Assessing Response of High-Grade Gliomas to Immune Checkpoint Inhibitors

Solmaz Sahebjam, MD, Dexter G. Stallworth, MD, Sepideh Mokhtari, MD, Nam D. Tran, MD, PhD, and John A. Arrington, MD

Background: Immunotherapeutic agents, especially checkpoint inhibitors, have emerged as the mainstay of therapy for several solid and hematological malignancies. These therapies are under investigation for the treatment of high-grade gliomas and brain metastases.

Methods: This article reviews the unique challenges encountered when evaluating changes on magnetic resonance imaging (MRI) of glioblastomas seen in response to immunotherapy and checkpoint inhibitors and how to effectively incorporate MRI findings into the response assessment of high-grade gliomas to these emerging therapies.

Results: An increase in tumor size or the appearance of new lesions on MRI may represent either an immune-mediated inflammatory response or true tumor progression, which may precede the subsequent stabilization or response of high-grade gliomas to immunotherapy. These MRI findings should not result in the mandatory cessation of immunotherapy in patients with high-grade glioma.

Conclusions: Although immunotherapy Response Assessment for Neuro-Oncology criteria have been developed to assist with response assessment of high-grade gliomas to immunotherapy and to provide guidance with treatment decisions, these criteria have not been validated in prospective clinical trials. In patients with brain tumors who are receiving immunotherapy, MRI findings suggestive of disease progression should be evaluated with caution to prevent premature discontinuation of potentially beneficial therapies. Close clinical monitoring with appropriate short-term, follow-up imaging is often necessary, and histopathological analysis may be required in some cases to confirm disease progression before a decision on continuation of these novel therapies can accurately be made.

Introduction

Immune checkpoint inhibitors have emerged as a mainstay of treatment for a variety of advanced malignancies. Antibodies against cytotoxic T-lymphocyte-associated protein 4, programmed death 1 (PD-1), and its ligand (PD-L1) have demonstrated significant clinical benefit in several solid and hematological malignancies, and their list of approved indications is expanding.

Anti–PD-1/PD-L1 antibodies alone or in combination with ipilimumab, an anti–cytotoxic T-lymphocyte-associated protein 4 antibody, is being investigated in patients with high-grade gliomas.1-3 These
Assessing Radiographical Findings

Initial increases in tumor size or the appearance of new lesions can precede the subsequent response of solid tumors to immunotherapeutic agents. Premature discontinuation of immunotherapy based on the initial increase in tumor burden can deprive patients of potentially beneficial treatments. To address this challenge, new guidelines for the evaluation of response to immunotherapeutic agents in solid tumors have been developed. Immune-related Response Criteria allows continuation of treatment with appropriate follow-up time points to confirm disease progression. Similar imaging findings have been observed in patients with high-grade glioma who have received immunotherapeutic agents such as immune checkpoint inhibitors. The appearance of a new lesion or the progression of existing lesions following the initiation of immunotherapy can represent either an immune-mediated inflammatory response or true tumor progression. It is often difficult to differentiate tumor growth from treatment changes on imaging within the first 6 months after the initiation of immunotherapy. An effective immune response may take time to develop, and brain tumors may initially progress after the initiation of immunotherapy. Therefore, an increase in tumor burden does not necessarily preclude subsequent clinical benefit, and delayed effective, immune response may result in subsequent stabilization or regression of the tumor. Differentiating high-grade gliomas that initially progress after immunotherapy but will subsequently respond from those tumors that will not respond is a critical challenge. Furthermore, in some cases, the appearance of new lesions or the increase in size of the enhancing lesions can be the result of immune-related responses rather than tumor growth. Hence, response criteria specific for GBMs treated with immunotherapies, such as checkpoint inhibitors, is critical to prevent the premature termination of these therapies.

To accurately assess the imaging changes of high-grade glial tumors and GBMs to immunotherapy, a historical perspective and an understanding of the evolution of imaging response assessment in neuro-oncology is helpful. Macdonald, Response Evaluation Criteria In Solid Tumors, and World Health Organization criteria assess the imaging response of brain tumors to the direct antitumoral effect of cytotoxic therapy with either single or bidimensional measurements of the contrast-enhancing component of the tumor. Macdonald criteria were developed for computed tomography prior to the advent of magnetic resonance imaging, which is now standard of care for evaluating the imaging response of high-grade gliomas to therapy. Macdonald criteria incorporate the changes in bidimensional tumor measurements with clinical assessment and steroid dose for the response assessment of high-grade gliomas such as GBM to therapy.

Bidimensional measurements of the contrast-enhancing component of a GBM is not always an accurate assessment of the overall extent of the tumor, and measurable change in the contrast-enhancing portion of a GBM does not always represent an accurate assessment of response to therapy. Rather than being an accurate surrogate of GBM response to therapy, change in contrast enhancement reflects changes in the vascular permeability of the brain and tumor to contrast agents and can be seen with nontumoral, treatment-related changes such as ischemia, inflammation, acute and delayed radiation effects, and tumor growth. Now that novel agents with different mechanisms of actions are being investigated, the response assessment of imaging changes is more complex because of treatment-related imaging findings that mimic tumor growth (pseudoprogression) and treatment-related imaging findings that mimic tumor response (pseudoresponse). Limiting the imaging response assessment of GBMs to bidimensional measurements of enhancing tumors and not incorporating the assessment of the nonenhancing portion of GBMs is a significant limitation of the Macdonald criteria. To adequately address the unique imaging challenges of GBM and provide guidance in distinguishing tumor growth from treatment-related responses, changes in response-assessment criteria were necessary.

Response Assessment in Neuro-Oncology (RANO) criteria published in 2010 were a collaborative effort to update and standardize response criteria for high-grade gliomas and replace the Macdonald criteria. RANO imaging criteria incorporate fluid-attenuated inversion recovery (FLAIR) with the bidimensional measurements of the enhancing portion of the GBM obtained on contrast-enhanced, T1-weighted imaging. By incorporating FLAIR signal changes into the imaging response assessment of GBM, RANO criteria allow the assessment of the non-enhancing component of the GBM as well as associated vasogenic edema and help distinguish treatment-related changes from true tumoral changes. RANO criteria give specific clinical and imaging findings required for the diagnosis of disease progression. Imaging findings that meet RANO criteria for tumor progression include:

- Development of new lesions outside the radiation field
- ≥ 25% increase in the sum of perpendicular diameters of enhancing lesions
- Substantial worsening of T2-weighted FLAIR signal changes

Critical to the RANO criteria is the guidance in assessing treatment-related imaging changes and distinguishing these changes from tumor growth or tumor
regression. Changes in bidimensional measurements of the enhancing component of a GBM can reflect nontumoral changes or treatment-related effects and do not always accurately assess response to therapy. Pseudoprogression represents imaging changes related to treatment effects and not true tumor progression. The imaging changes of pseudoprogression include increasing measurable enhancement of a lesion associated with increasing FLAIR signal changes and can be seen in patients with GBM in the first 3 months following postoperative radiotherapy and temozolomide (Fig 1).

RANO criteria require that progressive disease not be diagnosed within 3 months of the completion of therapy with radiation and temozolomide unless there is new enhancement outside of the radiation field or the patient has clinically declined. Although RANO criteria require the cessation of therapy when there is either clinical or imaging evidence of progressive disease, they do allow continuation of therapy in patients who demonstrate progressive imaging findings of an unclear etiology. Temozolomide should not be stopped in these patients until progressive changes are confirmed on follow-up imaging and as long as the patient remains clinically stable. Pseudoresponse, seen as decreasing le-
ion enhancement associated with increasing FLAIR signal changes, represents tumor growth that mimics the response of GBM to therapy. This can be seen in patients receiving antiangiogenic therapy, including therapy with bevacizumab. Tumor progression can be diagnosed per RANO criteria in these patients by the substantial worsening of FLAIR signal changes, even if there is stable or decreasing enhancement (Fig 2).

New and additional challenges are encountered when evaluating the imaging changes of high-grade gliomas in response to immunotherapy. Correctly assessing new or progressive lesions that occur during immunotherapy is critical, because early, progressive imaging findings may not preclude subsequent response to therapy and overall benefit. Changes in contrast enhancement and FLAIR signal remain the cornerstone of the imaging response assessment for GBM and high-grade glial tumors to immunotherapy. When GBMs demonstrate a decrease in measurable enhancement and a decrease in FLAIR signal changes after the initiation of immunotherapy, the diagnosis of positive response to therapy can confidently be made. When GBMs demonstrate an increase in measurable enhancement confirmed on subsequent follow-up imaging, the diagnosis of disease progression can also be made (Fig 3). Although advanced imaging

Fig 2A–D. — Pseudoresponse. (A, C) Axial FLAIR and (B, D) contrast-enhanced, T1-weighted images obtained at baseline (A, B) and after initiation of antiangiogenic therapy (C, D). (C, D) Post-treatment imaging demonstrates a significant increase in FLAIR signal changes (green arrows), with the areas of enhancement (red arrows) either remaining stable or decreasing. The substantial increase seen in FLAIR signal changes allows the diagnosis of disease progression to be made without progression of the enhancing tumor. FLAIR = fluid-attenuated inversion recovery.
Fig 3A–D. — Response to immunotherapy in combination with bevacizumab followed by progression. (A) Axial contrast-enhanced, T1-weighted images at baseline and surveillance examinations obtained at 6-week intervals following initiation of pembrolizumab and bevacizumab (B–D). (B) The 6-week, post-treatment imaging demonstrates an interval decrease in enhancement of the tumor following therapy. A decrease was observed in the enhancing tumor in both the superficial (red arrows) and deep anterior tumor margins (green arrows). (C) The 12-week, post-treatment imaging demonstrates increasing enhancement along the deep anterior tumor margin (green arrows) that continued to progress on (D) 18-week, post-treatment imaging, thus documenting disease progression. The superficial portion of the glioblastoma remained stable and did not progress (red arrows).

Fig 4A–F. — Response to immunotherapy in combination with bevacizumab. (A, D) Axial perfusion cerebral blood volume, (B, E) contrast-enhanced, T1-weighted, and (C, F) fluid-attenuated inversion recovery images are shown at baseline (A–C) and at 6 weeks following initiation of immunotherapy and bevacizumab (D–F). Post-treatment examination demonstrates an interval response to therapy with a decrease in perfusion (red arrows) and enhancement (green arrows) of the glioblastoma as well as a decrease in associated vasogenic edema (yellow arrows).
techniques, including perfusion imaging, are not part of the formal RANO or immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria for the response assessment of GBMs to immunotherapy, they can be helpful in distinguishing treatment effects from tumor growth. Perfusion imaging can estimate and evaluate changes in cerebral blood volume (CBV) and cerebral blood flow in tumors and can be helpful in distinguishing progressive enhancement related to tumor growth from progressive enhancement resulting from treatment effects. Enhancement related to tumor growth typically demonstrates increased perfusion and elevated CBV, whereas enhancement related to treatment-related changes or necrosis usually demonstrates decreased perfusion and decreased CBV. GBMs treated with immunotherapy in combination with bevacizumab will typically demonstrate an interval decrease in measurable enhancement and FLAIR signal changes, as well as decreased CBV on perfusion imaging (Fig 4).

Although RANO criteria allow for the continuation of therapy in patients with progressive imaging changes of unclear etiology, they do not permit the continuation of treatment after there is imaging evidence of disease progression. To allow patients with initial progression of imaging findings after the initiation of immunotherapy who meet the RANO criteria of progression of disease to continue therapy and potentially receive delayed or long-term clinical benefit, new guidelines and the iRANO criteria were developed.6 iRANO criteria integrate the immune-related Response Criteria concept of confirmation of radiographical progression with the RANO guidelines, defining complete response, partial response, stable disease, and progressive disease, and they allow the continuation of immunotherapy, such as immune checkpoint inhibitors, in patients who show early imaging progression within the first 6 months of initiating therapy until progression is confirmed on subsequent imaging and as long as the patient remains clinically stable (Fig 5).6 The progressive imaging findings are expected to stabilize or improve within 3 months in patients who will...
receive long-term clinical benefit. To clarify whether the progressive imaging findings represent tumor progression or treatment-related changes, follow-up imaging is typically obtained 3 months after the initial imaging evidence of progressive disease. It is noteworthy that iRANO criteria have yet to be validated in prospective clinical trials and clinical cohorts.

Conclusions
Response assessment of patients with glioblastomas treated with checkpoint inhibitors is challenging. Although immune-related Response Criteria and Response Assessment in Neuro-Oncology criteria were developed to assist with response assessment to immunotherapy and provide guidance with treatment decisions, Response Assessment in Neuro-Oncology criteria have not been validated in prospective clinical trials in assessing the response of high-grade gliomas treated with checkpoint inhibitors. Close clinical monitoring, short-term imaging follow up, and, in some cases, histopathological analysis may be required to prevent the premature discontinuation of potentially beneficial therapies.

References