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**Hyperprogression under treatment with immune-checkpoint inhibitors in patients with gastrointestinal cancer: A natural process of advanced tumor progression?**

Wang MX *et al*. Is hyperprogression unique to immunotherapy?

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**Abstract**

Immunotherapy has shown great promise in treating various types of malignant tumors. However, some patients with gastrointestinal cancer have been known to experience rapid disease progression after treatment, a situation referred to as hyperprogressive disease (HPD). This minireview focuses on the definitions and potential mechanisms of HPD, natural disease progression in gastrointestinal malignancies, and tumor immunological microenvironment.

**Key Words:** Hyperprogressive; Immunotherapy; Natural process; Gastric cancer; Colorectal cancer

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**Core Tip:** There have beenseveral literature reviews on the definition, incidence, predictors, potential biomarkers, and prognosis of hyperprogressive disease. However, this is a minireview of two conflicting concepts: HPD is a new form of immunological response *vs* anatural process of advanced tumor progression. It also takes a look at cellular and molecular mechanisms of the pathways of the tumor microenvironment and recent clinical trials exploring the risk factors and mechanisms of HPD in gastrointestinal cancer.

**INTRODUCTION**

A minority group of patients with gastrointestinal cancer during the treatment of checkpoint inhibitors (ICIs) show paradoxical acceleration in tumor growth. Patients with hyperprogressive disease (HPD) show a shortened progression-free survival or overall survival as compared to patients with natural progressive disease (PD)[1]. According to a recent meta-analysis, the overall incidence of HPD was 13.4% (95% confidence interval [CI], 10.2%-16.6%), with a range of 5.9% to 43.1%[2]. However, this might be an underestimation and the true incidence could be higher, as a certain number of patients might not be diagnosed due to clinical disease progression. Colonic and gastric cancers are the fifth and sixth most common types of cancer, ranking second and fourth worldwide in terms of mortality, respectively[3]. The survival benefits of ICIs such as nivolumab and pembrolizumab in gastrointestinal cancer vary in clinical studies due to different molecular targets and cytotoxicity[4]. To make ICIs safer and more effective in treating gastrointestinal cancer, there is an immense need to explore the molecular mechanism of HPD. This minireview will discuss two contradicting viewpoints in this regard: Is the development of HPD unique to immunotherapy in gastrointestinal cancer patients or is it a natural process of progression of advanced cancers?

**Definition**

The most widely used indexes for HPD diagnosis include tumor growth kinetics (TGK), time to treatment failure (TTF), response evaluation criteria in solid tumors (RECIST), and tumor growth rate (TGR) or their combinations. However, there has been no consensus on the medical diagnosis criteria for HPD so far.

Kato *et al*[5] suggested three criteria to define HPD in patients with non-small cell lung cancer (NSCLC): Progression increase (TGR) of at least two times, a tumor burden increase of 50%, and TTF < 2 mo. Kim *et al*[6] defined HPD as a progressive disease (PD) based on TGK or TGR, *i.e.*, an increase of more than two folds of TGR or TGK during the treatment time interval as compared to that of the reference times in sicker populations already diagnosed with PD by RECIST 1.1 at the first response assessment after PD-1/PD-L1 inhibitors. Ten Berge *et al*[7], Petrioli *et al*[8], and Refae *et al*[9] adopted the same definition for HPD by using RECIST 1.1 at first assessment and TGRPOST/TGRPRE ≥ 2.

In a retrospective analysis of 270 patients with pan-cancer, three criteria were used in defining HPD: (1) 40% increase in sum of target lesions (STL) *vs* baseline or/and; (2) 20% increase in STL *vs* baseline plus the appearance of new lesions in at least two different organs; and (3) Minimum increase in the measurable lesions of > 10 mm and PD by RECIST at first 8 wk after treatment initiation[10]. In the other two retrospective studies about advanced gastric cancer (AGC), HPD was similar for Aoki *et al*[2] and Lu *et al*[11], who defined it as TGKPOST/TGKPRE ≥ 2. There are a few retrospective AGC studies evaluating the incidence of HPD, which are summarized in Table 1.

In a recent meta-analysis, subgroup analysis of varied underlying malignancies suggested that the overall incidence of HPD was 19.4% (95%CI: 9.7%-29.1%) in patients with AGC[2]. An optimal definition of HPD should be comprehensive and contain few variables (early tumor burden increase, TGR, TGK, new lesions, TTF, and clinically associated criteria, *etc.*). There is a need to establish quantifiable criteria based on Eastern Cooperative Oncology Group (ECOG) performance status or Karnofsky Performance Scale score, a systematic measure of tumor growth acceleration, and alternative diagnostic criteria.

**Main viewpoints**

***natural process***

First, HPD is not caused by immunotherapy alone. A *post hoc* analysis from the OAK study (a randomized phase 3 study to describe results of atezolizumab therapy in NSCLC) suggested that fast progression is a universal phenomenon that coexists with ICIs and chemotherapy. The proportion of patients encountering fast progression criteria was analogous between the docetaxel and atezolizumab cohorts (*n =* 41 [9.6%] *vs* *n =* 44 [10.4%], respectively)[12]. However, a retrospective study by Aoki *et al* found that HPD incidence was slightly higher with nivolumab (29.4%) than irinotecan (13.5%) (*P* = 0.0656)[13], suggesting that hyperprogression after baseline is not unique to PD-L1 blockade therapy in NSCLC and AGC. There are also unbalances in the arms that may affect the therapeutic response. For instance, the irinotecan group had fewer patients with recurrent disease in contrast with the ICI group (18 of 66 [28.8%] *vs* 19 of 34 [52.9%]; *P* = 0.028 < 0.05). A higher proportion of patients treated with ICIs had posterior line therapy (13 of 34 [38.2%]) compared with those in the chemotherapy (20 of 66 [30.3%]; *P* = 0.502)[13]. After immunotherapy, it is possible that therapeutic resistance in patients who do not respond to ICIs developed secondarily to past chemotherapy. The large real-world data regarding gastric tumor treated with nivolumab had showed an insignificant difference in median overall survival (2.40 *vs* 2.79 mo;*P =* 0.8)[14] in patients with PD with or without HPD.

HPD is not unique to immunotherapy as it is also present in chemotherapy, but the incidence is higher in the former. This phenomenon also applies to NSCLC under treatment of Sorafenib (a multi-target tyrosine kinase inhibitor) and in metastatic renal cell carcinoma[15,16]. According to published data, HPD incidence is correlated to the type of tumor[17]. The incidence of immunotherapy-related HPD in AGC cases ranges from a few percent to about 21% (13 of 62)[18], according to a recent study, while the incidence stands at 6% in colorectal cases[19].

There is increasing evidence demonstrating that the predictive factors for HPD include age > 65 years, metastasis burden (number of sites of metastatic disease), local and regional relapse (TGKR ≥ 2: 90% *vs* TGKR < 2: 37%; *P* = 0.008 < 0.01), but do not include distant or local recrudescence, liver metastases, a large tumor at baseline, and ECOG performance status of 1 or 2[12,18-23].

A recent study suggested that hyperprogression is usually associated with high risk genetic alternations (*i.e.*, MDM2/4, epidermal growth factor receptor [EGFR], DNMT3A, AKT1 E17K, KRAS, and FBXW7) [18,23,24], which correlate with a shorter time to TTF. For instance, MDM2/4 is an oncogenic gene which functions through inactivation of p53, a tumor suppressing transcription factor. Experiments have demonstrated that MDM2 mediates resistance to immunotherapy by reducing T cell activation in malignancies[18]. However, the relationship between MDM2/4 amplification and hyperprogression remains unclear, although some scholars hypothesize about the involvement of a genomic site on the MDM2 amplicon[25,26]. Another study reported that one of 36 patients with AGC under nivolumab treatment had MDM2 gene amplification[27]. There is also evidence showing that two of 47 patients with AGC had MDM2 gene amplification, where one patient developed HPD under nivolumab treatment[18]. Data from a few studies investigating MDM2 inhibitors suggested that the combination of MDM2 inhibitors and immunotherapy could be an alternative strategy for patients with MDM2 AMP tumor and hyperprogression.

The EGFR signaling cascade is a key regulator in cancer development, survival, differentiation, and cell proliferation. It belongs to the ERBB family of tyrosine kinase receptors[28]. During nivolumab administration as anti-PD1 treatment in patients with AGC, three patients with ERBB2 mutation or amplification showed HPD (*P* = 0.48 or 1)[18]. Despite that all patients with FBXW7 mutation or KRAS amplification developed HPD in this study, the association between these genetic alterations and hyperprogression needs to be further explored. There is evidence supporting the presence of EGFR ­mutated tumors (EGFR E746-­A750 del and T790M mutation or EGFR exon 20 insertion mutation and MYC amplification) in patients with non-gastrointestinal (non-GI) cancer such as NSCLC who showed a less satisfactory response to ICIs and rapid progression[29]. According to a case report, the subtype of EGFR ­Kinase Domain Duplication, somatic alteration EGFR exon 2-28 duplication is present in a patient with esophageal squamous cell carcinoma who developed hyperprogression under camrelizumab treatment, existed[30]. A retrospective study on pan-cancer reported that the mutated type of KRAS mutation was associated with HPD in colorectal cancer (23.5% in non-HPD *vs* 80.0% in HPD;*P =* 0.039 < 0.05)[31].

A case report presented that a 64-year-old man with stage IIIA colon tumor remained disease-free for 10 years during the treatment with adjuvant chemotherapy. After recurrence in the liver, lymph nodes, and ureters, the patient was treated with FOLFIRI and bevacizumab, followed by cetuximab and irinotecan. In 2016, he was started on compassionate use of pembrolizumab for 9 mo until his CEA progressively increased and PET-CT imaging displayed progression in the liver and ureters. Atezolizumab was given for his urothelial tumor; however, the CEA rapidly increased 3 mo later. After discontinuing pembrolizumab and atezolizumab and following treatment with nivolumab and ipilimumab combination for four cycles, his CEA decreased to a stable level, and PET-CT imaging revealed a lower uptake in his original cancer as well as other metastases[32]. If hyperprogression is strongly correlated with immunotherapy, immunotherapy should be terminated after the occurrence of disease progression, although in this case, the patient was treated effectively with sequential PD-1/PD-L1 blockades as well as dual checkpoint inhibitors with good control of tumor burden. In the non-GI tumors, a patient with metastatic breast tumor developed HPD during the treatment of pembrolizumab, then the patient switched to the chemotherapy plus the PD-L1 inhibitor atezolizumab[33]. The patient maintained a partial response to rechallenge with atezolizumab for more than 8 mo. Repeated exposure to different ICIs after failure of initial ICI treatment existed in the other types of tumors, such as NSCLC[34-36].

These phenomena may indicate that PD-L1 blockade relieves B7.1 sequestration *in cis* through PD-L1 in dendritic cells[37], which leads to a B7.1/CD28 reaction to increase T cell priming, and rechallenging with other PD-L1/PD-1 inhibitors might synchronously revive immune response in the tumor microenvironment (TME)[38,39]. Further research is needed to explore what patient population are most likely to benefit from successive ICIs and the basic molecular and cellular mechanisms of different ICIs by analyzing gene expression and genetic mutations, and molecular dynamics simulations of the cancer microenvironment.

Most importantly, large-scale randomized controlled trials are urgently warranted to clarify the correlation among predictive factors for HPD, the molecular mechanisms of hyperprogression, and the natural progression of advanced malignant neoplasms in GI tumors. Prospective observational studies are also essential to compare treatment courses after each treatment.

This minireview has several limitations. Most of the referenced studies were not randomized controlled trials and instead were mostly retrospective. The incidence of HPD is lower in GI tumors than in lung cancers. The future perspective on HPD in GI tumor patients should be focused on the predictive biomarkers of response to immunotherapy, immuno-oncology mechanism, and the murine model of HPD.

***Clear effect of immunotherapy***

Tumor infiltrating lymphocytes in patients with HPD are rich in regulatory T (Treg) cells, a subset of CD4+ T cells with immunosuppressive function. They highly express PD-1 or CTLA-4 and thus can be targeted by ICIs[40,41]. PD-1 blockade or deficiency in T cells enhances T cell receptor and CD28 signaling, which leads to the activation of Treg and conventional T cells. The former suppresses and the latter promotes antitumor immunity[42,43]. Anti-PD-1 antibody in Treg cells highly augments their proliferation and inhibition of antitumor immunity[44] in AGC patients[45,46]. Up-regulation of the EGFR pathway suppresses immune responses by activating Tregs after using ICIs[23]. Moreover, high Treg ratio is associated with poorer survival in patients with colorectal carcinoma and gastric cancer[47,48].

***INF-γ hypothesis***

When utilizing ICIs, the CD8+ T cells release INF-γ and up-regulate PD-L1 expression in tumor cells to make NLRP3 induce immunosuppressive myeloid-derived suppressor cells into the TME, which results in suppression of P53 and tumor growth[49].

Indoleamine 2,3-dioxygenase, an immunosuppressive enzyme, contributes to immune tolerance, inhibition of inflammation, and autoimmunity[50]. Up-regulation of indoleamine 2,3-dioxygenase inhibitors (IDOI) promotes the release of the immunosuppressive cytokines IL-10, angiopoietin 2, and INF-γ into the TME. It enhances the infiltration and proliferation of effector T cells and hyperactivates the JNK pathway, resulting in P53 suppression and activation-induced cell death (AICD), which leads to T-cell depletion[50-53]. IFN-γ also induces overexpression of interferon regulatory factor 8 by activating JAK-STAT signaling, which might stimulate mouse double minute 2 homolog (MDM2) expression[54-56]. Mechanistically, MDM2 negatively regulates T-cell activation through degradation of the transcription factor NFATc2[57] or inhibits P53 activity by its direct interaction[58-60], suggesting a potential role of MDM2 in immune evasion.

***CD38 hypothesis***

CD38, a multifunctional ectoenzyme, modulates adenosine receptor signaling in the TME, leading to the inhibition of T-cell proliferation and function[49]. Adenosine in the TME has two dominating aspects: It increases the number of T-regulatory cells and the polarization of M2 macrophages; active adenosine A2A receptor in tumor cells induces treatment resistance and under-regulation of P53[61,62]. CD38 leads to the expression of AICD and FasL on T-cells[63] and angiopoietin 2 that promotes angiogenesis and triggers more invasive M2 macrophages expressing PD-L1. CD38 also makes tumor cells express HIF-1α to release insulin-like growth factor and vascular endothelial growth factor[64], which recruit Treg cells or promote tumor growth by initiating paracrine or autocrine signaling.

***Other mechanisms***

ICIs may stimulate tumor-infiltrating dendritic cells to secrete IL-10. It impedes antigen presentation and co-stimulation, which inhibits antigen-specific T cell responses. Alternative immune checkpoints increasing T cell depletion, such as LAG-3, T2M-3, and CTLA-4, might result in HPD[65]. TH1 and TH17 recruit neutrophil populations, causing inflammation that contributes to proliferation and survival of malignant cells, angiogenesis, metastasis, and subversion of adaptive immunity[66]. Group 3 innate lymphoid cells produce IL-22 to promote tumor growth through STAT3 activation[67]. Fc receptor promotes functional reprogramming by ICIs to make related immune cells, such as tumor-associated macrophages or M2-like CD163+CD33+PD-L1+ epithelioid macrophages, more aggressively cause HPD [68,69]. CD74-MIF was found absent in HPD, thus we speculated that it potentially impairs proliferation of effector T cells, resulting in HPD[54]. Radiotherapy can lead to changes in the TME by inhibiting TGF expression[70]. Studies have confirmed that TGF-derived epithelial-mesenchymal transition increases mesenchymal cells, leads to tissue fibrosis, and restricts T cell movement and anti-tumor responses[71-73]. By limiting the infiltration of inflammatory/immune cells, it suppresses CD8+ T cells and NK cell-mediated anti-tumor response[74]. HPD is associated with flared expansion of FoxP3 T-regulatory cells in gastric cancer patients[25].

**CONCLUSION**

The scientific community does not have a consensus on HPD definition, and different criteria are used for different cancer types. Whether ICIs are used or not, what appears to be HPD could be the natural progression of advanced cancer associated with MDM2/4 or EGFR signaling. The INF-γ and CD38 hypotheses have been studied in depth in the development of HPD. In the setting of immunotherapy, a large number of immunosuppressive and inflammatory factors affect the TME, resulting in decreased P53 expression or inducing oncogenic signaling, which are all potential mechanisms of HPD.

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**Table 1 Incidence and definition of hyperprogressive disease in advanced gastric cancer patients receiving immunotherapy**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study agent** | **Tumor** | **HPD definition**  | **Number of patients** | **Incidence of HPD, %** | **Ref.** |
| Nivolumab | AGC | (1) An increase of ≥ 50% in the sum of longest diameter (SLD) of target lesions at 8 wk post baseline; (2) An increase of ≥ 20% in the sum of longest diameter of target lesions at 8 wk post baseline; (3) An increase of ≥ 100% in the sum of longest diameter of target lesions at 8 wk post baseline | 243; 243; 243 | 5.4; 27.6; 1.2 | Feng *et al*[75], 2018 |
| PD-1 inhibitor monotherapy | AGC | TGKPOST⁄TGKPRE ≥ 2 | 9 | 55.6 | Sugimoto *et al*[76], 2018 |
| PD-1 inhibitor monotherapy | AGC | TGRPOST⁄TGRPRE ≥ 2 | 105 | 24.8 | Sunakawa *et al*[77], 2019 |
| PD-1 inhibitor monotherapy | AGC | TGRPOST⁄TGRPRE ≥ 2 | 218 | 17.4 | Suzuki *et al*[78], 2020 |

HPD: Hyperprogressive disease; AGC: Advanced gastric cancer; TGK: Tumor growth kinetics; TGR: Tumor growth rate.



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