Hyper-Progressive Disease (HPD) during Immune Checkpoint Inhibitor (ICI) Therapy

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Abstract

Keywords
► hyper-progression
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Immune checkpoint inhibitor (ICI) restores an efficient antitumor T cell response against tumor cells fostering durable responses that can persist even after the treatment. However, these treatment effects can manifest as an unusual pattern of disease progression, pseudo-progression, or hyper-progression. Differentiating hyper progressive disease (HPD) from pseudo-progression has significant clinical implications and further decision-making for the patient on ICI. HPD is a dramatic acceleration of the rate of tumor progression with the advent of immunotherapeutic agents causing detrimental effects on the disease outcome.

Introduction

Immune checkpoint inhibitors (ICIs) restore an efficient antitumor T cell response against tumor cells fostering durable responses that can persist even after the treatment. However, these treatment effects can manifest as an unusual pattern of disease progression, pseudo-progression, or hyper-progression. Differentiating HPD from pseudo-progression has significant clinical implications and further decision-making for the patient on ICI. HPD is a dramatic acceleration of the rate of tumor progression with the advent of immunotherapeutic agents, causing detrimental effects on the disease outcome, unlike pseudo-progression, a disease progression subsequently followed by tumor shrinkage.

Incidence

The incidence of HPD is varying from 5.9% to 43.1% across various studies, as the definition of HPD is not standardized.

Definition of Tumor Kinetics

Champiat et al[1] defined HPD as a tumor growth rate (TGR), which is at least a two-fold increase in tumor dimension on computer tomography (CT) scan before and after ICI therapy.

Ferrara et al[2] elucidated HPD as $\geq$ 50% increase in the sum of the longest diameter of target lesion at the time of first disease evaluation.

In addition, Kato et al[3] described HPD in terms of time-to-treatment failure (TTF) less than 2 months and more than 50% increase in tumor burden.

The tumor growth kinetic (TGK) ratio is defined as the ratio of TGK post- to TGK pre-immunotherapy. TGK $_{ratio}$ >1 indicates tumor growth acceleration, TGK $_{ratio} \geq 2$ is defined as hyper-progression.

Limitations in Defining HPD

HPD definition

- The current definitions do not take into consideration the natural course of disease progression (i.e., has no placebo control) and cannot differentiate the conventional progression or even the pseudo-progression.
- These are based on retrospective analysis of small, non-randomized, single-arm clinical trials and observations.

HPD needs to be distinguished from other overlapping clinical scenarios as depicted in ►Figs. 1 and 2.
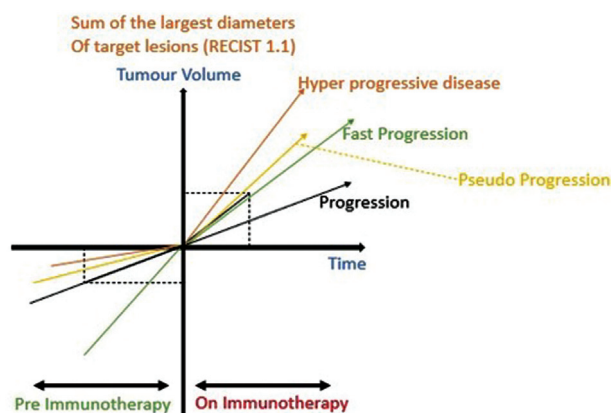
Fig. 1 Patterns of different responses and progression to immunotherapy at the first computed tomography evaluation. SLD, sum of the longest diameters of target lesions.
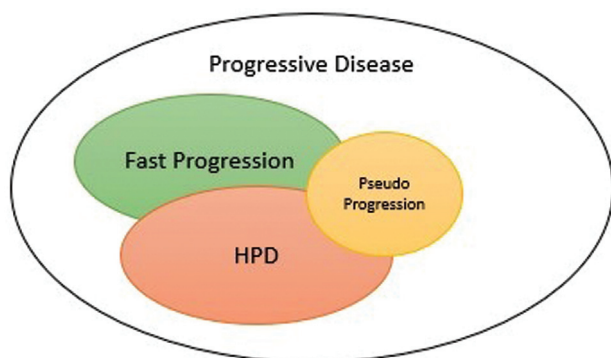
Fig. 2 Hyperprogressive disease (HPD) needs to be differentiated from other clinical realities (pseudo-/hyper-progression).

Clinicopathological Factors Associated with HPD

1. Elderly population (more than 65 years) is found to have a high incidence of HPD, with worse survival outcomes. Age-related immunity dysfunction adversely affects the T cell immunity against cancer.
2. A high metastatic burden in patients with advanced non-small-cell lung cancer (NSCLC) is shown to be more commonly associated with HPD.
3. Comprehensive genomic profiling of HPD patients showed that *MDM 2/4* gene amplification correlates with accelerated tumor growth and poor prognosis. Singavi et al[4] found the *MDM2/4* gene amplification in 66% of HPD patients. MDM2 inhibits the *P53* tumor suppressor gene and stimulates its degradation.
4. Studies have shown that patients with EGFR alteration dramatically progressed paradoxically on ICI therapy. Patients with *EGFR/ALK* mutation did not benefit from ICI. These patients have a lower expression of PD-L1 and decreased levels of CD8+ tumor-infiltrating lymphocytes.
5. Earlier studies revealed that prior radiation treatment may predispose to HPD, as it induces neoantigen production and is shown to be related to locoregional recurrence following IO (immuno-oncology) treatment.
6. Weiss et al[5] evaluated the evolution of genomic copy number instability (CNI) between each cycle of immunotherapy treatment and showed that the decrease in CNI score could accurately predict progression.
7. Certain cancers such as NSCLC, head and neck squamous cell carcinoma (HNSCC), or urothelial carcinoma are suspected to be more commonly associated with HPD.

Ferrara et al[2] reported 13.8% of HPD incidence in patients with NSCLC, Champiat et al[1] reported 34% in melanoma, 10% in the lungs, and Saâda-Bouzid et al[6] reported 29% in patients with HNSCC.

No association was found between the stage, performance status, previous chemotherapy, lymphocyte count, and serum albumin levels. In a study of pretreated patients with advanced NSCLC, HPD was observed in 13.8% of patients treated with PD-1/PD-L1 inhibitors compared with 5.1% of patients treated with single-agent chemotherapy.[2]
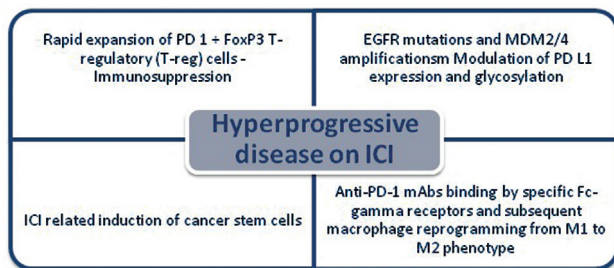
HPD is not unique to immunotherapy; it has been reported in patients receiving chemotherapy also. In a study of pretreated patients with advanced NSCLC, HPD was observed in 13.8% of patients treated with PD-1/PD-L1 inhibitors compared with 5.1% of patients treated with single-agent chemotherapy.[2]

Kim et al[7] comprehensively analyzed the clinical and genetic characterizations of NSCLC patients who progressed on ICI and elucidated that volumetric measurement was more explicit than one-dimensional measurement and the potential validity of pre-ICI-derived NLR, LDH levels, and concurrence of *STK11* and *KRAS* mutations as biomarkers.

Potential Pathological Mechanism of HPD

Modulation of the tumor microenvironment and varying T cell subtypes are postulated to have an intricate role in HPD. ►Fig. 3 shows potential mechanisms of HPD.

1. *MDM2* overexpression/amplification is detected in HPD on ICI, which is related to the inactivation of p53 and drives carcinogenesis. MDM2 inhibitors could be an effective strategy to counter the risk of HPD during ICI.
2. Alterations in the immune system such as intrinsic PD1 and PDL1 expression in the tumor cells and low baseline circulating highly differentiated CD28-CD27-CD4 T-cells (T HD cells) are found to be associated with HPD. PD1 inhibitors interfere with the PD1 mediated up-regulation of proapoptotic proteins.
3. Deleterious somatic mutation in cancer gene TSC2 and VHL; decreased immunogenicity with an increase in natural lymphocyte cells ILC3 and different proteomic

domain within the antibody complex Fc-F(ab)2 are plausible mechanisms of ICI-associated HPD.

Prognosis

HPD is linked to dismal prognosis and increased deleterious mutation in oncogenes. Kim et al[7] reported the median PFS for progressive disease with or without HPD to be 19 days versus 48 days (HR = 4.619) in patients with NSCLC (►Fig. 4).

In various phase III trials, such as checkmate 057 (NSCLC), IMvigor 211 (urothelial cancer), Checkmate 141 (HNCSCC), excess of early mortality and crossing-over of survival curves with the inception of ICI mono-therapy, in comparison with the conventional chemotherapy has been reported, likely related to HPD.

Conclusion

Immune checkpoint inhibitors have revolutionized the treatment strategies of metastatic cancers; still, response to these agents is limited to a particular subset of patients. Current biomarkers are not sensitive to neither predict the responding population nor exclude the patients at risk of HPD. A better understanding of the pathological mechanisms governing this phenomenon could lead the way to next-generation anticancer therapy.

Fig. 3 Potential mechanisms of hyperprogressive disease during immune checkpoint inhibitor therapy. PD1, programmed cell death protein 1; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor.

Authors' Contributions
The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.
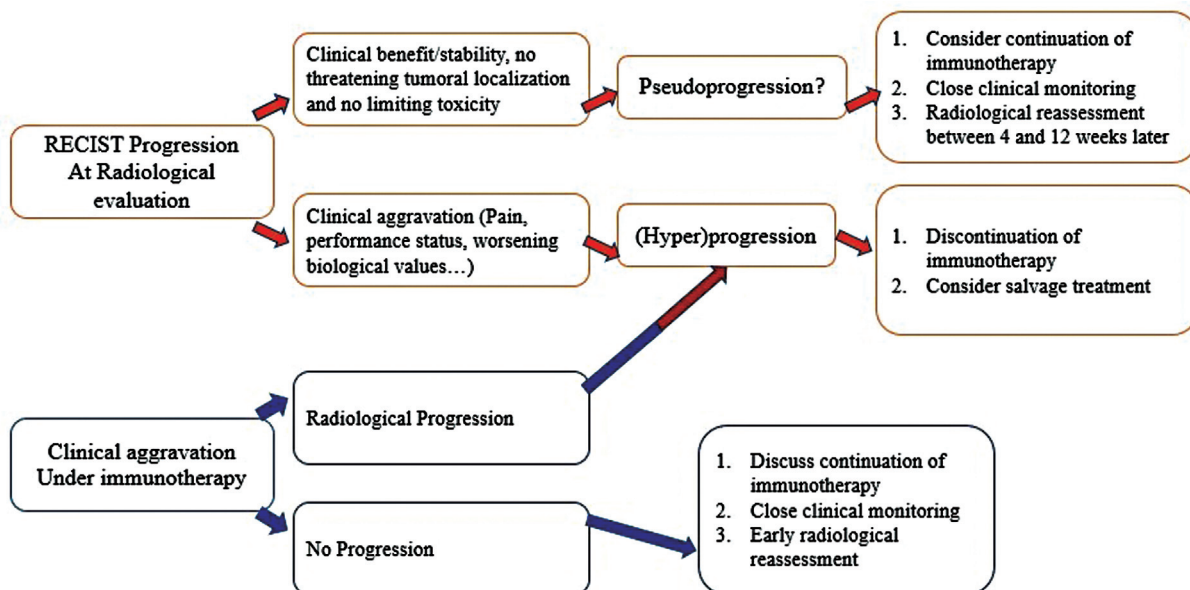
Fig. 4 Management of radiological progression and clinical deterioration during immunotherapy.

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