Abstract LB-131
Peptide Vaccine Therapy for Childhood Gliomas: Interim Results of a Pilot Study
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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. Bosudov et al. (1) have used a tumor-infiltrating lymphocyte (TIL) approach to treat patients with objective responses or stable disease after the initial 8 vaccine cycles had the option of receiving additional booster vaccines at 6-week intervals thereafter for up to 2 years.

For newly diagnosed patients with BSG or HGG, vaccination began 4-12 weeks after completion of irradiation. Chemotherapy was permitted during but not after irradiation. Eligible HGG histologies were glioblastoma, gliosarcoma, and anaplastic astrocytoma. For children with recurrent disease, recovery from the toxicity of prior therapies was required. Children with low-grade gliomas must have recurred despite at least 12 months of chemotherapy/biological regimens. Other key eligibility criteria included: Kamofsky or Lansky score ≥ 50, age 18 months to 19 years, and being on either no corticosteroids or no more than 0.1 mg/kg/d decadron for at least one week prior to registration and beginning vaccine therapy.

GAAs for the vaccine peptides were EphA2, interleukin (IL)-13 receptor-α2, and survivin. The primary endpoints were safety and T cell responses against the vaccine-targeted GAAs, assessed by Enzyme-linked immunospot (ELISPOT) and tetramer assays. Preliminary data on treatment response was evaluated clinically and by MR imaging.

Materials and Methods
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 (BSG), nonbrainstem malignant gliomas (HGG), or recurrent gliomas. A2+ children with objective responses or stable disease after the initial 8 vaccine cycles had the option of receiving additional booster vaccines at 6-week intervals thereafter for up to 2 years.

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Synthetic Glioma-Associated Antigen and Helper Peptides in the Vaccine

**Antigen Peptides**

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Presented By</th>
<th>Amino Acid Sequence</th>
</tr>
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<tbody>
<tr>
<td>IL-13Rα2</td>
<td>HLA-A2</td>
<td>AYPFSCPA</td>
</tr>
<tr>
<td>EphA2</td>
<td>HLA-A2</td>
<td>TLAQDPVR</td>
</tr>
<tr>
<td>Survivin-α</td>
<td>HLA-A2</td>
<td>LAQEFULV</td>
</tr>
<tr>
<td>Tetanus Toxoid(TE60)</td>
<td>Pan-DR</td>
<td>AAVCNKRSITEL</td>
</tr>
</tbody>
</table>

Strata C, D (Recurrent Gliomas)

Clinical Results

To date, 24 patients have been treated on this protocol: 10 with newly diagnosed BSG treated with irradiation alone, three with newly diagnosed BSG treated with irradiation and concurrent chemotherapy, five with newly diagnosed HGG treated with irradiation and concurrent chemotherapy, three with recurrent HGG, and three with multiply recurrent low-grade glioma, after failure of numerous prior regiments. Patients have received 1-11 courses of therapy (median 5 to date).

Systemic toxicities have been principally limited to fatigue, injection site reactions, and low-grade fever. However, there have been 7 cases of at least possible immunologically-mediated pseudoprogression. All but one case was associated with transient neurologic deterioration, which in two cases was severe. The first child had acute, neurologic worsening with central tachypnea associated with radiographic worsening 4 months after beginning vaccination (6 months after irradiation. 3 weeks after the sixth vaccine). Symptoms improved on corticosteroids and imaging one month later showed a dramatic PR (Figure 1), which was maintained after corticosteroids were weaned. Vaccination was resumed and the radiographic response was sustained for 11 months, although the child ultimately succumbed to tumor progression 19.5 months post-diagnosis. A second child developed acute worsening of lower brainstem function in conjunction with vomiting 48 hours after the 8th vaccine (5 months after RT) and presented to a local ER with a shock-like picture, felt secondary to aspiration pneumonia. An MRI scan done 48 hours after initiation of high-dose steroids showed new areas of nodular and patchy enhancement and increased tumor size. Lower brainstem dysfunction slowly improved over the next several weeks, and steroids were weaned. A repeat MRI done 6 weeks later, on much lower doses of steroids showed decreased enhancement with a decrease in tumor size. Serial qualitative analysis of ADC maps showed relatively increased signal in the medulla, and serial MR spectroscopy showed relative preservation of NAA/Choline and Choline/creatinine ratios suggestive of pseudoprogression. This was resolved after weaning high-dose steroids and vaccination was resumed. The patient remained alive 19.5 months after diagnosis, having received a total of 10 cycles of vaccination. A partial response was also observed in a child with a thalamic GBM, which was maintained for 14 months after diagnosis, and another with a multiply recurrent metastatic low-grade glioma, who remains on therapy, having received 11 vaccinations to date.

**Immunological Results**

ELISPOT analysis has been completed to date in seven of 19 children with evaluable samples, and showed responses in six: to IL13Rα2 in 5, EphA2 in 3, and survivin in 3. The child that had the sustained PR had striking persistence of ELISPOT response to IL13Rα2 extending over 33 weeks. Tetramer responses to both IL13Rα2 and EphA2 were noted in one child (Figure 2). Specimens in 12 other children are pending analysis.

Tissue was available for immunohistochemical assessment antigen expression in five children, and all five showed immunoreactivity for at least two vaccine antigens. Specimens have been obtained in three other children and are pending analysis.

Conclusions

Peptide-based vaccination has been well tolerated in children with gliomas, with no Grade 3 non-CNS toxicities. Distinguishing pseudoprogression from true progression has been challenging, and requires serial imaging studies, during which time vaccines have been withheld and corticosteroids used for symptom management. Immunological and clinical evidence of activity has been obtained. More extensive analyses of efficacy in a multi-institutional context are warranted.

References


Acknowledgements

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