Phase I Dose Escalation Study of Autologous Tumor Lysate-Pulsed Dendritic Cell Immunotherapy for Malignant Gliomas in Pediatric Patients

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2002 CDC Data for Children 0-19 Cancer Incidences per 100,000

- Renal: 0.6
- AML: 0.7
- Soft Tissue: 1
- Bones and Joints: 0.9
- Hodgkin Lymphoma: 1.1
- NHL: 1.1
- Brain and CNS: 2.9
- ALL: 3
- Other: 4.3

Total: 10.0
Pediatric Brain Tumor Survival

• WHO Grade III and IV astrocytomas 12%
  – 5 year OS = 40-50% Grade III
  – 5 year OS = 20% Grade IV (completely resected), almost 0% if not GTR

• Medulloblastoma 16-18%
  – 10 year OS = 50-60%
Standard Therapy for Pediatric Brain Tumors

• Varies immensely depending upon tumor histopathology
  – Medulloblastoma (Standard Risk)
    • Concurrent chemo/CS-XRT for about 6 weeks, and then 9 cycles (1 per month) of chemotherapy
  – High Risk (Metastatic dz., residual tumor)
    • No absolute consensus: Radiation therapy up-front (similar to standard risk) versus chemotherapy and ASCT followed by radiation therapy if necessary
    • Prognosis remains decent, but severe neurocognitive defects
Standard Therapy

• High grade astrocytoma
  – Largest pediatric cohort treated with XRT + vincristine followed by prednisone, CCNU, vincristine “maintenance” therapy
  – Attained about 30% 5-yr OS

• Infant Brain Tumors
  – Chemotherapy followed by consolidation with ASCT, trying to avoid XRT
Issues with Immunotherapy in Pediatric Patients

• Differences in immune function/responses between adult and pediatric patients
• Immune reconstitution following intensive chemotherapy regimens
• Potential unknown long-term side effects of active immunotherapy
• Feasibility of lymphocyte/dendritic cell collection and tumor tissue collection
Dendritic Cell-based Tumor Vaccines

- Tumors have immunogenic antigens, but are poor APCs

- DCs are “professional” APCs that process/present tumor antigens to activate T-cells to stimulate immune rejection of tumor cells
Dendritic Cells: “Professional” Antigen-Presenting Cells

1) Recruitment of the progenitors

2) Ag capture

Peripheral tissues

Blood

3) Migration/Maturation

Lymph

Bone marrow

Secondary lymphoid organs

4) Ag presentation to T cells
Dendritic Cell-based Tumor Vaccines

from Liau LM et al., *Brain Tumor Immunotherapy* (Humana Press, 2001)
Phase I Clinical Trial: Preparation of Autologous DCs

- Leukapheresis (Day –7)
- Monocyte (DC precursor) enrichment
- DCs develop in cell culture
  + GM-CSF
  + IL-4

Antigens (tumor lysates) from surgical resection

3 bi-weekly Injections (Days 0, 14, 28)

Cultured dendritic cells
Study Design

- Protocol has been reviewed and approved by the FDA, UCLA IRB, and JCCC ISPRC.
- Patients <18 years
- Source of tumor mandatory to obtain material for extraction of tumor lysate antigens
- Patients with grade III or IV gliomas:
  - Astrocytoma
  - Oligodendroglioma
  - Mixed oligoastrocytoma
Anti-tumor immune responses to be evaluated

- **Tetramer assay** – measure increase in number of T-cells specific for tumor antigens
- **T-cell proliferation assay** – measure the increase in T-cell proliferation in response to antigen
- **T-cell cytotoxicity assay** – measure increase in ability of T-cells to kill tumor cells *in vitro*
- **Humoral anti-tumor responses** – measure increase in tumor-specific antibodies following vaccination
Case #1: Patient Characteristics

- 14 y.o. boy from Romania with glioblastoma (grade IV glioma)
- Previous treatments with surgery, radiation therapy, and chemotherapy
- Relapse with multiple metastatic nodules in brain
Clinical Evaluations

Pre-op: 4/20/05
Post-op: 4/24/05
Clinical Evaluations

- Recurrence in posterior fossa after radiation → repeat surgery

Pre-op 7/9/05

Post-op 7/13/05
Clinical Evaluations

Recurrence Pre-DC vaccine

7/23/05
Clinical Evaluations

Post-DC vaccine

10/28/05
Future plans

• Continue current Phase I feasibility/toxicity trial
• Work with other institutions to develop protocols integrating immunotherapeutic approaches into standard therapies for poor prognosis pediatric brain tumors
• Modify immunotherapeutic approach using methods to potentially increase dendritic cell vaccine activity (for example, topical TLR-7 agonist imiquimod to promote dendritic cell maturation and migration)
TLR activities

From Kaisho et al 2006
TLR7 agonist potentiates dendritic cell vaccine therapy

Figure 1. Results of bioluminescent imaging of brain tumors in mice treated with tumor specific protein (MAA) loaded dendritic cells with and without topical imiquimod. From reference 1.

From Prins et al 2006
What should we target?

Angiogenesis

Drug efflux pumps

Cytotoxic tumor immunity

The Blood-Brain-Barrier

Tumor-related immune

- Notch
- Bmi-1
- β-catenin
- Shh

TUMOR STEM CELLS

↑ proliferation
↓ apoptosis

Growth factor inhibition

PI3K/Akt blockade or restoration of PTEN function

↓ self-renewal
THANK YOU