Assessing Immunotherapy Response and Progression

Apisada Suthepwanon, MD
Medical oncology, Division of medicine,
Vajira hospital, Navamindradhiraj university
Objectives

- Response evaluation criteria for chemotherapy
- Immunotherapy
  - Pattern of response e.g. pseudoprogression, hyperprogression
  - Response evaluation criteria e.g. irRC, irRECIST, iRECIST
• Importance of measuring tumor & determining response criteria
  - for making appropriate medical decision
  - for comparing clinical trial data, pooling databases
History of standard criteria for making a radiological tumor evaluation:

1981
• WHO response criteria (measuring all visible lesions in two dimensions)
• It is quite complex: time-consuming and risk of error

1994
• A large international working group was established to review guidelines
• Discussion and analysis of many large clinical trials (>6,500 pts)
• Conclusion: unidimensional tumor measurements provide results equivalent to bidimensional criteria and finally recommended other simpler new guidelines

2000
• Response Evaluation Criteria in Solid Tumors (RECIST) criteria
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RECIST</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response (OR)</td>
<td><strong>Target lesions</strong> change in sum of LDs, maximum 5 per organ up to 10 total (more than one organ)</td>
<td><strong>Measurable disease</strong> change in the sum of the products of LDs and greatest perpendicular diameters, no maximum number of lesions specified</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>Disappearance of all target lesions, confirmed at ≥ 4 weeks</td>
<td>Disappearance of all known disease, confirmed at ≥ 4 weeks</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>≥ 30% decrease from baseline, confirmed at ≥ 4 weeks</td>
<td>≥ 50% decrease from baseline, confirmed at ≥ 4 weeks</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>≥ 20% increase over smallest sum observed or appearance of new lesions</td>
<td>≥ 25% increase in one or more lesions or appearance of new lesions</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Neither PR nor PD criteria met</td>
<td>Neither PR nor PD criteria met (no change)</td>
</tr>
</tbody>
</table>
• However, multiple variations of guidelines still used across clinical trials
• RECIST working group: develop an updated version (RECIST 1.1) in 2009

• Main changes of RECIST 1.1 included:

  • Number of lesions to be assessed
    (10 lesions, 5 per organ □ 5 lesions, 2 per organ)

  • Assessment of pathological lymph nodes
    (not mentioned □ ≥ 15mm short axis for target, ≥10 to <15 mm for non-target)

  • Confirmation of response
    (CR, PR confirmed at 4 weeks □ confirmation is eliminated but only for non-randomized trial with primary endpoint of response)
Immunotherapy

• Immune checkpoint blocking antibodies can exhibit a significant activity by restoring an efficient antitumor T-cell response

• Now approved in various tumor types such as melanoma, NSCLC (squamous & nonsquamous), RCC, head & neck cancer, bladder cancer, and Hodgkin lymphomas

• Patterns of response to immune checkpoint inhibitor: differ from chemotherapy and molecularly targeted agents

Hypotheses might explain phenomenon of pseudo-progression:
IO drug initially induce the recruitment of activated T cells to tumor site before they have any tumor activity, which lead to an artificial increase in tumor size.
Assessment of Response to Immunotherapy by Radiographic Criteria

For immunotherapy,

• RECIST criteria resulted in premature discontinuation of therapy in patients with pseudo-progression

• Need for other criteria
Immune-specific related response criteria (irRC)

In 2009, irRC (bidimensional measurement similar to WHO criteria)

- Immune-related complete response (irCR; complete disappearance of all lesions)
- Immune-related partial response (irPR; reduction of ≥ 50% in disease burden)
- Immune-related stable disease (irSD; neither irCR nor irPR criteria met)
- Immune-related progressive disease (irPD; increase of ≥ 25% relative to nadir)

- Total 15 lesions (10 visceral, 5 cutaneous)
- Confirmation: 4 weeks from the first documented response
As expected, disadvantage of irRC:

• Bidimensional measurements were subject to variability in responses compared with unidimensional measurements

• In 2013, revised irRC using unidimensional measurements
Immune-related RECIST (irRECIST)

• In 2014, irRECIST (unidimensional measurement similar to RECIST) consisted of

  • irCR: disappearance of all target and nontarget lesions

  • irPR: decrease of ≥ 30% in tumor burden compared with baseline and no unequivocal progression in nontarget lesions

  • irSD like other response criteria, is neither CR or PR

  • irPD: increase of ≥ 20% in total measurable tumor burden from nadir, with a minimum of 5 mm of progression of nontarget lesions, or appearance of a new lesion

  • irPD will be confirmed at least 4 weeks and up to 12 weeks later
• However, many immunotherapy trials:
  • RECIST1.1 for primary & secondary endpoints
  • irRC/ revised irRC/ irRECIST or variant for exploratory endpoints
  • irRECIST had many variability in period of time to reassess

• Leading to concerns about
  • Comprability of data and results across trials
  • Difficulty with pooling databases
  • Poor clarity about new lesions (how many, incorporated into tumor burden?)

• In March 2017, RECIST working group and immunotherapy subcommittees was published a consensus guideline named immunotherapy RECIST (iRECIST)
Immunotherapy RECIST (iRECIST)

- iRECIST as a modified RECIST1.1 for immuno-oncology treatment

- To provide a consistent framework for management of data collected in clinical trial of immune-based therapy

- Not intended to define or guide clinical practice (treatment decisions rest with patient and their health care team)

- Definitions of measurable and non-measurable disease, as well as target and nontarget lesions: unchanged from RECIST1.1
• Terminology: a prefix of “i”

- immune complete response (iCR)
- immune stable disease (iSD)
- immune partial response (iPR)
- immune unconfirmed progressive disease (iUPD)
- immune confirmed progressive disease (iCPD)
• iUPD as PD in RECIST1.1,

• After iUPD, repeat scan must be performed at least 4 weeks but not more than 8 weeks, to ensure that patients remain fit for salvage therapies

• If target lesion is iUPD □ next timepoint response can be
  
<table>
<thead>
<tr>
<th>iCPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Existing iUPD “get worse”: ↑≥5 mm of SOM of target lesion from iUPD</td>
</tr>
<tr>
<td>Lesion category without iUPD now meet PD in RECIST1.1: ↑ non-target lesion or new lesion</td>
</tr>
<tr>
<td>= True progression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>iUPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(can be named multiple times in a patient on one therapy)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>iCR, iPR, or iSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(from baseline)</td>
</tr>
</tbody>
</table>

• If non-target lesion is unequivocal progression = iUPD

• Confirming iCPD

  • Existing iUPD “get worse”: ↑ non-target lesion

  • Lesion category without iUPD now meet PD in RECIST1.1: ↑ SOM of target lesion (≥ 20% of SOM from baseline) or new lesion
• If a new target lesion is identified in iUPD:
  - Not added to SOM
  (but included in separate iSOM, using RECIST1.1 principles)

<table>
<thead>
<tr>
<th>iRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measurement</strong></td>
</tr>
<tr>
<td><strong>Confirming iCPD</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Ex. Case NSCLC receiving anti-PDL1</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>- A lung mass 4 cm,</td>
</tr>
<tr>
<td>- Two liver nodules: 1 cm and 1.5 cm</td>
</tr>
<tr>
<td>- Clinical stable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOM (mm)</th>
<th>65</th>
<th>65</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>iSOM (mm)</td>
<td>45</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>iUPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iCPD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary: confirming of iCPD

Considered 3 parts e.g. target lesion, non-target lesion and new lesion

- PD according to RECIST1.1 (iUPD) + next 4-8 weeks
- PD of target lesion according to RECIST1.1 (iUPD) + next 4-8 weeks
- PD of new target lesion according to RECIST1.1 (iUPD) + next 4-8 weeks

\[ \text{PD of target lesion according to RECIST1.1} \]
\[ \geq 5 \text{ mm of SOM from iUPD} \]
\[ \text{PD of new target lesion according to RECIST1.1} \]
\[ \geq 5 \text{ mm of iSOM from iUPD} \]

\[ \text{PD according to RECIST1.1} = \text{iCPD} \]
\[ \text{PD of target lesion according to RECIST1.1} = \text{iCPD} \]
\[ \text{PD of new target lesion according to RECIST1.1} = \text{iCPD} \]
• The event date to be used for calculation of iPFS (Date of iProgression) = the first date at which progression criteria are met (ie, the date of iUPD) provided that iCPD is confirmed at next assessment.

• If progression is not confirmed due to any reason (e.g. stop treatment because of clinical unstable, no reassessment because of patient refusal, protocol noncompliance, or patient death), then iUPD date can be used.

Ex.
1. Baseline □ iUPD □ iCPD
2. Baseline □ iUPD □ iPR □ iUPD □ iCPD
3. Baseline □ iUPD □ death
In adjuvant trials of immunotherapy after curative surgery:

• Suspected new lesions should always be investigated e.g. biopsy

• If biopsy is not technically feasible, then iRECIST can be used (follow-up scan to confirm relapse)
Incidence of Pseudo-progression?
### Table: Rates of pseudo-progression in patients receiving PD-1/PD-L1 Inhibitors in selected phase II/III Clinical Trials

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Rate of Pseudoproggression, %</th>
<th>Number of patient of Pseudoproggression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab in melanoma (CheckMate 037)</td>
<td>8.3%</td>
<td>24 of 526</td>
</tr>
<tr>
<td>Nivolumab in squamous NSCLC (CheckMate 063)</td>
<td>3.4%</td>
<td>4 of 117</td>
</tr>
<tr>
<td>Nivolumab in RCC (CheckMate 025)</td>
<td>4.9%</td>
<td>20 of 406</td>
</tr>
<tr>
<td>Atezolizumab in NSCLC (OAK study)</td>
<td>3.6%</td>
<td>12 of 332</td>
</tr>
<tr>
<td>Atezolizumab in urothelial CA (phase II IMvigor210)</td>
<td>1.6%</td>
<td>5 of 310</td>
</tr>
</tbody>
</table>

• Most of patients were true progression

• Pseudo-progression had only about 2-4%

• Although early discontinuation of effective drug is not desirable, continued long-term treatment with non-effective drug past true progression might delay the next effective salvage therapy

• Continuation of IO treatment beyond iUPD should carefully selected patients whose clinical status have improved
Hyperprogression

- Some patients can experience progression rapidly and rapid clinical deterioration

**Definition:**
- Disease progression by RECIST with a 2-fold increase in tumor growth rate (TGR) upon treatment (experimental period) vs before treatment (reference period)
- Time to treatment failure less than 2 months

- Rate of hyperprogression: reported about 4% to 29%
• Natural history of hyperprogression remain unknown (cancer growth or immunotherapy-induced acceleration of tumor growth?)

• Not associated with higher tumor burden at baseline or with any specific tumor type

• Poor prognosis (unable to receive a subsequent potentially active treatment)
Future direction

• Need to identify predictive factors of pseudo-progression and hyperprogression

• Pseudo-progression or true disease progression:

  - Tumor biopsy at time of PD?
    (presence vs absence of tumor immune infiltration)

  - Circulating tumor DNA at baseline?
    (decrease in presence of pseudo-progression if ctDNA present)
• Hyperprogression was associated with
  - Older age
  - Recurrence in irradiated field in pts with H&N squamous cell cancer
  - MDM2/4 amplification
Conclusion

• Patterns of response of IO agent differ from chemotherapy, especially for disease progression pattern

• Management in patients who response to IO agent according to classic RECIST1.1 is similar to those treated with chemotherapy
Conclusion

• Rate of pseudo-progression: never exceeded 10% across tumor type

• Most progressions are real progression and not pseudo-progression

• Rate of hyperprogression: reported about 4% to 29%

Continuation of IO treatment beyond RECIST1.1-defined progression

“should be proposed only in carefully selected pts
whose clinical status have improved
(or stabilized in pts with rapid progression)
and no severe toxicity”

• By iRECIST, repeat scan performed at 4-8 weeks
For IO clinical trials, especially phase III trials,

- Recommend to use of both RECIST1.1 and iRECIST

- Recommend that primary outcomes such as PFS, OS should be based on RECIST1.1, especially planned for marketing authorization (allow comparison with reported IO trials or chemotherapy trials that have used RECIST1.1)

- Recommend that exploratory analyses should use iRECIST
<table>
<thead>
<tr>
<th></th>
<th>RECIST 1.1</th>
<th>iRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitions of measurable, non-measurable diseases</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Definitions of T and NT lesions</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Measurement and management of nodal disease</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Calculation of the sum-of-measurement (SOM)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Definitions of CR, PR, and SD, and their duration</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Definition of progression in T and NT</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Management of new lesions</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Time point response after RECIST 1.1 progression</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Confirmation of progression required</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Collection of reason why progression cannot be confirmed</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Inclusion and recording of clinical status</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Note: Validation of iRECIST is ongoing ☐ may result in update version?