Evolution of Response Evaluation in Oncology Trials

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Welcome & Introductions

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What We’ll Cover Today

• A Brief History and Overview of Response
• The Principles of Response Evaluation
• Response Evaluation Criteria (solid tumours)
• The Future of Response Evaluation
• Q&A
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Introduction

- Response evaluation necessary in clinical trial and practice
- Response in solid tumors done radiologically
- Response evaluation evolved over time
  - Reliability of data
  - Advances in radiological technique
  - Changes in mechanism of action drugs
- Covering only solid tumors
A Brief Overview
## Overview

<table>
<thead>
<tr>
<th>Year</th>
<th>Criteria</th>
<th>Technology</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>WHO</td>
<td>X-Ray/CT</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>2000</td>
<td>RECIST 1</td>
<td>CT MRI</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>2009</td>
<td>RECIST 1.1</td>
<td>CT MRI</td>
<td>Targeted Therapy</td>
</tr>
<tr>
<td>2009</td>
<td>PERCIST</td>
<td>PET</td>
<td>Targeted Therapy</td>
</tr>
<tr>
<td>2009</td>
<td>irRC</td>
<td>PET CT MRI</td>
<td>Immuno</td>
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</tbody>
</table>
Overview

Other Cancer Response Criteria

- Prostate
- EASL, mRECIST, RECICL
- RENO & iRENO
- CHOIR
- Mesothelioma
- Ovary
- Ovary
The Principles of Response Evaluation

• Quantitative evaluation of measurable lesions
• Qualitative evaluation of not measurable lesions
• Before and at regular intervals
• Same methods of investigation
• Four categories:
  o Complete response (CR)
  o Partial response (PR)
  o Stable disease (SD)
  o Progressive disease (PD)
• CR PR to be confirmed
Response Criteria
Pre-WHO

- Moertel and Hanley evaluated tumor size by palpation
- High false tumor deduction in 19-25% cases
- Recommended true tumor response to be >50%
- 25% reduction in product of diameters as a response
- 50% reduction as a significant reduction in size
WHO Criteria (1979)

• Unavailability of CT scan. Tumor measurements by palpation x-ray
• Sum of Bi-dimensional measurement (greatest perpendicular dimensions)
  o **CR**: Complete disappearance for at least 4 weeks
  o **PR**: 50% or greater reduction from baseline confirmed at 4 weeks
  o **No change**
  o **PD**: At least 25% increase or new lesion

Limitations:-
• PD with can occur with 11% increase in each dimension
• Not explicit on no of tumor foci to be measured
• How small a lesion could be measured
RECIST (2000)

• Up to 10 target lesions to assess
• Transaxial imaging with CT
• Only sum of single longest dimension
• Minimum size of the lesions 1 cm
• “Target” and “non-target” lesions
• Response
  o **CR:** Disappearance of all tumor for at least 4 weeks
  o **PR:** At least 30% decrease for at least 4 weeks
  o **SD:** Neither PR nor PD
  o **PD:** At least a 20% increase from nadir of new lesion
Comparing WHO and RECIST

20% Increase
is 44% increase in the bi-dimensional

Less Frequent PD using RECIST than WHO

Time to PD can be shorter with WHO
Limitations with RECIST

- Is assessing less than 10 lesions adequate?
- Phase III trials has OS as endpoints
- Use of FDG-PET and MRI
- Assessment of lymph nodes?
- Response confirmation is truly needed?
- Applicability for targeted non-cytotoxic drugs
- Volumetric or functional assessment?
RECIST 1.1 (2009)

- Longest dimension for tumour and short axis for lymph nodes
- Minimum measurable lesion size
  - Long axis $\geq 10$ mm (CT + MRI) and 2x slice thickness
  - Long axis $\geq 20$ mm on chest x-ray
  - Lymph Nodes: Short Axis $\geq 15$ mm
- Up to 5 target lesions total, 2 per organ
- **PD:** Same but the increase should also be at least 5 mm from nadir
  - Non-measurable assessment: substantial worsening
- **PET:** May for PD, confirmation of CR
- Confirmation of PR or CR Only for non-randomized trials with ORR as endpoint
Definition of Nontarget = Nontarget Lesions

• Small lesions and not qualifying as Target Lesions

• Truly non-measurable lesions:
  o Bone lesions
  o Leptomeningeal disease
  o Pleural/pericardial effusion and ascites
  o Inflammatory breast disease
  o Lymphagitis
  o Cystic lesions
Also Worth Noting...

- Patients with measurable disease should be included in protocols with ORR
- Select largest reproducibly measurable lesions
- To record multiple non-target lesions of same organ as a single item
- Lesions with prior local treatment not as (unless PD)
- Osteolytic lesions (soft tissue component)
- Lesions that split or coalesce on treatment
- Additional requirement for PD
  - Also a $\geq 5$ mm absolute increase in the SLD
  - Non-target – representative of change in overall tumour burden
## RECIST 1 vs. RECIST 1.1

<table>
<thead>
<tr>
<th></th>
<th>RECIST 1</th>
<th>RECIST 1.1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumour Burden</strong></td>
<td>10 Targets (5 per organ)</td>
<td>5 Targets (2 per organ)</td>
</tr>
<tr>
<td><strong>Lymph Nodes</strong></td>
<td>Like any other lesion</td>
<td>Short axis, defined Nr size</td>
</tr>
<tr>
<td><strong>PD Definition</strong></td>
<td>20% Increase in SLD</td>
<td>20% Increase in SLD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mm absolute increase</td>
</tr>
<tr>
<td><strong>Non-Measurable PD</strong></td>
<td>Unequivocal</td>
<td>More details</td>
</tr>
<tr>
<td><strong>Confirmation</strong></td>
<td>Required for CR &amp; PR</td>
<td>Required in non-randomised trials with RR as 1ry endpoint</td>
</tr>
<tr>
<td><strong>New Lesions</strong></td>
<td></td>
<td>Section on FDG-PET</td>
</tr>
</tbody>
</table>
Common Mistakes Made in RECIST 1.1

1. Assignment of non-qualifying lesions (number, size etc.)
2. Measurement of irregular, non-reproducible targets
3. Inclusion of bone metastases
4. Evaluation of cystic/necrotic tumor changes
5. Reappearing lesions as PD
6. Baseline/Nadir as reference for PD
7. Inconsistencies in follow-up
Limitations of Anatomic Response Criteria

- Cytostatic drugs with longstanding stable disease
- OS benefit with limited antitumor size seen in hepatomas treated by sorafenib
PET Response Criteria in Solid Tumors (PERCIST)

• 18F-FDG PET for tumor response of breast cancer in 1993
• PET can detect cancers that are smaller than depicted on CT
• The EORTC PET proposed in 1999 and PERCIST 1.0 in 2009
• Response is assessed as continuous variable as % SUL peak (or sum of lesion SULs)
• **CR:** Disappearance of all metabolically active tumors
• **PR:** <30% and 0.8 unit decline in SUL peak between the most intense lesions (not necessarily the same lesion)
• **PD:** >30% and 0.8 unit increase in SUL peak or new lesions or >75% increase in total lesion glycolysis
Ipilimumab Trials Have Shown:

SD and then decrease in tumour mass

PD (increase and/or new lesions) followed by response or SD

May take longer

Discontinuation of therapy unless PD is confirmed

Allowance for “clinically insignificant” PD is recommended

Durable SD may represent antitumor activity

RECIST may not do justice to Immuno-Oncology Drugs
Immune Related Response Criteria (irRC)

- Assessment as a continuous variable (lesions at baseline or new)
- Only measurable lesions with bidimensional measurement
- Sum of the perpendicular diameters (SPD) at baseline is added to new lesions to calculate total tumor burden
- Response categories (irCR, irPR, irSD, and irPD) same as WHO
- New lesions alone is not irPD (if not >25% add to tumor burden)
- New lesions but overall tumor burden decrease = irPR (50% decrease) or irSD (<50% decrease to >25% increase)
To Revisit...

Other Cancer Response Criteria

- RENO & iRENO
- Mesothelioma
- Ovary
- Bone Mets
- Prostate
- Choi
- EASL, mRECIST, RECICL
RANO Criteria for High-Grade Gliomas

- Macdonald (1990) response criteria for high-grade gliomas
- Based on CT scan (like WHO), corticosteroids use and changes in the neurologic status
- Pseudoprogression (20%) following TMZ/RT→TMZ
- PD after 3 months post t/t unless new lesion, patho confirmation
- RANO permits PD to continue t/t pending follow-up imaging
<table>
<thead>
<tr>
<th></th>
<th>RANO</th>
<th>iRANO (&lt;6m of t/t)</th>
<th>iRANO (&gt;6m of t/t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is repeat scan required to confirm PD w/o significant change in clinical?</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Minimum time to confirm PD (clinically stable)</td>
<td>N/A</td>
<td>&gt;3m</td>
<td>N/A</td>
</tr>
<tr>
<td>If further immno t/t allowed after initial PD (if clinically stable) pending PD confirmation</td>
<td>N/A</td>
<td>✓</td>
<td>N/A</td>
</tr>
<tr>
<td>Dose a new lesion define PD</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
</tbody>
</table>
MDA Criteria for Bone Metastasis

• Bone mets non-measurable in WHO and RECIST
• Hamaoka (2004) using X-ray (XR), CT, MRI, or Skeletal scintigraphy and SPECT Scans (supportive)
• Recommended follow up imaging every 2-6 months
• CR: Complete fill-in or sclerosis of lytic lesion, normalization of osteoblastic lesion
• PR: Sclerotic rim about initially lytic lesion or sclerosis of previously undetected lesion, partial fill-in or sclerosis of lytic lesion or regression of measurable lesion, decrease in blastic lesion
• Every lesion need not regress, but no lesion should have progressed
• WHO criteria are retained
Choi Criteria for Gastrointestinal Stromal Tumor

- **RECIST 1.0** significantly underestimated initial tumor response to imatinib in GISTs.
- Significant changes in tumor density, enhancing intratumoral tumor nodules, and tumor vessels was noted.
- Choi criteria used a combination of the values of tumor size and tumor density on CT scan.
- **CR**: Disappearance of all lesions, no new lesions.
- **PR**: Decrease in size of 10% or a decrease in tumor density 15% on CT.
- **SD**: No change.
- **PD**: Increase in tumor size of 10% or new lesions or new intra-tumoral nodules or increase in the size of the existing intra-tumoral nodules.
Choi Criteria for Gastrointestinal Stromal Tumor

• Rules for definitions of lesions, measurement rules, calculation rules, response determination rules, reporting guidelines were not reported

• Also used in metastatic renal cell carcinoma, high grade soft tissue sarcoma, solitary fibrous tumor and hepatocellular carcinoma response evaluation
Hepatocellular Carcinoma: EASL, mRECIST, RECICL

- Simple bi-dimensional determinations as tumor necrosis is not accounted
- European Association for the Study of Liver (EASL) criteria is based on WHO criteria
- American Association for the Study of Liver Disease (AASLD) modifying RECIST
- Liver Cancer Study Group of Japan proposed revisions to Response Evaluation Criteria in Cancer of the Liver (RECICL)
- Tumors are measured in two dimensions, and the dense accumulation of lipiodol is regarded as necrosis
- 3 tumor markers including alpha-fetoprotein, AFP-L3 and des-gamma-carboxy protein (DCP) were also added
Prostate Ca (PCWG2 Criteria)

• Limitations with RECIST:
  o Bone scans have shown PD far more quickly
  o Uncertainty of interpreting the significance of PSA change
  o Approvals for CRPC drugs on reduction in skeletal-related events
• For soft-tissue disease in nodes and/or viscera follow RECIST
• PSA progression as an increase of >25% or increase of >2 ng/mL from nadir
• PSA decline to be confirmed by 3 or more weeks later
• PSA progression alone is not an indication to stop treatment
• Bone scan progression as either:
  o Two new lesions noted on the first on-treatment scan followed by two additional lesions on the next scan
  o Or two new lesions seen on any scan after the first on-treatment scan that are confirmed on a subsequent scan
Malignant Pleural Mesothelioma

• Typically demonstrates a non-spherical growth pattern
• Difficult to document tumour response by RESIST
• New functional imaging techniques, such as PET, diffusion-weighted MRI and dynamic contrast-enhanced MRI (DCE-MRI) improve assessment
Ovarian Cancer

• Gynecologic Cancer Intergroup (GCIG) criteria
• PD on basis of either RECIST criteria or CA 125 criteria
• Doubling in CA 125 from the upper limit of normal reliably predicts objective progression
IN CONCLUSION

The Future of Response Evaluation

Use of continuous, as opposed to discrete, sets of response

Individualized medicine era (type of cancer and the patient)

Tumor response criteria should be based on treatment and type of tumor

Validation of functional biomarkers like FDG PET to prove correlation with OS
Questions?

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