IMMUNOTHERAPY: CLINICAL, IMAGING AND PATHOLOGICAL EVALUATION OF A NEW TREATMENT MODALITY FOR CANCER

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LEARNING OBJECTIVES / OUTCOMES

To demonstrate clinical, imaging and pathological aspects related to cancer immunotherapy, a novel treatment with emerging response patterns and immune-related adverse events.
IMMUNOTHERAPY

BACKGROUND

• **Passive immunotherapy** (preformed antibodies directed against tumor-associated antigens): bevacizumab, rituximab

• **Active immunotherapy** (modulates the immune system against tumor cells): cytokines, vaccines, monoclonal antibodies (ipilimumab, nivolumab)
TUMORAL RESPONSE IMAGING EVALUATION

- Chemotherapy guidelines: WHO, RECIST
- New lesions or tumor increase: progression
- New therapies: different response patterns
- Immunotherapy: tumor increase or even new lesions may represent response
- New criteria for tumor response
a) ↓ size without new lesions (~Chemo)
b) Clinically stable disease
c) Initial tumor ↑ (followed by tumor ↓)
d) New lesions (followed by tumor ↓)
TYPE A PATTERN OF RESPONSE
Tumoral size reduction, without new lesions
Type A response (tumor regression)

Squamous cell cancer in the RUL, pre and post treatment with immunotherapy
78 yo male with lung adenocarcinoma without clinical conditions for surgery. First line chemotherapy showed no response. Initiated treatment with Nivolumab.

Baseline
3 months
5 months

Type A response (tumor regression)
TYPE B PATTERN OF RESPONSE

Clinically stable disease

- Clinically stable disease
- Sometimes, long period of stability then a decline in tumor burden.
- Time while immune system mounts response

**TYPE C PATTERN OF RESPONSE**

Response after initial increase in total tumor volume

- Initial increase
- Then delayed tumor response
- Initial continued increase
  - before sufficient immune response
  - immune cell infiltration of the tumor

Lung adenocarcinoma

Immunotherapy

Baseline

6 weeks

10 weeks

Type C response (pseudoprogression)
Histological pattern of inflammation seen in cases of pseudoprogression

Type C response (pseudoprogression)

Courtesy of Dr. ES Mello, São Paulo, Brasil
TYPE D PATTERN OF RESPONSE

- in total tumor burden after the appearance of new lesions

- New lesions after treatment

- Then a decrease in tumor burden

- New lesions
  - Increased micrometastases because of immune cell infiltration

IMMUNOTHERAPY RESPONSE PATTERNS

- Complete response: all lesions disappear
- Partial response: decrease > 50%
- Progressive disease: increase > 25%
- Stable disease: other criteria not met
81 yo male with lung adenocarcinoma and brain metastasis. First line chemotherapy showed no response. Initiated treatment with Nivolumab.

Baseline

8 weeks

Type A response (tumor regression) – Partial response

Courtesy of Drs. A Calabrich, T Lessa and I Santana (Salvador, Brazil)
72 yo male with lung adenocarcinoma with EGFR and KRAS mutations. Evolved with failure of treatment after second line of chemotherapy. Iniciated Selumetinib associated with Docetaxel.
65 yo female with lung adenocarcinoma, being treated with nivolumab (3 cycles).
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Follow-up PET/CT, after 3 cycles of nivolumab Progression
Follow-up PET/CT, after 3 cycles of nivolumab (3 cycles).

65 yo female with lung adenocarcinoma, being treated with nivolumab (3 cycles).
IMMUNOTHERAPY RESPONSE ASSESSMENT

• New or enlarging lesions do not necessarily represent progression of disease immediately after completion of treatment.

• Imaging assessment of treatment response or disease progression after completion of treatment should be made with 2 consecutive follow-up imaging studies performed at least 4 weeks apart.
<table>
<thead>
<tr>
<th>WHO</th>
<th>irRC</th>
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<tbody>
<tr>
<td>New, measurable lesions (i.e., ≥5 × 5 mm)</td>
<td>Always represent PD</td>
</tr>
<tr>
<td>New, nonmeasurable lesions (i.e., &lt;5 × 5 mm)</td>
<td>Always represent PD</td>
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<tr>
<td>Non-index lesions</td>
<td>Changes contribute to defining BOR of CR, PR, SD, and PD</td>
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<tr>
<td>CR</td>
<td>Disappearance of all lesions in two consecutive observations not less than 4 wk apart</td>
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<tr>
<td>PR</td>
<td>≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions</td>
</tr>
<tr>
<td>SD</td>
<td>50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions</td>
</tr>
<tr>
<td>PD</td>
<td>At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)</td>
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IMMUNOTHERAPY COMPLICATIONS

• Adverse events are a result of the induction of autoimmunity or related to a pro-inflammatory state.

• Can occur early (after the 1st treatment), demonstrating that some patients may more be susceptible.

• The majority of adverse events occurs during the 12-week treatment induction period.

• Probably a positive correlation between response to treatment and development of adverse effects.

IMMUNOTHERAPY COMPLICATIONS

- Diffuse or segmental colitis (8 weeks): related to bad outcomes if severe
- Hepatitis (3-9 weeks)
- Dermatitis (3 weeks)
- Hypophysitis and thyroiditis (7-20 weeks)
- Organizing pneumonia and pneumonitis
- Autoimmune pancreatitis
- Sarcoid reaction

66 yo male with gastric adenocarcinoma. Started treatment with Pembroluzumab and had cough and fever during the 1\textsuperscript{st} cycle.

Baseline CT
Follow-up CT after the 1st cycle of pembroluzumab
Baseline CT
Organizing pneumonia in a patient being treated with immunotherapy

Baseline CT

11 weeks

15 days after therapy withdrawal
REFERENCES


CONCLUSIONS

• Advances in cancer immunotherapy challenge the current imaging approach for assessing cancer treatment response and treatment-related complications.

• Clinicians, radiologists and pathologists should be aware of these novel response patterns and immune-related adverse events in order to successful management of patients being treated with this new treatment modality.
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