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Review Article

How to differentiate pseudoprogression from true progression in cancer patients treated with immunotherapy

Yiming Ma, Qiwei Wang, Qian Dong, Lei Zhan, Jingdong Zhang

Medical Oncology Department of Gastrointestinal Tumors, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, No. 44, Xiaohe Road, Dadong District, Shenyang 110042, Liaoning Province, China

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Abstract: Immunotherapy has achieved unprecedented clinical efficacy in patients with various types of advanced tumors; however, some patients experience delayed tumor shrinkage following an increase in tumor burden after such a therapeutic method. This phenomenon is called pseudoprogression and can lead to premature cessation of efficacious immunotherapeutic agents. Consequently, we summarized the available data on methods to differentiate pseudoprogression from true progression in patients who have been treated with immunotherapy including biomarkers, medical imaging techniques and biopsy. We also introduce hyperprogression and special pseudoprogression for improved evaluation of immunotherapy.

Keywords: Immunotherapy, psuedoprogression, ctDNA, PET, biopsy, hyperprogression

Introduction

Over the last few years, immunotherapy, which induces a persistent antitumor response in patients by stimulating immune recognition of tumors, has emerged as a promising treatment strategy for advanced tumors [1-3]. Immune checkpoint inhibitors (ICI), such as blockades that target programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte associated antigen (CTLA-4), are one of the most powerful tools in the immunotherapy armamentarium and offer a beneficial immunotherapeutic regimen to patients with various types of cancers [4-8]. The emergence and wide use of ICI has resulted in a dramatic breakthrough in cancer immunotherapy.

Immunotherapy is a completely new treatment pattern that is distinct from other therapeutic modalities, thus bringing major challenges to clinicians who are not familiar with it. One of these challenges is pseudoprogression, a transient increase of tumor burden followed by delayed tumor shrinkage, which clinicians may occasionally encounter while assessing the efficacy of immune checkpoint blockades.

Pseudoprogression during immunotherapy was first characterized in a phase II trial that evaluated the efficacy of ipilimumab, an anti-CTLA-4 antibody, in advanced melanoma [9]. The authors described a patient who experienced initial increased size of tumor lesions followed by a delayed partial response. Treatment with ICI targeting PD-1 or PD-L1 may also result in pseudoprogression in other types of solid tumors, such as bladder cancer, breast cancer, colorectal cancer, esophageal cancer, gastric cancer, head and neck cancer, lung cancer, pancreaticoduodenal cancer, ovarian cancer, renal cell cancer, sarcoma, and uterine cancer [10].

Pseudoprogression is defined as an increase in the size of the primary tumor or the appearance of a new lesion followed by tumor regression. Pseudoprogression is not true tumor progression, which has been proven by histopathological biopsies that found infiltration and recruitment of various immune cells, such as T or B lymphocytes, in the tumor [9, 10]. The occurrence of pseudoprogression has led to the development of immune-related response-evaluation criteria, such as irRC [11], irRECIST [12],

and iRECIST [13]. Treatment beyond progression is permitted under these modified criteria [14], which more accurately evaluate the efficacy of immunotherapy than the conventional criteria.

The incidence of pseudoprogression reported in prior studies was less than 10% [11, 14, 15]. However, a recent study determined that the incidence of atypical response is as high as 20%, which included new lesions and a greater than 10% increase in the total sum of the longest dimension that subsequently returned to below the baseline [16]. Thus, pseudoprogression, referring to all types of atypical response modes with a perceptible increase in tumor burden followed by subsequent clinical benefits, was underestimated in prior studies.

Currently, pseudoprogression is diagnosed using retrospective imaging data, which critically impedes the optimal application of immune checkpoint inhibitors because clinicians cannot accurately evaluate the treatment. At the rate at which immunotherapeutics are widely being utilized to treat tumor patients, determining how to accurately discriminate pseudoprogression from true progression is quite important for helping clinicians to avoid premature cessation of immunotherapeutic treatment and initiation of alternative treatments. Several studies have elucidated that some potential methods and factors were able to predict pseudoprogression. Therefore, this review summarizes the existing studies on pseudoprogression in immunotherapy that aimed at determining earlier and more accurate methods of identifying pseudoprogression in patients receiving immunotherapeutics.

Biomarkers

Cell-free DNA (cfDNA), also named circulating cell-free DNA (cfcDNA), is DNA fragments from dying cells that are freely circulating in the bloodstream [17]. In cancer patients, circulating tumor DNA (ctDNA), a subset of cfDNA, is a type of detectable DNA originating from tumor cells that have undergone apoptosis or necrosis. Several studies revealed that ctDNA, which is often referred to as a liquid biopsy for cancer, could be an applicable and noninvasive approach to monitor and evaluate many types of early stage cancers [18-20]. In addition, ctDNA is also an effective tool to evaluate the therapeutic response to immunotherapies [21, 22].

In a previously published case report, Guibert et al. [23] found a rapid and dramatic decrease in the level of KRAS-mutated ctDNA from two patients with KRAS-mutated adenocarcinoma who exhibited pseudoprogression in contrast with an increase in the level of ctDNA from a patient who exhibited true progression. A potential association probably exists between pseudoprogression and decreased ctDNA levels. Moreover, 9 pseudoprogression patients had either a ctDNA profile that was undetectable or was detectable at baseline with a subsequent decrease greater than 10-fold over the first 12 weeks of ctDNA detection [24]. This study demonstrated that ctDNA from patients with melanoma receiving PD-1 inhibitors, by either being undetectable at baseline or having a dramatic decrease in the baseline level, could predict pseudoprogression with a sensitivity of 90% (95% CI, 68%-99%) and a specificity of 100% (95% CI, 60%-100%). Consequently, we can conclude that decreased or low-level ctDNA correlates with pseudoprogression. Though there are only a few previously published studies on the correlation between ctDNA and immunotherapy pseudoprogression, this noninvasive method is promising in clinical practice. A larger cohort of patients, other types of cancers, and other immunotherapy agents are required in future studies to further validate the relationship between ctDNA and pseudoprogression in immunotherapy.

Chromosomal instability quantification of cfDNA is an effective indicator to evaluate the efficacy of immunotherapy [25]. Previous studies have reported cases of pseudoprogression that have manifested in decreased chromosomal instability quantification or genome instability number of cfDNA [25, 26]. It is not surprising that an index for the evaluation of immunotherapy may also be a biomarker to identify pseudoprogression, and further studies are needed to explore this association. Interleukin-8 (IL-8) levels were reduced and maintained lower than baseline in three tumor patients who had partial responses after first exhibiting increases in tumor burden [27]. The level of IL-8 is not only an important clinical marker of pseudoprogression but also a biomarker to monitor the clinical benefit of immune checkpoint inhibitors. Thus, all biomarkers that are capable of assessing the efficacy of immunotherapeutics may also be utilized to identify pseudoprogression. Consequently, oncologists ought to pay

more attention to these biomarkers in future studies and assessments of patients.

Moreover, since distinguishing pseudoprogression from true tumor progression in brain tumors is a challenging task for clinicians, multiple molecular changes have been validated as potential predictors for pseudoprogression, including p53 [28], small extracellular vesicles [29], O6-methylguanine-DNA methyltransferase methylated (MGMT) [30, 31], interferon regulatory factor (IRF9), X-ray repair cross-complementing gene (XRCC1) [32], isocitrate dehydrogenase 1 (IDH1) [33], Ki67 expression [34], and CDH2 protein alone or in combination with ELAVL1 protein [35]. Despite the fact that these potential biomarkers could distinguish pseudoprogression from true progression, the actual predictive value of these markers remains unclear in immunotherapy as well as in other types of tumors, and thus, they need to be further explored.

Medical imaging techniques

Computed tomography (CT) and magnetic resonance imaging (MRI) are conventional imaging methods that are utilized in the evaluation of tumor burden in patients during diagnosis, treatment, and follow-up. A previous study revealed that 12 out of 28 patients who had confirmed pseudoprogression by salvage pathologies experienced an unnecessary surgery risk because their tumors were misclassified as true tumor progression by MRI [36]. Therefore, there is an urgent need to obtain a novel imaging technique instead of conventional imaging to identify pseudoprogression.

Currently, positron emission tomography (PET) is one of the main techniques used for tumor evaluation and examination. This technique provides additional information correlated with tumor metabolism by labeling specific molecules with tracers that emit positrons and, thus, provides a more accurate diagnosis and treatment plan. Parametric response analysis of C-methionine (^{11}C-MET) PET was found to be an effective tool to evaluate immunotherapy response in brain tumors [37]. PET imaging is capable of identifying early pseudoprogression and delayed pseudoprogression in glioma patients under chemoradiotherapy [38, 39]. Moreover, PET was also capable of detecting pseudoprogression in immunotherapy. In a small retrospective study by Kebir et al. [40], PET imaging was utilized to distinguish pseudoprogression, which exhibited a low tracer uptake, from true tumor progression, which exhibited an intense tracer uptake, in 5 patients with melanoma brain metastasis undergoing treatment with ipilimumab or nivolumab. It appears that PET imaging, which can detect the degree of uptake of radiotracers, can differentiate true tumor progression from pseudoprogression better than conventional imaging techniques. Nevertheless, some practical and unknown factors should be taken into account when evaluating the predictive value of PET. A study showed that patients with pseudoprogression and a delayed partial metabolic response were incorrectly evaluated as having progressive metabolic disease by ^{8}F-FDG PET/CT [41]. Moreover, a prostate cancer patient with confirmed pseudoprogression showed intense radiotracer activity in a new lesion and in the enlarged tumor by prostate-specific membrane antigen (PSMA) PET/CT imaging [42]. Increased PSMA molecular expression and increased vascular permeability may explain why elevated tracer levels were reflected in a confirmed pseudoprogression case [42]; however, this report shed increased uncertainty of utilizing PET for evaluating pseudoprogression in a given type of carcinoma. Hence, increased tracer intake is currently not a feasible indicator of pseudoprogression in patients undergoing immunotherapy. The practical efficiency of PET to predict pseudoprogression is still controversial and needs further investigation.

Ultrasound (US) is a potential imaging method to detect pseudoprogression. US imaging detected pseudoprogression in metastatic melanoma patients undergoing PD-1 blockade with nivolumab by finding a decreased blood flow pattern in tumors [43]. US is superior in blood flow evaluation. When tumors enlarge with decreased blood flow inside, this enlargement may indicate pseudoprogression.

There are much more available studies on pseudoprogression and imaging in patients undergoing chemotherapy than immunotherapy. Imaging methods and imaging biomarkers used to differentiate pseudoprogressive from true progressive disease in patients undergoing chemoradiotherapy were introduced in previous studies, including parametric response

map [44], volume-weighted voxel-based multiparametric clustering [45], ferumoxytol [46], percent change of perfusion skewness and kurtosis [47], gadolinium contrast enhanced MRI [48], and interval change in diffusion and perfusion MRI parameters [49]. These potential imaging methods and imaging biomarkers should be considered in subsequent exploration of pseudoprogression in immunotherapy. Although most of the existing studies on pseudoprogression and imaging in patients undergoing immunotherapy are preclinical, the outcomes are propitious and hopeful. Therefore, this poorly explored domain merits further investigation to determine a clinically useful imaging tool that can identify pseudoprogression in immunotherapy.

Biopsy

Initially, histopathology revealed the presence of dense CD8+, TIA1+ and granzyme B+ lymphoid infiltrate in a lesion biopsy from a patient with pseudoprogression [9]. Therefore, histopathology of the enlarged tumor or new lesion biopsies is useful for making clinical decisions before utilizing imaging techniques. A case report recorded histological analysis of pseudoprogression [50]. The biopsy showed infiltration lymphocytes that were positive for CD3, CD4, or CD8 instead of tumor cells located at the metastatic lesion in a pseudoprogression patient with NSCLC receiving nivolumab treatment. From these two studies, we inferred that pseudoprogression consists of infiltration of multiple sorts of immune cells, which can be visualized by histopathology of a biopsy. Moreover, any single type of immune cell might appear in a pseudoprogression case. A recent case report by Masuhiro K revealed that CD3+ lymphocytes were infiltrated in the lesion that was considered to be pseudoprogression [51].

Currently, clinicians deduce pseudoprogression mostly by outcomes of lesion biopsy, which show infiltration of normal lymphocytes rather than tumor cells, before acquiring follow-up imaging of the patients. Meanwhile, it's necessary that researchers exclude infection or other situations that increase the number of immune cells. Notwithstanding that lesion biopsy is helpful to differentiate diagnosis outcomes, it is an invasive examination that requires suitable conditions. Thus, if necessary, oncologists should attempt to perform a tumor biopsy at the moment of disease progression to distinguish pseudoprogressive from true progressive disease and guide patient management.

Hyperprogression and special pseudoprogression in immunotherpy

Immunotherapy may present in various patterns and some special response patterns were recorded in former reports. In lung cancer, lung cavitation or pericardial effusion induced by pseudoprogression manifested in patients undergoing PD-1 inhibitor treatment [51, 52], which demonstrates that pseudoprogression in the same tumor type could have different clinical manifestations as a result of immune cell infiltration. Regarding prostate cancer, 86Ga-radiolabeled ligand (a radiotracer with high affinity to prostate specific membrane antigen) activity increased in PET of a patient with delayed tumor decrease, which may be explained by upregulation of PSMA molecular expression or increased vascular permeability [42].

Pseudoprogression can also be continuous. In a patient with malignant melanoma, when their liver metastasis was shrinking, a new peritoneal nodule appeared that had a subsequent remission [53]. According to a case report by Curioni-Fontecedro et al. [54], diffuse pseudoprogression appeared in a NSCLC patient taking Nivolumab, manifesting as multiple enlargements and metastases of tumors with an improved general condition. Pseudoprogression is generally accompanied with an improved general condition, whereas a deteriorating general condition may indicate true progression or even hyperprogression [55].

Hyperprogression is characterized as accelerated tumor progression and usually results in deterioration of disease following immunotherapy. Of note, a new pattern of progression, hyperprogression, is correlated with some predictive factors, including older age (more than 65 years old) [56], more than 2 metastatic sites [57], alterations of EGFR, MDM2/4 and DNMT3A [58], Pre-ICI dNLR, LDH, and concurrence of STK11 and KRAS mutations [59], but these predictive factors are poor at predicting hyperprogression.

Patterns of response in immunotherapy are quite complicated. Therefore, for improved patient management, clinicians should be aware

of these special patterns and carry out more careful evaluations when using immunotherapeutics. More potential or unconventional patterns are still needed to be reported.

Conclusion

In recent years, since immunotherapy has become more widespread, the correct evaluation of patients with this therapeutic modality has become a problem. Although some current biomarkers and medical imaging techniques are beneficial to differentiating pseudoprogression and true progression, they are still controversial and not sufficient to be applied in clinical practice. Currently, the confirmation of pseudoprogression is still conducted mostly by retrospective image analysis, resulting in premature cessation of effective treatment. Notably, biopsy is an effective diagnostic method that is usually used to deduce pseudoprogression before retrospective image analysis. However, biopsy is an invasive method that requires suitable conditions and chance. Consequently, liquid biopsies, such as ctDNA, are expected to be a noninvasive surrogate for tumor biopsies and have an outstanding potential to differentiate pseudoprogression from true progression in the future. Moreover, for better management of patients treated with immunotherapy, hyperprogression and special pseudoprogression should be paid extra attention to by clinicians. Further studies are imperative to develop a noninvasive method capable of differentiating pseudoprogression from true progression with proper clinical application.

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Disclosure of conflict of interest

None.

Address correspondence to: Jingdong Zhang, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, No. 44, Xiaohe Road, Dadong District, Shenyang 110042, Liaoning Province, China. Tel: +86-24-31916391; Fax: +86-24-31916391; E-mail: jdzhang@cancerhosp-ln-cmu.com

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