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

Is hyperprogression unique to immunotherapy?

Mo-Xuan Wang, Shu-Yue Gao, Fan Yang, Run-Jia Fan, Qin-Na Yang, Tian-Lan Zhang, Nian-Song Qian, Guang-Hai Dai

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 a case of hyperprogressive disease (HPD). This mini review focuses on issues surrounding the definitions and potential mechanisms of HPD, natural disease progression, and tumor immune microenvironment.

Key Words: Hyperprogressive; immunotherapy; natural process; gastric cancer; colorectal cancer

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Core Tip: Several literature reviews exist on the definition, incidence, predictors, potential biomarkers and prognosis for HPD. However, this is a mini review of two contending viewpoints: HPD as a new form of immunological response vs. natural advanced tumor progression. It also takes a look at cellular and molecular mechanisms of the pathways of tumor microenvironment and recent clinical trials exploring the risk factors and mechanisms of HPD in gastrointestinal cancer.

INTRODUCTION

A minority group treated with immune checkpoint inhibitors (ICIs) showed paradoxical acceleration in tumor growth. Patients with HPD showed shorter progression-free survival(PFS) or overall survival(OS) as compared to patients with natural progressive disease (PD)[1]. According to a recent meta-analysis, the combined incidence of HPD was 13.4% (95%CI, 10.2%-16.6%), with a range of 5.9% to 43.1%[2].However, this might

be an underestimation and true incidence could be higher, as few patients may not be diagnosed due to clinical disease progression. Colon and stomach cancers are the fifth and sixth most common types of cancer, ranking second and fourth worldwide in terms of mortality, respectively[3]. ICIs' survival benefits in gastrointestinal cancer (such as nivolumab, pembrolizumab, *etc.*) have been proved clinically due to differ from molecularly targeted agents and traditional cytotoxic in mechanism of action[4]. To make ICIs safer and more effective in treating gastrointestinal cancer, there is immense need to explore the HPD mechanism. This mini review takes a look at two contending viewpoints on the question: Is HPD incidence unique to gastrointestinal cancer patients undergoing immunotherapy or what appears is a natural progression of advanced cancers?

DEFINITION

The most widely used criteria for HPD 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 is no consensus on the medical diagnosis criteria for HPD so far.

Kato *et al* suggested three criteria to define HPD in patients with non-small cell lung cancer (NSCLC): progression increase of at least 2 times, a tumor burden increase of fifty percent, and TTF<2 mo [5]. Kim *et al* defined HPD as a progressive disease (PD) based on TGK or TGR, with more than double increase in TGR or TGK during the treatment time interval as compared to that of the reference times in sick persons ascertained to be diagnosed with PD by RECIST 1.1 at the first response assessment after PD-1/PD-L1 inhibitors[6]. Ten Berge *et al*, Petrioli *et al*, and Refae *et al* used the same definition as HPD by RECIST 1.1 at first assessment and TGRPOST/TGRPRE ≥ 2[7–9].

In a retrospective analysis of clinical trial of 270 patients with pan-cancer, three criteria were used in defining HPD: 1.forty percent increase in sum of target lesions(STL) *vs* baseline or/and; 2.twenty percent increase in STL *vs* baseline add the appearance of

new lesions in at least two different organs; 3.minimum increase in the measurable lesions of ten mm plus and PD by RECIST at first eight weekends after treatment initiation[10]. In the other two retrospective studies about AGC, HPD was similar for Aoki *et al* and Lu *et al*, who defined it as TGKPOST/TGKPRE ≥ 2[2,11]. It has been reported few evaluations of HPD in retrospective AGC studies to assess its incidence, and are summarized in Table1.

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

MAIN VIEWPOINTS

A NATURAL PROCESS

First, HPD is not caused by immunotherapy alone. A post hoc analysis from the OAK study (the randomized phase 3 research to describe results of atezolizumab therapy in NSCLC) suggests that fast progression is a universal phenomenon that coexists with ICIs and chemotherapy. The proportion of patients encountering fast progression criteria was analogous between doc and atezo cohorts(n = 41 [9.6%] *vs* n = 44 [10.4%], respectively)[12]. However, Masahiko Aoki found in a retrospective study of AGC that HPD incidence was slightly higher after nivolumab (29.4%) than after irinotecan (13.5%) (=.0656)[13], meaning that hyperprogression after baseline was unspecific to PD-L1 blockade therapy in NSCLC and AGC. There are also unbalances in the arms that may affect the pattern and likelihood of any therapeutic response. For instance, the irinotecan group had less patients with recurrent of the disease status contrasted with the ICI group (18 of 66 [28.8%] vs. 19 of 34 [52.9%]; =.028). A higher

proportion of the patients in the ICIs had posterior line therapy(13 of 34[38.2%]) compared with those in the chemotherapy(20 of 66[30.3%]; χ^2 =.502) [13]. After immunotherapy, it possibly occurs therapeutic resistance from past chemotherapy in pts who do not respond to ICIs. The large real-world data regarding gastric tumor during the treatment with nivolumab has been reported that PD without HPD arms and HPD are not different in median overall survival (2.40 *vs* 2.79 mo, $\chi^2 P = 0.8$)[14].

HPD is not unique to immunotherapy as it also exists in chemotherapy, but the incidence is higher in the former. This phenomenon also occurred in NSCLC during the treatment of Sorafenib (a multi-target tyrosine kinase inhibitor) and in metastatic renal cell carcinoma[15,16]. According to published research data, the 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].

According a research, the HPD predicted factors include age (>65 years), metastasis burden (number of sites of metastasis disease), local regional relapse(TGKR ≥ 2: 90% *vs* TGKR < 2: 37%, P = 0.008), but not with distant or local recrudescene, liver metastases, a large tumor at baseline, and ECOG performance status of 1 or 2[12,18–23].

Second, a research suggests that hyperprogressors usually have poor-risk genomic alternations (MDM2/4, EGFR, DNMT3A, AKT1 E17K, KRAS, and FBXW7)[18,23,24]. These genomics mutations correlate with shorter time to treatment failure (TTF).

For instance, MDM2/4 are oncogenic through the inaction of p53, a tumor suppressing transcription factor. Experiments have affirmed that MDM2 can mediate immunotherapy resistance by reducing T cell activation in malignancies[18]. However, in terms of mechanism, the relationship between MDM2/4 amplification and hyperprogression is ambiguous. Other hypotheses confer the involvement of a genomic that sits on the MDM2 amplicon and is co-amplified with it[25,26]. In a study on HPD during nivolumab treatment in patients with AGC, as was previously reported , one of 36 patients had an MDM2 gene amplification[27]. In other researches, during nivolumab treatment in patients with AGC, two of 47 patients had MDM2 gene amplification, with

one patient having HPD[18]. There have been few clinical studies about MDM2 inhibitors, which could be an optimal combination strategy for patients with hyperprogressors with immunotherapy and MDM2 AMP tumor.

The epidermal growth factor receptor (EGFR) signaling cascade is a key regulator in division, cancer development, survival, differentiation, and cell proliferation. It's 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($\chi^2 P$=.48 or 1)[18]. Despite all patients with FBXW7 mutation or KRAS amplification occurred HPD in this study, the association between these genetic alterations and hyperprogression needs to be explored. Some cases exposed that EGFRmutated tumors (EGFR E746-A750 del and T790M mutationor EGFR exon 20 insertion mutation and MYC amplification) also showed in patients with non-gastrointestinal(non-GI) cancer such as non-small cell lung cancers(NSCLCs) as a fewer satisfactory rate of response to ICIs and existed rapid progression[29]. Per a case report, in a patient with esophageal squamous cell carcinoma, who developed hyperprogression during the camrelizumab treatment, existed the subtype of EGFR-Kinase Domain Duplication (KDD), somatic alteration EGFR exon 2–28 duplication[30]. A retrospective research for pan-cancer believed that the mutated type of KRAS mutation was associated with HPD in colorectal cancer (23.5[redacted] in Non-HPD *vs* [redacted] in HPD, [redacted])[31].

Third, a case report presented that a sixty-four years old male with stage IIIA colon tumor had remained disease free ten years during the treatment with adjuvant chemotherapy. After the recurrence in the liver, lymph nodes, urothelial, the patient was treated with FOLFIRI and bevacizumab, followed by cetuximab and irinotecan. In 2016, he was begun on compassionate use pembrolizumab during the nine months until the patient's CEA increasingly rose, PET-CT imaging displayed progression of his hepatocellular carcinoma and ureters. Added the atezolizumab for patients with urothelial tumor, three months later, the CEA rapidly increased. After discontinuing pembrolizumab and atezolizumab following the treatment with nivolumab and

ipilimumab during the four cycles combination, his CEA decreased to a stable level, and PET-CT imaging revealed a lower response in uptake in his original cancer as well in other metastatic implant[32]. If hyperprogression is strongly correlated with immunotherapy, it 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 beyond progression with good carcinoma control. 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 PDL-1 inhibitor atezolizumab[33]. The patient maintained a partial response to rechallenge with atezolizumab for more than eight months. Repeated exposure with different ICI after unsuccess of initial ICI treatment has existed in the other types tumors, such as NSCLC[34–36].

These phenomena may be indicating that PD-L1 blockades relieve B7.1 sequestration incis through PD-L1 conveyed in DCs[37], which leads into a B7.1/CD28 reaction to increase the igniting of T cells, and rechallenging with other PD-L1/PD-1 inhibitors might synchronously revive immune response in tumor microenvironment (TME)[38,39]. Research is needed to resolve which patients are most possibly to benefit from this tactic of successive ICIs and to explore the basic molecular and cellular mechanisms of different ICIs by analyzing gene expressions, genetic mutations, and molecular dynamics simulations of the cancer microenvironment.

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

This minireview has limitations. Collected study is not the randomized controlled trail, and most studies were retrospective. The incidence of HPD is lower in GI tumors compared with in pts with lung cancers. The future approach about HPD in GI patients

is focus on the predictive biomarkers of response to immunotherapy, immuno-oncology mechanism, and the murine model.

A CLEAR EFFECT OF IMMUNOTHERAPY

Tumor infiltrating lymphocytes (TILs) in patients with HPD are rich in regulatory T(Treg) cells, a subset of $CD4^+$ T cells of immunosuppressive function, which are highly expressed in 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 (TCR) and CD28 signal intensity, which leads to the activation of Treg and conventional T (Tconv) cells. The former suppresses and the latter heightens 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 EGFR pathway suppresses immune responses by activating Tregs after using ICIs [47]. Moreover, high Treg ratio is associated with poorer survival in colorectal carcinoma and gastric cancer[48,49].

INF-γ HYPOTHESIS

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 (MDSCs) into TME, which results in suppression of P53 and tumor growth[50].

Indoleamine 2,3-dioxygenase (IDO1), an immunosuppressive enzyme, contributes to immune tolerance, restrain of inflammation and autoimmunity[51]. Up-regulation of IDOI secretes the immunosuppressive cytokines, IL-10, ANGPT2 and INF-γ into TME. It enhances the infiltration and proliferation of effector T cells and presents a hyperactivated JNK pathway, resulting in P53 suppression and activation-induced cell death (AICD), which leads to T-cell depletion[51–54]. IFN- γ also establishes an overexpression of interferon regulatory factor 8 (IRF-8) by active JAK-STAT signaling, which might stimulate mouse double minute 2 homolog (MDM2) expression[55–57]. Mechanistically, MDM2 negatively regulates T-cell activation through degradation of

the transcription factor NFATc2[58] or inhibits P53 activity by its direct interaction[59–61], suggesting a potential role of MDM2 in immune evasion.

CD38 HYPOTHESIS

CD38, a multifunctional ectoenzyme, modulates adenosine receptor signaling in TME, leading to the inhibition of T-cell proliferation and function[50]. Adenosine in TME has two dominating aspects: it increased the number of T-reg cells and the polarization of M2 macrophages; and active adenosine A2A receptor (ADORA2a) in tumor cells induces medicine resistance and under-regulation of P53[62,63]. CD38 Leads to AICD and FasL expression on T-cells[64] and angiopoietin 2 (ANGPT2) with function of angiogenesis that triggers more invasive and M2 macrophages expressing PD-L1. CD38 also make tumor cells express HIF-1α to release insulin-like growth factor (IGF) and vascular endothelial growth factor (VEGFR)[65] to recruit Treg cells or promote tumor growth by establishing paracrine or autocrine signaling.

OTHER MECHANISMS

ICIs may stimulate tumor-infiltrating dendritic cells (DCs) to secrete IL-10. It impedes antigen presentation and co-stimulation, which inhibits antigen-specific T cell responses. Substitute immune checkpoints, such as LAG-3, T2M-3 and CTLA-4, increasing T cell depletion might result in HPD[66]. TH1 and TH17 recruit neutrophil populations, causing inflammation that contributes to proliferation and survival of malignant cells, angiogenesis, metastasis and subversion of adaptive immunity[67]. ILC3 produces interleukin (IL)-22 to promote tumor growth through STAT3 activation[68]. Fc receptor (FcR) promotes functional reprogramming by ICIs to make relative immune cells, such as tumor-associated macrophages (TAM) or M2-like $CD163^{+}CD33^{+}PD\text{-}L1^{+}$epithelioid macrophages, more aggressively cause HPD[69–71]. CD74-MIF was found absent in HPD, thus we speculated that it had potentially impaired proliferation of effector T cells, resulting in HPD[55]. Radiotherapy can lead to changes in TME by inhibiting TGF expression[72]. Studies have confirmed that TGF-derived epithelial-

mesenchymal transition (EMT) increases mesenchymal cells and leads to tissue fibrosis, restricting T cell movement and anti-tumor responses[73–75]. By limiting the infiltration of inflammatory/immune cells, it suppresses $CD8^+$ T cells and NK cell-mediated anti-tumor response [76]. HPD is associated with flared expansion of FoxP3 T-regulatory (T-reg) 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 vis-à-vis MDM2/4 or EGFR influence and so on. The INF-r and CD38 hypotheses have been studied in depth to exhibit HPD. After immunotherapy, large number of immunosuppressive and inflammatory factors affect TME, resulting in decreased P53 expression or inducing oncogenic signaling, which are all potential mechanisms of HPD.

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