Results of A Pilot Study of Vaccinations with HLA-A2-Restricted Glioma Antigen-Peptides in Combination with Poly-ICLC for Children with Newly Diagnosed Malignant Brain Stem Gliomas, Non-Brainstem High-Grade Gliomas, or Recurrent Unresectable Gliomas

Ian F. Pollack MD; Regina Jakacki; Lisa H. Butterfield; Hideho Okada MD, PhD

Children's Hospital of Pittsburgh and the University of Pittsburgh Cancer Institute, University of Pittsburgh School of Medicine

CONGRESS OF NEUROLOGICAL SURGEONS
2011 ANNUAL MEETING
WASHINGTON, DC
OCTOBER 1-6, 2011

Introduction

Malignant astrocytomas are among the most common and deadly brain tumors of childhood, and most children succumb within several years of diagnosis, despite current treatments. New therapeutic approaches are needed that target the unique features of these tumors. During the last decade, we have gained significant preclinical and clinical experience with immunotherapy for adult gliomas (1), and extended these insights to the treatment of childhood gliomas, based on our observation of substantial similarities between these tumors in their expression of selected glioma-associated antigens (GAAs) (2).

Methods

Building upon these data, we initiated a pilot trial of subcutaneous vaccinations with synthetic peptides for GAA epitopes emulsified in Montanide-ISA-51 every 3 weeks for 8 courses, and intramuscular administration of poly-ICLC on the day of each vaccination in HLA-A2+ children with newly diagnosed malignant brainstem gliomas, non-brainstem malignant gliomas, or recurrent gliomas. GAAs for these peptides were EphA2, interleukin (IL)-13 receptor-a2, and survivin. The primary endpoints were safety and T cell responses against the vaccine-targeted GAAs. Preliminary data on treatment response was evaluated clinically and by MR imaging.

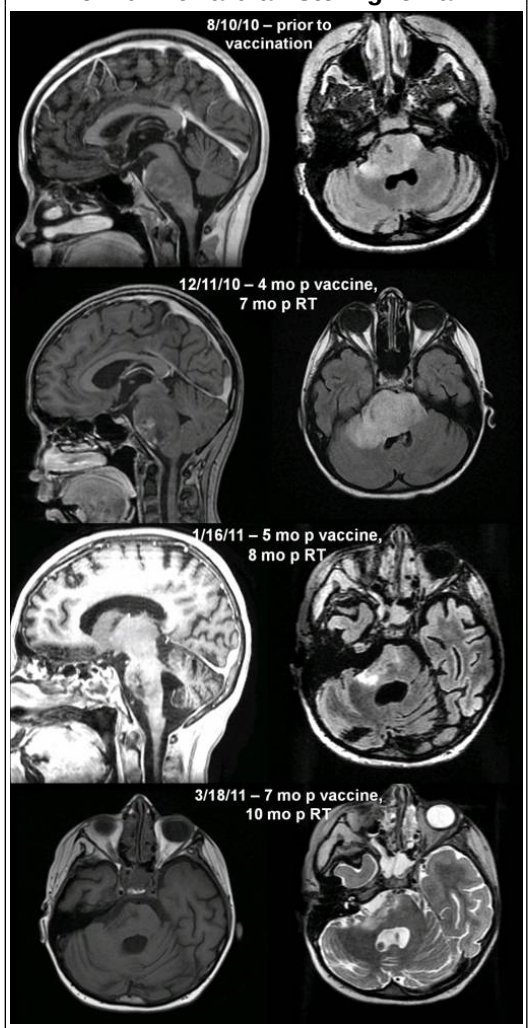
Results

To date, 18 patients have been treated on this protocol, 10 of whom had newly diagnosed brainstem gliomas. Toxicities have been principally limited to fatigue, injection site reactions, and low-grade fever. One child with a BSG had transient tumor enlargement 4 months after beginning vaccination (7 months after irradiation) that later regressed and culminated in a sustained partial response (PR), consistent with pseudoprogression (Figure 1). Two other children with BSG who had transient neurologic deterioration followed by subsequent stabilization also remained alive > 11 months from diagnosis without further intervention. Among 16 patients evaluable for response, 12 had sustained stable disease, 1 had a PR, and 1 has a continuing complete response after surgery. Thirteen patients exceeded the expected median progression-free survival for BSG or HGGs, and 6 are on long-term maintenance vaccine therapy. Seven of 10 BSG patients have survived > 11 months after diagnosis. ELISPOT analysis, completed in five children, showed response to IL13Ra2 in 4, EphA2 in 2, and survivin in 1 (Figure 2). Tetramer responses to both IL13Ra2 and EphA2 were also noted. Additional ELISPOT and tetramer assays will be performed as the patients complete vaccination or come off study.

Conclusions

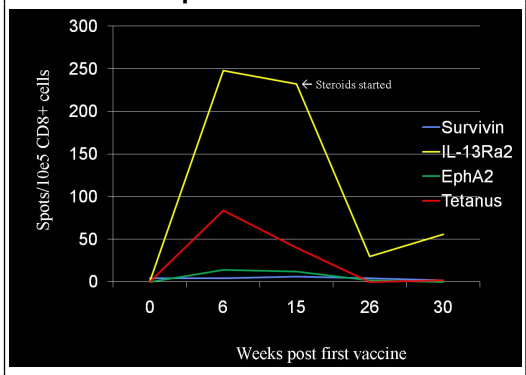
Our preliminary results indicate that a multipeptide vaccination approach is well tolerated in children with gliomas, and has evidence of both immunological and clinical activity.

Figure 1. MRI evolution of response in a child with a brainstem glioma



Initial pseudoprogression was followed by a sustained response.

Figure 2. Evolution of ELISPOT Response Over Time



Response correlated with radiological evidence of tumor pseudoprogression and subsequent regression.

Learning Objectives

1) Understand the rationale for vaccine-based immunotherapy as a treatment strategy for gliomas; 2) Gain familiarity with the issues underlying immunological response and corrrelative laboratory monitoring; 3) Be familiar with the results of the current trial.

References

1.Okada H., et al. Induction of CD8+ T cell responses against novel glioma-associated antigen peptides and clinical activity by vaccinations with a-type-1-polarized dendritic cells and poly-ICLC in patients with recurrent malignant glioma. J Clin Oncol 29: 330-336, 2011.

2.Okada H, Low KL, Kohanbash G, McDonald HA, Hamilton RL, Pollack IF. Expression of glioma-associated antigens in pediatric brain stem and non-brain stem gliomas. J Neuro-Oncol 88: 245-250, 2008.