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REVIEW

Research progress of hyperprogression in immunotherapy of gastrointestinal tumors

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Abstract: CTLA-4 and PD-1/PD-L1 are common immune checkpoints targeted in clinical. Immunotherapy has made a breakthrough in the treatment of gastrointestinal tumors. However, some patients may experience hyperprogression (HPD) during immunotherapy, which is characterized by abnormally accelerated tumor growth. Previous studies have shown that the incidence of HPD in gastrointestinal tumor immunotherapy is about 4%-29.4%, but the overall survival of patients with HPD is only a few months. HPD is a difficulty in immunotherapy. This review summarizes the definition, identification, incidence, mechanism and related predictors of hyperprogression in gastrointestinal tumor immunotherapy.

Key words: gastrointestinal tumors, immune checkpoint inhibitors, hyperprogression, predictors, pseudoprogression.

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***Abbreviations*:** CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; HPD, hyperprogression; ICI, immune checkpoint inhibitors; TGR, tumor growth rate; TGK, tumor growth kinetics; TTF, tumor treatment failure; irRC, Immune-related Response Criteria; HCC, hepatocellular carcinoma; ECOG, Eastern Cooperative Oncology Group; NLR: Neutrophil/Lymphocyte Ratio.

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Introduction

Since the 1990s, immunotherapy represented by immune checkpoint inhibitors (ICIs) has made remarkable progress in many types of tumors, such as lung cancer, digestive malignancy, lymphoma, malignant melanoma, head and neck squamous cell carcinoma, etc [1-4]. Through the mechanisms of immunogenicity loss, antigenicity loss or immunosuppressive microenvironment, tumor cells form immune escape, which ultimately leads to tumor development [5]. CTLA-4 and PD-1/PD-L1 are the most commonly targeted immune checkpoints in clinical practice. Notably, hyperprogression (HPD), characterized by abnormally accelerated tumor growth compared to normal progression, may occur in some patients receiving immunotherapy. Previous literature has reported that the incidence of HPD for gastrointestinal malignancies varies from 6.0%-29.4% after immunotherapy, and the survival time of patients with HPD is sharply shortened, with the median overall survival time only 3-6 months [6-13]. HPD can occur at any stage of immunotherapy and seriously affect patient survival. At present, there are few studies on HPD in gastrointestinal tumor immunotherapy worldwide. Among different studies, the diagnostic criteria of HPD, as well as the incidence and prognosis of HPD in different tumor types are all heterogeneous. Therefore, this review summarizes the definition, identification, incidence, mechanism, and related predictors of HPD in gastrointestinal tumor immunotherapy.

1. The definition of HPD

At present, although the phenomenon of HPD after immunotherapy has been widely discussed by experts worldwide, there is defined standard for HPD evaluation, and there are differences in the definition of HPD in different international clinical studies. In the field of gastric cancer, the JACCRC-08 study prospectively analyzed the clinical data of 487 patients with advanced gastric cancer who received nivolumab. The study defined HPD as: a. Tumor growth rate (TGR) increased ≥ 2 times after nivolumab treatment; b. The tumor growth kinetics (TGK) ratio was ≥2 times after nivolumab treatment; c. Increase of tumor burden by 50% [8,14]. In the field of liver cancer, respectively, Won-Mook Choi [11] and Chang Gon Kim [15] performed retrospective analyses of 194 and 189 patients with advanced hepatocellular carcinoma (HCC) treated with nivolumab. HPD in both studies was defined as: from the beginning of nivolumab treatment to 12 weeks after the end of treatment, more than four-fold increase in TGR or TGK ratio, and a 40% increase in TGR; or time to tumor treatment failure (TTF) < 2 months. In the field of esophageal cancer, Wei Wang et al. defined HPD as ≥2 times increase of TGR, 50% increase of tumor burden, and TTF < 2 months after immunotherapy. They also, for the first time, reported a case of advanced esophageal cancer with replication of EGFR exons 2-28, who developed HPD within 4 weeks after the camrelizumab treatment [16]. Shiyun Chen et al. retrospectively analyzed 377 patients with malignant tumors treated with PD-1 inhibitors (nivolumab/pembrolizumab) [12], including lung cancer (133 cases), gastrointestinal cancer (135 cases), and other cancers (109 cases).In this study, HPD was defined as TGR greater than 50% 6-8 weeks after the end of immunotherapy(Table 1). All of the above studies referred to the clinical efficacy evaluation criteria for solid tumors (RECISTV1.1). TGR was defined as the percentage of tumor volume increase, excluding new and immeasurable lesions. TGK was defined as the change in the sum of the longest diameters of the target lesions [17]. In recent years, various clinical trials of immunotherapy for malignant tumors have been carried out, but there is no unified diagnostic standard for HPD in studies worldwide. Unlike cytotoxic therapy, tumor immunotherapy could frequently lead to non-typical responses. These non-typical responses might include phenomena such as increasing of tumor burden at the beginning but later tumor shrinkage (tumor relapse/ pseudoprogression), or initial reduction of tumor volume but concurrent appearance of new lesions, and the new lesions finally regress. Thus, traditional RECIST may not be sufficient to accurately assess the outcome of patients receiving immunotherapy. Therefore, a multidisciplinary group of oncologists, immunotherapy specialists and regulatory experts discussed and developed the Immune-related Response Criteria (irRC). Compared with conventional RECIST, irRC requires performing of two consecutive radiographic assessments (at least 4 weeks apart) for disease progression or tumor response, and follow-up radiographic studies at least 4 weeks later to assess new lesions. New lesions that met tumor size criteria were defined as "new measurable lesions" and included into the "total tumor load". IrRC has been included in the regulatory guidance of the US FDA and the European Medicines Agency (EMA). Its application has expanded beyond melanoma to several cancers types, such as lung cancer, kidney cancer and lymphoma. However, it is rarely applied in clinical trials of immunotherapy for gastrointestinal malignancies [18]. Patients with HPD have a poor prognosis. Actively exploring other indicators for immunotherapy efficacy based on irRC, might optimize and standardize the diagnosis of HPD, and improve the prognosis.

2. Identification of HPD and pseudoprogression

Pseudoprogression was defined as the presence of a significant growth trend of the target lesion, or the presence of new lesions in the radiographic assessment after the initial antitumor therapy, but the target lesion remained stable, shrunk, or disappeared in subsequent assessments. Pseudoprogression was first reported in patients with brain tumors treated with temozolomide [19]. Pseudoprogression is not real tumor progression. Due to inflammatory infiltration of tumor cells by immune cells, resulting in tumor cell edema and necrosis, its imaging manifestations include tumor volume increase or new lesions. Thus, pseudoprogression is easily misdiagnosed as HPD. Ultimately, the tumor load was actually reduced. Previous studies have shown that the incidence of pseudoprogression was about 1%-10%, which was lower compared to HPD [20,21]. There are no studies on HPD and pseudoprogression in the field of gastrointestinal tumors. In a multi-center retrospective study, 406 patients with advanced lung cancer who received immunotherapy were analyzed for HPD. In this study, 4.7% (19/406) of the patients initially presented with disease progression (PD). However, this subset of patients subsequently achieved complete response (CR) or partial response (PR) or stable disease (SD) for more than 6 months. Eventually, these patients were classified as "pseudoprogression".Additionally, six patients in this entire subset were initially classified as HPD. But then the patient's tumor regressed, and eventually they were classified as "pseudoprogression".Excluding these 6 patients, 13.8% (56/406) patients still developed HPD [7]. The issue of HPD and pseudoprogression in immunotherapy is still a great challenge. At present, there are still no effective biochemical or immune detection indicators or imaging markers to distinguish pseudoprogression from HPD, and irRC may help make up for the deficiency of RECIST in evaluating the efficacy of immunosuppressant [18]. Focusing on the "progressive tumor tissue", analysis of the immune microenvironment, different cell populations, cytokines such as interleukin-8 (IL-8) and peripheral blood circulating tumor DNA may be helpful in differentiating pseudoprogression and HPD. Since HPD significantly affects patient prognosis, misjudgment of pseudoprogression will lead to the continuation of ineffective immunotherapy. Therefore, prospective studies are urgently needed to promote the evaluation and differentiation of HPD and pseudoprogression in solid tumor immunotherapy.

3. Incidence of HPD in gastrointestinal tumor immunotherapy

The incidence of HPD in gastrointestinal tumor immunotherapy ranged from 4% to 29.4%, and the incidence of HPD varied greatly among different tumor types and different immunotherapy regimens. However, HPD can seriously affect the prognosis of patients, and the survival time of patients with HPD is significantly shorter than that of patients without HPD. Previous studies reported an 8.9% to 29.6% incidence of HPD in 839 patients with advanced gastric cancer who received immunotherapy, including nivolumab (817) and others (22).Median overall survival of patients with HPD ranged from 3-6 months [8,9,13,14,22,23].The incidence of HPD in patients with advanced liver cancer who received immunotherapy was generally lower than that of advanced gastric cancer, with the rate of 8.0%-14.5% VS. 8.9%-29.4%. The median overall survival of advanced liver cancer patients with HPD is about 2.0-7.9 months [10-12,15,24,25]. A retrospective study with small sample size analyzed the incidence of HPD in immunotherapy for esophageal cancer, pancreatic cancer, gallbladder cancer and colorectal cancer, and the incidence was 20.00%, 28.00%, 13.64% and 22.73%, respectively (Table 1) [12]. As differences in diagnostic criteria of HPD, immunotherapy drugs, tumor types and patient stages of disease exist among studies, the incidence of HPD in gastrointestinal tumor immunotherapy varies. According to the current knowledge, the incidence of HPD during immunotherapy for gastric cancer, esophageal cancer, pancreatic cancer and colorectal cancer is slightly higher than that for liver cancer and gallbladder cancer, and the overall survival time of patients with HPD is significantly lower than that of patients without HPD. Therefore, early diagnosis and early treatment of HPD may help to further improve the prognosis of patients.

4. Pathogenesis of HPD

HPD can be regarded as a type of primary resistance against immunotherapy, and its occurrence may be related to the following mechanisms. Takahiro Kamada et al. found that FoxP3+ Treg cells were highly expressed in tumor tissues of gastric cancer patients with HPD after immunotherapy. They then genetically knocked out PD-1 in Treg cells or used a PD-1 monoclonal antibody to block PD-1 binding to the ligand in Treg cells. Consequently, the activity of Treg cells increased and the tumor inhibition effect was enhanced, which further confirmed that blocking PD-1/PD-L1 may enhance PD-1+ regulatory T cells, lead to immunosuppression of tumor microenvironment and promote the occurrence of HPD [22]. When PD-1/PD-L1 is blocked, compensatory upregulation of other alternative checkpoints such as CTLA-4 and CD96 may lead to proliferation of Treg cells, thereby inhibiting immune function, resulting in immune escape of tumor cells and promoting the occurrence of HPD [26,27]. Blocking PD-1/PD-L1 may affect the polarization of immunosuppressive cell subsets, such as M2 macrophages, DCs or MDSCs,

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through Fc-Fc receptors or secretion of galectin-3, thereby reducing tumor immunogenicity and promoting HPD [27-29]. Blocking PD-1/PD-L1 may also lead to activation of other alternative oncogenic pathways, such as IGF-1, ERK/MAPK, PI3K/AKT and TGF-β signaling pathways, which directly affect tumor cell growth and promote HPD [17,30]. The pathogenesis of HPD is complex and has not been determined yet. Previous studies have explored the internal mechanism of HPD from different perspectives, which is of great significance for clarifying the molecular mechanism of HPD. Revealing the pathogenesis of HPD can help to screen high-risk populations for HPD, guide follow-up immunotherapy or targeted therapy, avoid ineffective immunotherapy, and improve the prognosis of patients.

5. Predictive markers of HPD

The incidence of HPD varies greatly among different tumor types, and the incidence of HPD, ranging from 6.0% to 29.4%, is relatively high in gastrointestinal malignancy cases receiving immunotherapy. In a study with 194 HCC patients receiving immunotherapy involved, Won-mook Choi et al. retrospectively analyzed the relationship between HPD and clinical characteristics. The clinical characteristics included age, gender, score of ECOG performance status, kinetic index of NLR and other factors. In this study, the kinetic index of NLR was defined as the rate of change of NLR between baseline and the fourth week of immunotherapy, namely ΔNLR. The study found that the increase in ΔNLR was an independent predictor of HPD (HR 1.79; 95% CI 1.19-2.68) [11]. In a retrospective analysis of 69 HCC patients who received immunotherapy, LuZhang et al. found that hemoglobin level, portal vein thrombosis of HCC and Child-Pugh score were correlated with the occurrence of HPD [10]. Akinori Sasaki et al. retrospectively analyzed 62 patients with gastric cancer who received nivolumab and found that the incidence of HPD in the whole group was as high as 21%. The survival of patients in the HPD group was significantly shorter than that in the non-HPD group, with a median progression-free survival (PFS) of 0.7 months VS 2.4 months. Hepatic metastasis, ECOG scoring of 1-2, and large tumor size at baseline (mean diameter 104.2mm) were associated with HPD. The value of absolute neutrophil count (ANC) and C-reactive protein (CRP) in HPD patients significantly increased within 4 weeks of immunotherapy(Table 1) [14]. Some retrospective studies have shown that genomic changes, such as MDM2/4 amplification and EGFR mutations, are associated with HPD. MDM2 is a negative regulator of p53. Via binding to the N-terminal transactivation domain of p53, MDM2 blocks p53-mediated transactivation, and interferes with p53-mediated tumor inhibition [31]. Immune checkpoint inhibitors may trigger MDM2 amplification and mediate HPD by acting on IFN-γ and JAK-STAT signaling pathways [32]. EGFR mutations can upregulate PD-1, PD-L1 and CTLA-4 mediated immune escape, thus subsequently inducing HPD [33,34]. There are few studies on the predictive markers of HPD in gastrointestinal malignancies after immunotherapy. Wei Wang et al. reported occurrence of HPD after camrelizumab treatment in a case of advanced esophageal squamous cell carcinoma with EGFR 2-28 exon replication [16]. At present, there are no reports on the risk factors of HPD after immunotherapy for colorectal cancer, gallbladder cancer, pancreatic cancer and other gastrointestinal malignancies. With the increasing number of prospective clinical trials related to immunotherapy of gastrointestinal malignancies, it is necessary to pay more attention to the occurrence of HPD, explore related predictors of HPD, identify high-risk populations of HPD at the early stage, avoid ineffective immunotherapy, and intervene as early as possible to improve the prognosis of patients.

6. Summary

HPD occurs in almost all malignancies, regardless of the specific drug class of ICIs. The differences in the reported incidence of HPD in gastrointestinal malignancies after immunotherapy may be related to the different definitions of HPD in different clinical trials, but the prognosis of HPD patients is generally poor. HPD is a brand new mode of tumor progression, and the understanding of its pathogenesis and molecular mechanisms is still limited. Moreover, there is no unified diagnostic standard for HPD. Tumor HPD still needs to be discriminated from ordinary progression and pseudoprogression. IrRC combined with other effective evaluation indicators of immunotherapy may be helpful for diagnosis and defining of HPD. Therefore, in future prospective clinical trials of ICIs, HPD related clinical, laboratory and imaging indicators should be actively explored, and relevant clinical predictions should be established, so as to standardize the diagnosis and treatment of HPD.

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