Hyperprogression and Pseudoprogression with Immune Based Therapies:

Am I doing well or getting affairs in order?

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Presenter Disclosure

- **Faculty/Speaker:** Brady Anderson

- **Relationships with financial sponsors:**
  - **Grants/Research Support:** N/A
  - **Speakers Bureau/Honoraria:** N/A
  - **Consulting Fees:** Novartis – BRAF/MET dysregulated NSCLC treatment
  - **Other:** N/A

Mitigating Potential Bias

- Will not discuss BRAF or MET dysregulated lung cancer or proprietary tyrosine kinase inhibitors for this indication

Equity Commitment

- In preparing for this presentation, I have considered the Health Equity Resource for Presenters provided by the conference planning committee.

Learning Objectives

- 1. Be able to understand “Pseudoprogression” and “Hyperprogression” as concepts applying to your patients on treatment

- 2. Understand the clinical scenarios where pseudoprogression is more likely and differentiating between real disease progression.

Hyperprogression

- Poorly defined
  - Historically labelled as >50% disease burden from presentation to treatment (assuming no unreasonable delays)
- In Immunotherapy Era, described as “rapid” progression after starting IO therapy with no realized benefits

Hyperprogression

- Matos et. al. 2018
  - Retrospective review of 214 patients in pooled Phase I immune checkpoint inhibitor trials
  - 15% Hyperprogressive Disease (HPD) based on:
    - TTF < 2months and Increase in target lesion(s) of at least 10mm and increase in tumor burden of ≥40% or ≥20% with a new metastasis

- All retrospective data, doesn't prove HPD as this could be natural history of disease. Would need prospective randomization to a placebo group which is unethical given the significant benefit to most treatments in first line setting.

Hyperprogression

- Another review by Singavi et. al in 2017
  - 696 patients from molecular database
  - 5/696 met definition of HPD (0.72%)
  - 4/5 with HPD had amplifications of MDM2/4 and/or EGFR
    - Cohort reviewed for MDM2/4 and EGFR amplifications
      - 10/696 present

- Presence of objective higher frequency “HPD” in subgroup of patients with MDM or EGFR amplification
  - ++ Caution interpreting subgroup analysis of post hoc studies and database registries. Enough of association to explore further.

Hyperprogression

- Proposed mechanisms
  - F_c region mediated oncogenic signaling with mutant/overexpression EGFR
    - Mouse cell lines with xenograft NSCLC tx with Nivo (complete antibody) vs F_{ab} fragments only
      - F_{ab} did not induce HPD/rapid growth in the xenograft
  - Increased proportion of senescent CD4+ T_H cells
    - Correlation between increased proportion of senescent CD4+ and HPD/progressive disease
    - Lower proportion of senescent CD4+ after first checkpoint inhibitor associated with disease response

Hyperprogression

- Still poorly defined
- Likely exists, but may just be observation of the "bad behaviors" that comparatively do worse now that outcomes in general are better in many metastatic cancers
- Some postulates as to mechanisms at the molecular level may lead to novel strategies to increase responses/prime tissues for immune checkpoint inhibitors in the future

Pseudoprogression

- Historically seen in context of post chemoradiation for glioma
  - Resections for enlarging disease would show increased necrosis and decreased tumor viability
- Now seen uncommonly across a number of malignant settings secondary to immune checkpoint inhibition becoming standard of care in many places

Pseudoprogression

- Some increase in tumor burden measured (usually radiographic) after initiation of treatment
  - Usually at first re-assessment; sometimes can see in real time with skin lesions that enlarge before shrinking

Pseudoprogression

- Early (<12 weeks treatment) vs Late
- Frequency (based on post-hoc clinical trial data)
  - 2.8-9.7% melanoma
  - 1.8-5.8% NSCLC
  - 2.9-8.8% RCC
  - 11.1% uveal melanoma
  - 1.8% HNSCC
  - 1.1% Merkel Cell
  - 6.9% Mesothelioma

irRC

- Created in 2009 following larger Ipilimumab trials
- Require follow up imaging no earlier than 4 weeks apart
  - After 4-8 weeks + repeat scans either:
    - Confirmed → further growth of target lesion or appearance of new target lesions
    - Unconfirmed → Everything else that does not meet definition of objective response

Other Tests

- ctDNA decrease associated with pseudoprogression
  - ctDNA not in routine use and not for this indication yet
- IL-8
  - Levels seem to consistently drop from baseline in true pseudoprogressers
    - Not useful in routine clinical practice

Clinical Status

- Prevailing opinion is “pseudoprogressors” clinically improve or remain stable whereas increasing symptoms suggests true progression
  - Observation suggests not as clear cut as we’ve made it

Prognosis

- If pseudoprogression confirmed
  - Some post-hoc studies suggest higher OS
    - Interpret cautiously, this is not high level evidence, and comparing something low incidence

Take Home Messages

- Hyperprogression and Pseudoprogression are not masterfully refined definitions
- Pseudoprogression is a real phenomenon that complicates assessment of patients on immunotherapy, and provides a basis to consider treatment “beyond progression”
- Hyperprogression may exist
  - Enough evidence to avoid IO in known activating EGFR mutations

References

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