
<td>• Randomisation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tested vs standard treatment</td>
</tr>
</tbody>
</table>

- End-point to selecting drugs for further Phase III studies

- Objective treatment response (RR)
- Classification of response:
  - Complete remission
  - Partial remission
  - Stable disease
  - Progressive disease
Imaging Modalities Used For Response Assessment

- X-ray
- Ultrasound
- CT
- MRI
- PET
**RECIST 1.1: Response Assessment**

New response evaluation criteria in solid tumours:
Revised RECIST guideline (version 1.1)

E.A. Eisenhauer\(^a\)\(^,\)\(^b\), P. Therasse\(^b\), J. Bogaerts\(^c\), L.H. Schwartz\(^d\), D. Sargent\(^d\), R. Ford\(^d\), J. Dancey\(^g\), S. Arbuck\(^h\), S. Gwyther\(^i\), M. Mooney\(^j\), L. Rubinstein\(^g\), L. Shankar\(^g\), L. Dodd\(^g\), R. Kaplan\(^d\), D. Lacombe\(^c\), J. Verweij\(^g\)

Lesion >1cm
Reproducibly measured
Selection must reflect different sites
Max: 5 lesions; 2 per organ

- **Classification of Response:**
  - Complete remission
  - Partial remission
  - Stable disease
  - Progressive disease

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\(^a\)Eisenhauer, E.A., \(^b\)Therasse, P., \(^c\)Bogaerts, J., \(^d\)Schwartz, L.H., \(^e\)Sargent, D., \(^f\)Ford, R., \(^g\)Dancey, J., \(^h\)Arbuck, S., \(^i\)Gwyther, S., \(^j\)Mooney, M., \(^k\)Rubinstein, L., \(^l\)Shankar, L., \(^m\)Dodd, L., \(^n\)Kaplan, R., \(^o\)Lacombe, D., \(^p\)Verweij, J.
Response criteria for solid tumours

- Response based on changes to sum of the longest diameters of target lesions
  - Longest diameter irrespective of shape change subsequently
  - Nodes: short axis NOT longest dimension

- Changes in burden of non-target lesions & non-measurable disease also taken into account
## RECIST 1.1: Response Assessment

<table>
<thead>
<tr>
<th><strong>Response criteria for evaluation of target lesions</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response (CR):</strong></td>
</tr>
<tr>
<td>Disappearance of all target lesions (TL). All nodes &lt;10 mm</td>
</tr>
<tr>
<td><strong>Partial Response (PR):</strong></td>
</tr>
<tr>
<td>&gt;30% decrease in the sum of TL diameters</td>
</tr>
<tr>
<td><strong>Stable Disease (SD):</strong></td>
</tr>
<tr>
<td>Neither PR nor PD</td>
</tr>
<tr>
<td>** Progressive Disease (PD):**</td>
</tr>
<tr>
<td>&gt; 20% increase in the sum of TL diameters</td>
</tr>
<tr>
<td>Absolute increase of at least 5 mm</td>
</tr>
<tr>
<td>Any new lesion = progressive disease</td>
</tr>
</tbody>
</table>

RECISt 1.1: Response Assessment

Target lesion

Node: Short axis: 2.5cm

Non-target lesion

Node: Short axis: 1.0-1.5cm

Baseline

Sum of maximal diameter = 2.5 cm
RECIST 1.1: Response Assessment

Target lesion
Node: Short axis: 1.0 cm

Non-target lesion
Node: Short axis: <1.0 cm

Post 2 cycles
% change: 2.5 - 1 / 2.5 * 100 = 60% decrease

Partial Response
RECIST 1.1: Response Assessment

Baseline

Sum of maximal diameter = 12.9 + 8.3 = 21.2 cm
Post 2 cycles
Sum of maximal diameter = 12.1 + 11.3 = 23.4
% change = (23.4 - 21.2) / 21.2 * 100 = 10% increase
Stable Disease
RECIST 1.1: Response Assessment

Sum of max diameters = 7.5 + 4.5 + 2.4 = 14.4
RECIST 1.1: Response Assessment

Post 2 cycles

Sum of max diameters = 10.5 + 4.7 + 3.6 = 18.8
RECIST 1.1: Response Assessment

Post 2 cycles

% change = \frac{18.8 - 14.4}{14.4} \times 100 = 30.6 \text{ increase}\%
RECIST 1.1: Response Assessment

Baseline

Post 2 cycles

Non Measurable Disease: Increase

Progressive Disease
RECIST 1.1 Assessment

Does it work in practice?

- Imaging established & widely available in the clinic
- High patient acceptability
- Reproducible
- Response categorisation clinically meaningful & reflects clinical outcome
Imaging Evaluation: Limitations

- May not reflect changes in z-axis
- Uni & bi-dimensional measurements are adequate surrogates for changes in tumour volume only if these changes occur in a spheroid manner

Change in uni, bi-dimensional measurements & volume: 0.4%, 24.4%, & 33.2%

From: Zhao et al. JNM 2009
Imaging Evaluation: Limitations

Background changes may make response evaluation difficult:
Schirrous change in liver
Imaging Evaluation: Limitations

Target lesions: Change in other morphological characteristics are not part of categorisation
Baseline

Post Tyrosine Kinase Inhibitor

RECIST RESPONSE: STABLE DISEASE 12.7 to 12.1cm
# Response Assessment: Beyond RECIST

<table>
<thead>
<tr>
<th>Response criteria</th>
<th>Based on</th>
<th>Tumour type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified RECIST</td>
<td>Size (Arterial phase)</td>
<td>HCC</td>
</tr>
<tr>
<td>EASL</td>
<td>Size (Arterial phase)</td>
<td>HCC</td>
</tr>
<tr>
<td>Crabb</td>
<td>Size &amp; cavitation</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Lee</td>
<td>Size &amp; cavitation</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Choi</td>
<td>Size &amp; enhancement</td>
<td>GIST</td>
</tr>
<tr>
<td>Modified Choi</td>
<td>Size &amp; enhancement</td>
<td>Renal cell cancer</td>
</tr>
<tr>
<td>MASS/SACT</td>
<td>Size &amp; enhancement</td>
<td>Renal cell cancer</td>
</tr>
<tr>
<td>PERCIST</td>
<td>Size &amp; metabolic response</td>
<td>All</td>
</tr>
</tbody>
</table>

Ongoing work on validation in clinical trials
Cavitation is taken into account & subtracted from the total diameter


From: Nishino et al. AJR 2012; 198:737–745
# Size & enhancement: Choi & Modified Choi Criteria

<table>
<thead>
<tr>
<th>Response Criteria</th>
<th>Partial Response</th>
<th>Stable Disease</th>
<th>Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RECIST</strong></td>
<td>&gt;30% size reduction</td>
<td>&lt;30% size reduction or &lt;10% size increase</td>
<td>&gt;10% size increase</td>
</tr>
<tr>
<td><strong>Choi</strong></td>
<td>&gt;10% size reduction OR &gt;15% attenuation reduction</td>
<td>&lt;10% size reduction OR &lt;15% attenuation reduction</td>
<td>&gt;10% size increase &amp; does not meet attenuation criteria of PR New lesions</td>
</tr>
<tr>
<td><strong>Modified Choi</strong>*</td>
<td>&gt;10% size reduction AND &gt;15% attenuation reduction</td>
<td>&lt;10% size reduction AND &lt;15% attenuation reduction</td>
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*Nathan et al. Cancer Biol Ther. 2010;9:15-9*
Size change 29%, density change 71%
SD by RECIST & PR by Choi & modified Choi criteria
Size & metabolic response:
PET response criteria

From RECIST to PERCIST: Evolving Considerations for PET Response Criteria in Solid Tumors

Richard L. Wahl¹,², Heather Jacene¹, Yvette Kasamon², and Martin A. Lodge¹

¹Division of Nuclear Medicine, Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland; and
²Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland

MRI: T1 + contrast

$^{18}$F-FDG PET

Rate metabolic response is achieved reflects cell kill:
> $10^7$ cells lower limit of PET detection
PERCIST

PERCIST 1.0

1. Measurable target lesion is hottest single tumor lesion SUL of “maximal 1.2-cm diameter volume ROI in tumor” (SUL peak). SUL peak is at least 1.5-fold greater than liver SUL mean + 2 SDs (in 3-cm spherical ROI in normal right lobe of liver). If liver is abnormal, primary tumor should have uptake > 2.0 x SUL mean of blood pool in 1-cm-diameter ROI in descending thoracic aorta extended over 2-cm z-axis.

2. Tumor with maximal SUL peak is assessed after treatment. Although typically this is in same region of tumor as that with highest SUL peak at baseline, it need not be.

3. Uptake measurements should be made for peak and maximal single-voxel tumor SUL. Other SUV metrics, including SUL mean at 50% or 70% of SUV peak, can be collected as exploratory data; TLG can be collected ideally on basis of voxels more intense than 2 SDs above liver mean SUL (see below).

4. These parameters can be recorded as exploratory data on up to 5 measurable target lesions, typically the 5 hottest lesions, which are typically the largest, and no more than 2 per organ. Tumor size of these lesions can be determined per RECIST 1.1.

- **Complete Response:** Disappearance of all disease
- **Partial Response:** >30% decrease FDG SUL\text{peak} (AND -0.8 SUL units), <30% size increase & no new sites
- **Stable disease:** Neither PR not PD
- **Progressive Disease:** >30% increase FDG SUL\text{peak} (AND +0.8 SUL units), increase in TLG volume, new lesions
EORTC PET Response Criteria

- **Complete Response:**
  Disappearance of all uptake

- **Partial Response:**
  >25% decrease FDG SUV_{mean} A reduction in the extent of the tumour [18F]-FDG uptake is not a requirement for partial metabolic response

- **Stable disease:**
  Neither PR not PD

- **Progressive Disease:**
  >25% increase FDG SUV_{mean} visible increase in the extent of [18F]-FDG tumour uptake (20% in the longest dimension) or the appearance of new [18F]-FDG uptake in metastatic lesions

Complete Metabolic Response
Partial Metabolic Response
# Role of Imaging

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  - Safety | - Large no. of patients  
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- Exploratory imaging biomarker of drug efficacy
What Determines Choice of Imaging Method?

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<td></td>
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- Purported mechanism of action of drug
- End points being collected
- Appropriateness of imaging method
  - Technical issues: Reproducibility, etc.
  - Local expertise
  - Cost
What Can We Measure?

- Cellular metabolism
- Vascularization
  - Perfusion
  - Angiogenesis
  - Hypoxia
- Cellular proliferation, differentiation, survival & apoptosis

FDG

$H_2O$
Integrin
F-MISO
Cu-ATSM

DCE-CT
DCE-MRI
ISW-MRI

Choline
FLT
(Annexin)

DW-MRI
1H-MRS

1H-MRS
Cellular Metabolism

FDG PET/CT
Assessment of cellular metabolism

- Change from oxidative phosphorylation to glycolysis may occur despite adequate oxygen supply in tumours
- Upregulation of glucose transporter protein in tumours

Perfusion & Angiogenesis

Water PET:
Provides information regarding perfusion

Integrin (αvβ3) PET: ¹⁸F-Galacto-RGD
Provides information of the degree of tumour angiogenesis

DCE-MRI and DCE-CT
Parameters indirectly reflect perfusion, hypoxia & the functioning microvasculature
Hypoxia

Hypoxia PET
Provides information of the level of perfusion & tumour oxygenation

\(^{18}\)F-fluorimidazole (F-MISO) PET
\(^{64}\)Cu-ATSM PET

Intrinsic susceptibility weighted MRI
Sensitive to paramagnetic deoxyhemoglobin in red blood cells in perfused vessels

Provides information of red cell delivery & level of blood oxygenation
Proliferation
Apoptosis

3´-deoxy-3´-¹⁸F-fluorothymidine (FLT) PET
Informs on active DNA synthesis

Annexin-PET
Informs on apoptosis.
¹²⁴I-labelled or ¹⁸F-labelled annexin
Have showed potential in animal studies
Proliferation
Apoptosis

**Diffusion weighted MRI**
Assessment of water diffusion
Informs on cell density, extracellular space tortuosity & integrity of cellular membranes

**1H-MRI Spectroscopy**
Informs on cell density, & cellular membrane turnover

**Common metabolites:**
Choline: cell membrane synthesis & degradation
Free Lipids: necrosis & apoptosis

Choline: 3.2ppm
Water: 4.7ppm
Lipid: 0.9-2.2ppm
Imaging Signatures

Pre therapy

Post therapy
Multi-modality approaches

PET/CT acquisition

Dynamic contrast enhanced helical acquisition

Single combined examination
Multi-modality approaches

Vascular – metabolic relationship
## Imaging Response

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Response</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Tumour Size Change</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vascular Response</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cellular Response</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Overall response</td>
<td>Responder</td>
<td>Functional Responder</td>
<td>Partial Functional responder</td>
<td>Non-responder</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Good</td>
<td></td>
<td></td>
<td>Poor</td>
<td></td>
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</table>
Functional Mapping of Heterogeneity in Treatment Response

Changes in Tumour Heterogeneity

Primary rectal cancer
Challenges for Novel Imaging Methodologies in Clinical Trials

- Novel imaging biomarkers
  - Increasing number available
  - Challenges for translation
    - Technical validation
    - Biological validation
  - Validation as a trial end point
  - Health economic evaluation

- Single expert Centre
- Several key Centres
- Multiple Centres
Challenges for Novel Imaging Methodologies in Clinical Trials

Validation of novel imaging methodologies for use as cancer clinical trial end-points

D.J. Sargent\textsuperscript{a,*}, L. Rubinstein\textsuperscript{b}, L. Schwartz\textsuperscript{c}, J.E. Dancey\textsuperscript{d}, C. Gatsonis\textsuperscript{e}, L.E. Dodd\textsuperscript{b}, L.K. Shankar\textsuperscript{b}

Criteria necessary prior to definitive evaluation studies
Technology stable & broadly available
Imaging acquisition parameters specifiable
Normal ranges defined
Standardised interpretation
Documented reproducibility

Sargent et al. EJC 2009
Challenges for Novel Imaging Methodologies in Clinical Trials

Validation of novel imaging methodologies for use as cancer clinical trial end-points

D.J. Sargent\textsuperscript{a,*}, L. Rubinstein\textsuperscript{b}, L. Schwartz\textsuperscript{c}, J.E. Dancey\textsuperscript{d}, C. Gatsonis\textsuperscript{e}, L.E. Dodd\textsuperscript{b}, L.K. Shankar\textsuperscript{b}

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<tr>
<th>Attribute</th>
<th>Early phase validation</th>
<th>Late phase validation</th>
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<tr>
<td>Goal</td>
<td>Individual patient level outcome prediction</td>
<td>Trial level outcome prediction</td>
</tr>
<tr>
<td>Setting</td>
<td>Single randomised trials or uniformly treated patients from non-randomised trials</td>
<td>Meta-analysis of randomised clinical trials</td>
</tr>
<tr>
<td>Methods</td>
<td>Correlation analyses between end-points within patients</td>
<td>Correlation analyses between trial level effects on both end-points</td>
</tr>
</tbody>
</table>

For an imaging end point to serve as an early accurate indicator of promising treatment effect it needs to correlate with Phase III end points i.e. PFS, OS

Sargent et al. EJC 2009
Summary

- Imaging has an important role in clinical trials
- Objective response assessment; trial end point
- RECIST 1.1 remains the international standard for response assessment
- Other response criteria may be appropriate but require further validation
- Imaging biomarkers may have a role in early phase clinical trials as a PD tool
- Challenges remain to implementation of novel imaging biomarkers
Case Example: CA4P

- *Combretum caffrum*
- Bark of the African Bush Willow tree
- Used as a tonic, as well a poison for Zulu spears
CA4P Mechanism

Vascular disrupting agent
Selective to immature tumour vessels

- Rapid change in endothelial cell shape
- Increase in permeability
- Further increase of already high interstitial fluid pressure
- Vascular collapse and shutdown
CA4P Mechanism

Control
1hr
24hr

Blood flow (ml/g/min)

untreated tumors

CA-4-P treated tumors

Tozer et al. Cancer Res 1999
Biologically active dose 52 mg/m²

MTD 88 mg/m²

DLT 114 mg/m²

19 patients; 4 & 24 hours after 1st dose of CA4P

Fig 4. Absolute change in tumor $\log_{10} K^{\text{trans}}$ 4 and 24 hours after the first dose of combretastatin A4 phosphate for patients in the phase I trial.
Phase I – Toxicities\textsuperscript{a}

- DLT – reversible ataxia at 114mg/m\textsuperscript{2}, vasovagal syncope and motor neuropathy at 88mg/m\textsuperscript{2}
- Other toxicities – tumour pain, dyspneoa, hypertension, QTc prolongation

\textsuperscript{a} Rustin et al
Phase 1B study: CA4P & RT

- Rationale:
  - Potential synergy between CA4P and RT
  - CA4P targets blood vessels at the centre of the tumour
  - RT can target well vascularised viable tumour blood vessel at the tumour periphery
  - Non-overlapping toxicity
| Cohort | Dose | M | T | W | Th | F | S | S | M | T | W | Th | F | S | S | M | T | W | Th | F | S | S | M | T | W | Th | F | S | S | M | T | W |
| 1      | NSCLC| R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| 2      | NSCLC| R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| 3      | Prostate| R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| 4      | Prostate| R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| 5      | Prostate| R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| 6      | NSCLC| R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |
| 7      | SCCHN| R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R | R |

C, CA4P treatment; CA4P, combretastatin-A4-phosphate; NSCLC, non-small-cell lung cancer; R, radiation treatment; SCCHN, squamous cell carcinoma of the head and neck.

n=39 received 121 doses of CA4P
DLTs at 63 mg/m2
No additional toxicity when administered with RT
Baseline

Contrast enhanced CT  Blood Volume  Vessel Permeability

4 hours post administration vascular disrupting agent