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Pseudoprogressions in Oncolytic Therapy: Alerts and Regulations Needed

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Commentary

Pseudoprogression (PsP) refers to either visually observed or imaging-detected tumor enlargement followed by regression after cancer therapies. Characterized by robust localized immune infiltration, PsP is most commonly seen in immunotherapies, with an occurrence rate of around 10% [1]. However, there was limited discussion of oncolytic therapy-related PsP. We argue that PsP is a commonly encountered phenomenon in oncolytic virotherapy, warranting increased attention during assessments in clinical applications and trials.

In a phase 1/2 study, PsP occurred in 45% of patients who received AdAPT-001 local injections [2]. Tumor enlargement was typically observed within the initial month, whereas tumor regression or stabilization at three months indicates PsP. Patients with PsP had superior daily functioning and prolonged survival compared to those with genuine progressions [3]. Delayed PsP, detected within a 10-month timeframe, was also noted with oncolytic treatments [4].

Currently, imaging plays a primary role in evaluating tumor stages. While assessing tumors typically follows the guidance of Response Evaluation Criteria in Solid Tumors (RECIST), it is challenging yet crucial to distinguish PsP from actual tumor progression in the initial stages. Patients with PsP may continue with current therapy, while individuals with confirmed tumor progression should contemplate a more forceful treatment approach. However, even with the utilization of CT and PET, precise inspection of the tumor is unattainable. Histological remission may occur far earlier than radiographic remission, and immune immersion may lead to an overestimation of tumor size in imaging.

While biopsy directly demonstrates therapeutic responses and immune infiltrations, it is invasive, regionalized, and not routinely done during follow-ups. In clinical research and applications, biomarkers indicating PsP should be acknowledged. Inflammatory indicators like viral-specific antibodies, IL-8, and HMGB1 are actively investigated. Non-invasive imaging techniques, such as PET-based T cell imaging and PD-L1 imaging, are also incorporated into clinical trials to enhance the comprehensiveness of evaluations [5,6].

Alongside the difficulties of evaluating diseases at therapeutic checkpoints, clinical ramifications caused by PsP should also be noted. While local injection of oncolytic virus facilitates accurate and optimal oncolysis, insitu inflammatory response and tissue necrosis can threaten adjacent blood vessels and nerves. Nerve compressions and vasculitic infiltrations adversely impact the

quality of life and may even pose life-threatening risks. Therefore, it is imperative to do comprehensive evaluations regarding the tumor locations and implement preventive strategies during oncolytic virotherapies.

As oncolytic virotherapies gain prominence in clinical practice, whether administered independently or alongside other treatments, it is imperative to underscore the necessity for enhanced restrictions. Essential inquiries must be posed:

1. Definition of PsP from both radiological and histological perspectives;
2. The gold standard for determining PsP, including its specificity and sensitivity;
3. The appropriate time window for differentiating PsP and tumor progressions;
4. Methodology for conducting prognostic assessments of patients with PsP;
5. Criteria for altering therapy;
6. Strategies for handling the local side effects of oncolytic virotherapy.

It is crucial to consider the impact of the focal mass effect on the infiltration of inflammation post-treatment. During the trial therapy, it is essential to implement modifications based on the staged assessment. Hence, we call on standardized assessments for oncolytic virotherapies, which would offer insights into infrequent adjustments to loading dosages, injection frequencies, and alterations in combination therapies.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Informed consent was obtained for this publication.

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