Neuroimaging of Peptide-based Vaccine Therapy in Pediatric Brain Tumors: Initial Experience

Andre D. Furtado, MD[a], Rafael Ceschin, BS[a,b], Stefan Blüml, PhD[c], Gary Mason, MD[d], Regina I. Jakacki, MD[d], Hideho Okada, MD[e], Ian F. Pollack, MD[f,g], Ashok Panigrahy, MD[a,*]

KEYWORDS

• Pseudoprogression • Vaccine therapy • Pediatric brain tumors • MR spectroscopy

KEY POINTS

- Peptide-based immunotherapy for pediatric brain tumors is associated with the presence of treatment-related heterogeneity, including that of pseudoprogression.
- Conventional MR imaging has limitations in the assessment of treatment-related heterogeneity, particularly regarding distinguishing true tumor progression from efficacious treatment responses.
- Advanced neuroimaging techniques, including diffusion magnetic resonance (MR), perfusion MR, and MR spectroscopy (MRS), may add value in the assessment of treatment-related heterogeneity.
- Recent delineation of specific response criteria for immunotherapy of adult brain tumors (Immunotherapy Response Assessment in Neuro-Oncology [iRANO]) is likely to be relevant to the pediatric population.

INTRODUCTION

There has been significant progress in the field of immunotherapy, within oncology, with recent Food and Drug Administration approval of immunotherapeutics for metastatic melanoma and non–small cell lung cancer and the advent of multiple immunotherapy clinical trials for primary and metastatic adult brain tumors.[1–4] These adult immunotherapy studies have identified unique responses in regard to treatment response heterogeneity (as characterized by pseudoprogression, delayed responses, therapy-induced inflammation, and so forth) and resulting radiographic challenges. As such, new guidelines have been recently published by the iRANO group to allow for refinement of response assessment criteria for neuro-oncology patients

Disclosure: See last page of the article.

[a] Department of Radiology, University of Pittsburgh, 3600 Forbes Avenue, Pittsburgh, PA 15213, USA; [b] Department of Bioinformatics, University of Pittsburgh, 5607 Baum Boulevard, Suite 500, Pittsburgh, PA 15206, USA; [c] Department of Radiology, Children's Hospital of Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA 90007, USA; [d] Department of Pediatrics, University of Pittsburgh, 4401 Penn Avenue, Pittsburgh, PA 15224, USA; [e] Department of Neurosurgery, University of California, San Francisco, 505 Parnassus Avenue, M-779, San Francisco, CA 94143, USA; [f] Department of Neurosurgery, University of Pittsburgh, 200 Lothrop Street, Pittsburgh, PA 15213, USA; [g] Children's Hospital of Pittsburgh, University of Pittsburgh Cancer Institute, University of Pittsburgh School of Medicine, University of Pittsburgh, 4401 Penn Avenue, Pittsburgh, PA 15224, USA

* Corresponding author. Department of Pediatric Radiology, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Avenue, Pittsburgh, PA 15224.

E-mail address: panigrahya@upmc.edu

Neuroimag Clin N Am 27 (2017) 155–166
http://dx.doi.org/10.1016/j.nic.2016.09.002

receiving immunotherapy.[4] These iRANO criteria suggest that among adult patients who demonstrate imaging findings meeting RANO (response assessment in neuro-oncology) criteria for progressive disease within 6 months of initiating immunotherapy, including the development of new lesions, confirmation of radiographic progression on follow-up imaging is recommended provided that the adult patient is not significantly worse clinically.[4]

The authors' institutions is currently engaged in multiple peptide-based vaccine trials for children with diffuse intrinsic pontine glioma (DIPG), recurrent high-grade glioma, recurrent low grade-glioma, and recurrent ependymoma,[5–7] The authors have recently described the occurrence of heterogeneous treatment response (including pseudoprogression), which has remarkable similarity with what has been seen in some adult immunotherapy studies. The purpose of this review article is to highlight the authors' initial experience with regard to the emerging radiographic challenges related to heterogeneous treatment response, including that of pseudoprogression, with the use of peptide-based vaccine therapy in pediatric brain tumors. The authors' initial experience with some of the advanced neuroimaging techniques, including diffusion MR and MRS, is also described to help address some of these radiographic challenges.

CONVENTIONAL MR IMAGING

The authors have noted multiple forms of treatment-related heterogeneity in different pilot studies of peptide-based vaccine therapy for pediatric brain tumors, particularly in DIPG, recurrent supratentorial high-grade tumors, and recurrent low-grade gliomas. Conventional MR imaging supplemented with MRS, diffusion MR, and perfusion MR was typically performed serially at regular intervals depending on the specific protocol while on the peptide-based vaccine therapy (**Fig. 1**) (ie, every 6 weeks for newly diagnosed patients receiving radiation). The different forms of treatment-related heterogeneity that have resulted in radiographic challenges include (1) pseudoprogression, characterized by transient enlargement of the tumor with associated clinical symptoms, recently published for the authors' DIPG cohort (**Fig. 2**A) and recurrent low-grade

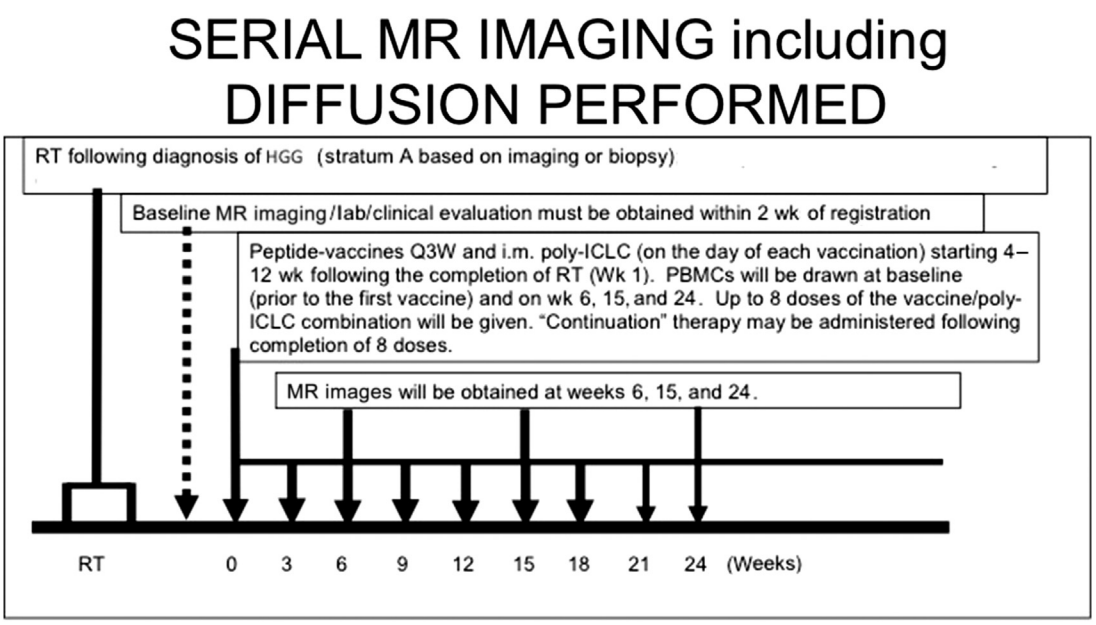

Fig. 1. Example of timing of MR imaging scans for new diagnosis of high-grade pediatric glioma treated with radiation and serial peptide-based vaccine therapy. The time of conventional MR imaging during the course of peptide-vaccine therapy for this particular stratum (A) of the vaccine study was approximately every 6 weeks after initiation of therapy. Straum A of included new diagnosis of high-grade gliomas based on imaging (DIPG) or biopsy and included initial radiotherapy followed by peptide-based vaccine. Note, additional time points of imaging were obtained during clinical pseudoprogression. The timing of serial MR imaging was different for different strata. Diffusion imaging was integrated with all conventional MR imaging scans. MRS and perfusion MR were performed in conjunction with only certain conventional MR imaging scan for logistic reasons. HGG, high grade glioma; i.m., intramuscular; PBMC, peripheral blood mononuclear cell; Q3W, every 3 weeks; RT, radiotherapy.