International Immunopharmacology 58 (2018) 125–135

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Pseudoprogression and hyperprogression after checkpoint blockade

Qiaohong Wang, Jingze Gao, Xia Wu*

Department of Obstetrics & Gynecology, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200127, PR China
Shanghai Key Laboratory of Gynecologic Oncology, Shanghai 200127, PR China

ARTICLE INFO

Keywords:
Checkpoint inhibitor
Hyperprogression
Pseudoprogression
Tumor growth rate

ABSTRACT

Immune checkpoint inhibitors appear to be one of the most promising immunotherapies with significant clinical benefits and durable responses in multiple tumor types. A heterogeneity of responses appears in patients receiving checkpoint blockade, including pseudoprogression where the tumor burden or number of tumor lesions increases initially before decreasing. Another special response observed after checkpoint blockade is hyperprogression, a phenomenon reflecting a very rapid tumor progression following immunotherapy, suggesting that checkpoint blockade could impact detrimentally on a small subset of patients. As immunotherapeutics, especially anti-PD-1/PD-L1 agents, become more widely available, evaluating the efficacy of these novel drugs poses a major challenge to clinicians, who aim to avoid either premature withdrawal of the treatment or prolonging ineffective treatment. Although the mechanism and recognition of pseudoprogression have gradually come to light, the incidence, basis, identification and predictive biomarkers of hyperprogression have been largely unknown, and this review documents the existing research findings and points out the areas where further studies are badly needed.

1. Introduction

Immunotherapy that reestablishes antitumor response within the host is rising as a promising treatment strategy for cancer patients [1–3]. Immune checkpoint inhibitors, such as monoclonal antibodies (mAb) targeting cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) and programmed death-1 (PD-1), are profoundly changing cancer patient management [4–7]. At the forefront of this novel class of antitumor agents, anti-PD-1/PD-L1 antibodies exhibit a significant activity and induce durable disease control by restoring an efficient antitumor T-cell response. It has become a standard of care for multiple cancer types including melanoma, non-small-cell lung cancer (NSCLC), renal-cell carcinoma (RCC), bladder cancer, Hodgkin's lymphoma, head and neck squamous cell carcinoma (HNSCC) and Merkel cell carcinoma [8–11]. Overall, the response rates for single agent of PD-1/PD-L1 inhibitors in solid malignancies range from 20% to 40% [12–14]. Till now, five immune checkpoint inhibitors targeting PD-1 and PD-L1 have been approved by the U.S. Food and Drug Administration (FDA), including PD-1-blocking mAbs pembrolizumab and nivolumab, and PD-L1-targeted mAbs atezolizumab, durvalumab and avelumab. Apart from CTLA-4 and PD-1, multiple inhibitory receptors, such as T-cell immunoglobulin mucin 3 (TIM3), lymphocyte activation gene 3 (LAG3) and B and T lymphocyte attenuator (BTLA), also compose the family of immune checkpoint and transmit similar inhibitory functions, and, hence, call for further exploration [15,16].

As immunotherapeutics, particularly anti-PD-1/PD-L1 agents, are more widely available to patients, clinicians face a great challenge in accurately evaluating the clinical efficacy of these novel drugs. WHO and RECIST criteria have historically been taken as standard guidelines in defining a tumor response to therapy. Although imperfect, the RECIST are commonly accepted norms defining the moment of disease progression and have guided the defining of tumor response and driven consequent drug approval for years [17,18]. The development of new lesions and a significant increase in the size of tumor lesions are considered definite disease progression by RECIST criteria. However, during checkpoint blockade some patients experienced immune-related responses such as initial increased size of tumor lesions or appearance of new lesions, confirmed by biopsy as necrosis or inflammatory cell infiltrates, with subsequent reduction in tumor burden. The unconventional clinical response is recognized as pseudoprogression, and would be misclassified as progressive disease (PD) according to the size-based WHO or RECIST criteria.

In addition to pseudoprogression, there is another special response pattern during checkpoint blockade named tumor flare or hyperprogression. Unlike pseudoprogression, a disease progression subsequently followed by tumor shrinkage, hyperprogression is characterized as the disease whose dramatic progression outpaces the expected rate of growth in the absence of checkpoint inhibitors, based primarily on

* Corresponding author at: Department of Obstetrics & Gynecology, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200127, PR China.
E-mail address: wuxia1225@aliyun.com (X. Wu).

https://doi.org/10.1016/j.intimp.2018.03.018
Received 17 January 2018; Received in revised form 10 March 2018; Accepted 19 March 2018

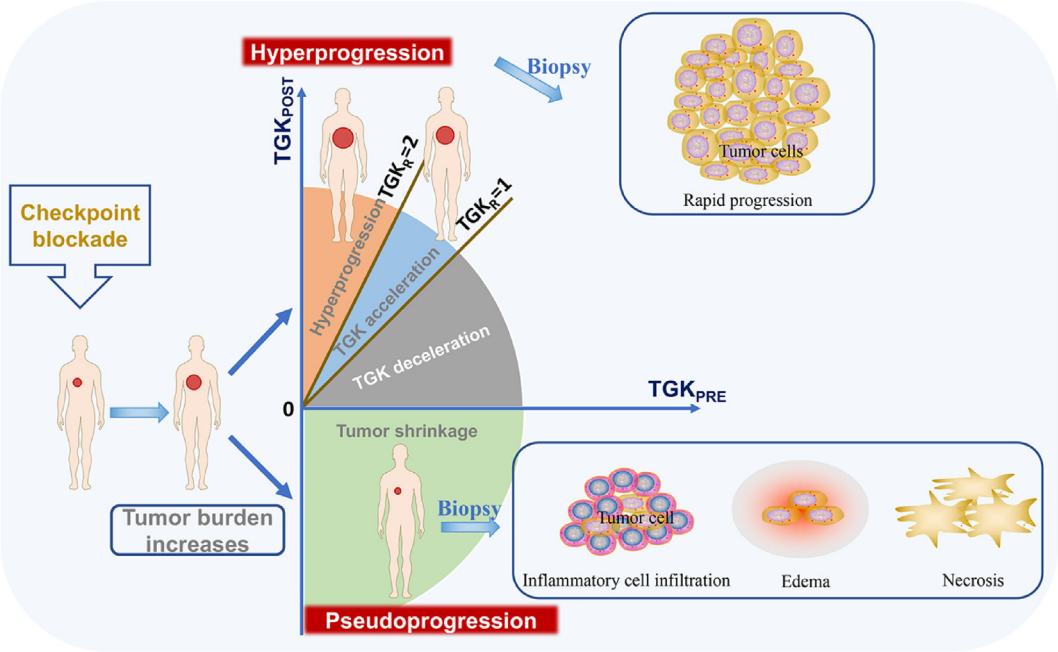

Fig. 1. The pseudoprogression and hyperprogression after checkpoint blockade. A subset of patients experienced initial increase in the size of tumor lesions or appearance of new lesions, confirmed by biopsy as necrosis or inflammatory cell infiltrates, with subsequent reduction in tumor burden. This unconventional clinical response is recognized as pseudoprogression. The hyperprogression is characterized as the disease whose dramatic progression outpaces the expected rate of growth in the absence of checkpoint inhibitors. Hyperprogression is usually defined as ≥2-fold increase in the tumor growth kinetics ratio (TGK_R) during checkpoint inhibitors treatment compared with the reference (prior to treatment onset) period. $TGK_R > 1$ indicates tumor growth acceleration, while $0 < TGK_R < 1$ and $TGK_R < 0$ indicates tumor deceleration and shrinkage, respectively [19].

evidence from prior imaging scans (Fig. 1). The patients with disease hyperprogression have a course that is more deleterious than they might have had with other therapies, or even in the absence of therapy. Although the mechanism and recognition of pseudoprogression have gradually come to light, the incidence, basis, identification and predictive biomarkers of hyperprogression have been largely unknown. As immunotherapeutics, especially anti-PD-1/PD-L1 agents, become more widely available, the discernment in differentiating pseudoprogression from real progression or even hyperprogression by clinicians will tremendously help evaluate the efficacy of these novel drugs and avoid either premature withdrawal of the treatment or prolonging ineffective treatment. Therefore, this review focuses on the existing researches in related areas and clarifies potential topics for future studies.

2. Pseudoprogression after immune checkpoint blockade

2.1. The occurrence of pseudoprogression after immune checkpoint blockade

The concept of "tumor pseudoprogression" was first introduced in brain tumors treated with non-immune therapy agent, temozolomide, which is a prodrug that works through alkylation (methylation) of DNA. It is discovered that brain tumors might increase in size before responding to temozolomide treatment [20]. Pseudoprogression in immune checkpoint inhibitor therapy was initially found in melanoma, at first in the research of the anti-CTLA4 inhibitor ipilimumab [21] and then in the studies of anti-PD-1 therapies, pembrolizumab and nivolumab [22]. Pseudoprogression is not genuine tumor progression, but just radiographic growth demonstrated pathologically by the infiltration of immune cells like cytotoxic T lymphocytes around tumors, edema, and necrosis [22]. It is also possible that delayed immunologic response may play some roles in the phenomena of pseudoprogression in addition to inflammatory response with tumor infiltration of immune cells, especially in patients who experience delayed tumor regression after pseudoprogression.

In melanoma, unconventional immune-responses, or pseudoprogression followed by a delayed response, has been observed in 2.8–15.8% patients treated with checkpoint inhibitors [23–26]. The occurrence of pseudoprogression with checkpoint inhibitors across other solid tumors, although relatively rarely, has been also reported. In the clinical trials, the incidences of pseudoprogression are 0.6–5.8%, 1.8%, 1.5–7.1%, 6.9%, 5.7–8.8% and 1.1% in NSCLS, HNSCC, urothelial carcinoma, mesothelioma, RCC and Merkel cell carcinoma respectively (Table 1). In addition, there are also case reports of pseudoprogression in NSCLS, small cell lung cancer, hepatocellular carcinoma and colorectal cancer. Although the vast majority of reported pseudoprogression happened in the patients received single checkpoint inhibitors, pseudoprogression is also observed in those with dual immunotherapy. Chae et al. presented a case study where the microsatellite instability (MSI)-high metastatic colorectal cancer is treated with a combination of PD-L1 antagonist and OX40 agonist that displayed pseudoprogression with a size growth of 163% from baseline tumor burden [27]. Tumor shrinkage was observed subsequently and the patient has undergone a stable disease. The frequency of pseudoprogression in combined immunotherapy calls for more study.

The scale of maximum increase in tumor burden linked with pseudoprogression reported ranges from 20%–163% [27]. The case report from Chae et al. [27] shows extraordinary magnititude of pseudoprogression, with 163% of tumor increase from baseline. This large increase in tumor size presents a challenge to differentiate pseudoprogression from true progression or even hyperprogression supported only by radiological evidence when they first appear during therapy. Therefore, treating clinicians need to rely on other information to accurately assess tumor response. As pseudoprogression rarely appears in advanced solid tumors apart from melanoma, the possibility that initial radiographic progression might be pseudoprogression should be weighed against adequate vigilance for the most likely potential of true progression. The optimism for pseudoprogression with a delayed response shall be balanced with the detriments of overtreatment with immunotherapy that could lead to missed chances for alternative therapeutic strategies, such as both standard of care and novel combination immunotherapy options.