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# Do we need novel radiologic response criteria for brain tumor immunotherapy?

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**“As our knowledge of immunologic science has evolved and novel immunomodulatory agents have become available, we have begun to face unique challenges in the radiologic evaluation of patients...”**

Early phase studies of glioma vaccines have shown encouraging preliminary clinical activity. However, as the therapeutic basis of immunotherapy involves the induction of an inflammatory response in the lesion, it is often challenging to properly evaluate radiological responses. Long-term survival and/or regression are sometimes seen after initial imaging changes that can suggest immunotherapy failure, which highlights the limitations of conventional response evaluation approaches and calls attention to the need for more therapeutically relevant strategies to provide a reliable assessment of response to brain tumor immunotherapy.

As our knowledge of immunologic science has evolved [1], and novel immunomodulatory agents have become available, we have begun to face unique challenges in the radiologic evaluation of patients, given that inflammatory responses induced by vaccine strategies can mimic radiologic features of tumor progression [2]. A series of published studies of vaccination in brain tumor patients has suggested that the incidence of ‘tumor pseudoprogression’ following vaccine treatments is not insignificant, which may result in the possible unnecessary withdrawal of patients from these studies. Conversely, objective tumor regressions have been reported following postvaccine chemotherapy [3–5], which complicates the determination of whether efficacy resulted from a delayed response

to the immune therapy, a direct effect of the chemotherapeutic agent, or a combination of both. In this regard, Wheeler *et al.* reported that vaccinated patients receiving subsequent chemotherapy exhibited significantly longer times to tumor recurrence after chemotherapy, relative to their own previous recurrence times [5]. Furthermore, they demonstrated a correlation between vaccine responses and time-to-progression (TTP) spanning chemotherapy [4]. These findings imply that the biological status of these tumors at the time of switching from immunotherapy to chemotherapy may not represent pure tumor progression, but rather an effect of vaccine-induced immune responses within the persisting tumors. Indeed, we recently reported pathological evidence of pseudoprogression in a patient who participated in our Phase I/II vaccine study using type-1 polarizing dendritic cells and a potent immunoadjuvant, polyinosinic-polycytidylic acid (poly[I:C]) stabilized by lysine and carboxymethylcellulose (poly-ICLC) [6]. Following vaccination, this patient demonstrated enlargement of the gadolinium-enhanced lesion on MRI scans, and thus underwent craniotomy. However, the resected tissue revealed no evidence of a mitotically active tumor, and remarkable infiltration of CD68<sup>+</sup> macrophages and CD8<sup>+</sup> T cells. This implies that MRI-based evaluation of TTP requires careful interpretation

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of imaging data and, potentially, points to the significance of pathological confirmation to determine whether imaging changes reflect true progression versus pseudoproggression.

**“As the induction of inflammatory responses in the tumor microenvironment is the primary mechanism of action in immunotherapeutics, careful interpretation of radiological information is especially critical in brain tumor vaccine studies.”**

Pseudoproggression, however, is not a unique observation in immunotherapeutics. It has been well-recognized that concurrent chemo–radiotherapy may cause changes mimicking radiological progression as a consequence of therapeutic effects [7–10]. Although modern advancements with magnetic resonance spectroscopy (MRS), diffusion-weighted imaging (DWI) and PET scans have demonstrated promise for distinguishing tumor recurrence from treatment effects, further investigations are necessary to assess the imaging algorithms and accuracy of these modalities for differentiating true progression versus pseudoproggression. In terms of conventional MRI-based assessments, recently published recommendations for updated response criteria in high-grade gliomas by the Response Assessment in Neuro-Oncology (RANO) Working Group suggest that within the first 12 weeks of completion of radiotherapy, when pseudoproggression is most prevalent, progression can only be determined if the majority of the new enhancement is outside of the radiation field or if there is pathological confirmation of progressive disease [10]. Although the kinetics and time course of immunotherapy effects may not fit in the same time frame (i.e., within 12 weeks post-treatment), the proposed RANO criteria clearly have implications that can be reflected in the development of appropriate response criteria for brain tumor immunotherapy. As the induction of inflammatory responses in the tumor microenvironment is the primary mechanism of action in immunotherapeutics, careful interpretation of radiological information is especially critical in brain tumor vaccine studies.

Traditionally, most clinical studies have relied upon the modified WHO criteria [11], or more recently, the Response Evaluation Criteria In Solid Tumors (RECIST) [12,13] to assess clinical activity of anticancer agents. The Macdonald criteria [14], which is based on the WHO criteria, has been most commonly used in neuro-oncology. These standard criteria were primarily designed to capture effects of cytotoxic agents and depend on tumor shrinkage to demonstrate activity. However, it has been increasingly well-recognized in the field of cancer immunotherapy that immunotherapies demonstrate different kinetics compared with cytotoxic agents. Immunotherapeutics first induce cellular immune responses before influencing tumor burden or patient survival, whereas cytotoxic (e.g., chemotherapeutic) agents manifest their effects rather more immediately. Therefore, the unique characteristics of immunotherapeutic agents in clinical trials were extensively characterized in systemic cancers, especially malignant melanomas, and novel immune-related response criteria (irRC) were proposed [15–17]. Complete details of the new irRC

are described by Wolchok *et al.* [17]. The main considerations that constitute the irRC are that the appearance of measurable clinical activity at the tumor site may take longer for immunotherapies than for cytotoxic therapies; responses to immunotherapies may occur after conventional progressive disease (tumor burden increase); discontinuation of immune therapy may not be appropriate in some cases, unless progressive disease is confirmed; there should be allowance for ‘clinically insignificant’ progressive disease (e.g., small new lesions in the presence of other responsive lesions); and durable stable disease may represent clinical benefit. Response categories under the irRC are defined as immune-related (ir) complete response (irCR), ir partial response (irPR), ir stable disease (irSD) and ir progressive disease (irPD) using the same thresholds to distinguish between categories as defined under the standard WHO criteria [15,17]. According to irRC, an early increase in the size of lesions or the appearance of new lesions, which may be attributable to the infiltration of lymphocytes, does not preclude an irCR, irPR or irSD from being obtained at the next consecutive time point unless it adds to the tumor burden by at least 25%. These new patterns are considered clinically meaningful because they appear to be associated with favorable survival [15–17].

The irRC criteria were not necessarily designed for patients with brain tumors. However, it may be feasible to incorporate at least some aspects of the irRC into future radiological response criteria for brain tumor immunotherapy. Obviously, there are some unique factors that have to be carefully taken into consideration for the adaptation of the irRC to brain tumor settings. For example, most recurrences of malignant gliomas take place locally at the site of the residual tumor, and there has only been one reported case of leukoencephalopathy-like enhancing lesions that appeared transiently following glioma vaccines [18]. Nevertheless, if such observations are associated with overall positive clinical response and improved survival of patients without clinical signs of autoimmunity, such immune responses may be directed against infiltrative brain tumor cells but not normal brain cells, and may represent beneficial anti-tumor responses in the brain. Further radiological, pathological and immunological studies are warranted to determine the nature of those events.

**“The immune-related response criteria were not necessarily designed for patients with brain tumors. However, it may be feasible to incorporate at least some aspects of the immune-related response criteria into future radiological response criteria for brain tumor immunotherapy.”**

The original irRC also requires confirmation of irPD by a second scan at least 4 weeks apart. Considering the particularly delicate nature of the brain, it is necessary that this confirmation be carried out under very careful observation of the patient's condition. However, in this regard, the abovementioned RANO recommendations also emphasize various criteria, such as pathological assessment, to allow confirmation of progression within

the first 12 weeks of completion of radiotherapy [10], which may be appropriate considerations in the immunotherapeutic context. Perhaps, in brain tumor immunotherapy, it may also be acceptable that patients with a 25–50% increase in tumor cross-sectional dimension on the first MRI (i.e., unconfirmed progressive disease [PD]) would stay on the study, provided they were clinically stable or had symptoms that responded rapidly to the introduction of steroids. In such cases, the nature of the unconfirmed PD would be determined by whether the tumor shrinks on repeated imaging, with clinical stability on declining doses of steroids. In uncertain cases in which biopsy is safely feasible, pathological assessment may also provide direct confirmation of true progression versus pseudoprogression.

With these unique factors taken into consideration, adaptation of irRC and a part of the RANO recommendations seems feasible and may allow for more appropriate evaluation of clinical benefits in patients undergoing brain tumor immunotherapy. Further prospective evaluation of irRC in brain tumor immunotherapy trials is required to confirm their clinical utility.

In addition to the careful adaptation of new response criteria for the evaluation of radiological responses, the primary clinical end point used to define efficacy for brain tumor immunotherapy should also reflect the unique characteristics of immunotherapeutics, as discussed above. For example, given the dismal prognosis of malignant glioma, sustained stable disease would be considered to be a clinical benefit. As discussed above, immunotherapies often demonstrate delayed clinical effects. For example, in randomized trials, in which immunotherapies are compared with either placebo or inactive controls, Kaplan–Meier curves of overall survival (OS) may be superimposable for a time, before separation is observed at certain periods after random assignments (for a review, see [15]). Our recent Phase I/II study also demonstrated

prolonged OS (median 12 months in patients with recurrent glioblastoma multiforme), despite the fact that the early response rate based upon conventional criteria was modest [6]. Interestingly, in a recent Phase III study that led to the first FDA approval of vaccines for metastatic castration-resistant prostate cancer [19], vaccination prolonged OS but had no effects on TTP. These independent observations may reflect the challenges for accurately evaluating TTP, and also point to the significance of considering OS to be an important, and perhaps the primary, end point for cancer immunotherapy.

In conclusion, many observations and considerations for improved evaluation systems in the field of cancer immunotherapy and neuro-oncology seem relevant to our goal of improving patient management in brain tumor immunotherapy. Careful adaptation of these systems and end point designs will probably allow us to more properly assess clinical benefits of brain tumor immunotherapy.

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