Immune Activation by Antigen-specific T Cells Elicited in Patients Receiving Standard Therapy for Pediatric Solid Tumors

Jillian P. Smith MD, Naomi Field, Catherine Bollland MD MBCb, Amy Hort MD
Children’s National Hospital, Washington, DC

INTRODUCTION
Antigen spreading, the expansion of the immune system’s anti-tumor response through exposure to new antigens, is demonstrative of the anti-tumor immune response and has been shown following treatment with immunotherapy agents (e.g., cancer vaccines) and in some patients receiving chemotherapy for malignancies with typically higher mutational burdens. In an ongoing clinical trial, we demonstrated the safety of autologous tumor-associated antigen-specific T lymphocytes (TAAT1) specific for WT1, PRAME, and Survivin (REST trial, NCT02871928) and identified antigen spreading post-infusion with increased T cells specific for non-targeted antigens MAGE-A3, MAGE-A4, SSX-2, and SOX-2 in responding patients (Hort et al, JCO, 2019). However, this phenomenon has not been observed in pediatric patients with solid tumors after standard treatments.

OBJECTIVES
We aimed to compare antigen spreading responses in pediatric patients with solid tumors who received TAAT1 products specific for WT1, PRAME, and Survivin versus patients receiving standard-of-care chemotherapy and radiation.

HYPOTHESIS
We hypothesized that antigen spreading would be greater in patients who received TAAT1 than in those who received standard chemotherapy or radiation therapy.

METHODS
14 patients with pediatric solid tumors who received standard-of-care therapy were enrolled on the standard chemotherapy arm and were compared to 14 age and disease matched matched relapse/refractory (RR) patients who received TAAT1 infusion. Peripheral blood samples were taken prior to therapy, during therapy, and post therapy if available. Samples were evaluated using IFN-γ ELISPOT for the presence of T cells specific for antigens known to be expressed in pediatric solid tumors (MAGE-A3, MAGE-A4, SSX-2, and SOX-2).

RESULTS
Our results demonstrated the presence of antigen spreading in newly diagnosed patients who receive standard therapy and patients who receive TAAT1 as evidenced by the detection of T cells specific for MAGE-A3, MAGE-A4, SSX-2, and SOX-2.

FIGURE 1: Pediatric Solid Tumor Cell Lines Demonstrate Surface Expression of WT1, PRAME, and Survivin by Immuno-fluorescent Staining

FIGURE 2: Standard Chemotherapy and REST Trial Patients Demonstrate Variable Levels of Antigen Spreading as Measured by IFNγ ELISPOT

FIGURE 3: Mean IFNγ ELISPOT SFC Demonstrates Significantly Higher Levels of Antigen Spreading as Measured by SOX-2 and SSX-2 Specificity Between REST and Standard Chemotherapy Arm Patients

TABLE 1: Patient Characteristics of Standard Chemotherapy/Radiation Arm

CONCLUSIONS
- Pediatric solid tumor cell lines demonstrate surface expression of WT1, PRAME, and Survivin
- Similar levels of antigen spreading as demonstrated by 1 T cell responses to MAGE-A3 and MAGE-A4 were observed in responding patients who received TAAT1 for r/r disease at standard of care chemotherapy.
- Significantly more T cell responses against SOX-2 and SSX-2 were observed in patients who received TAAT1 for r/r disease compared to patients receiving standard of care chemotherapy.
- Future directions include evaluating the functional and phenotypic attributes of the epitope spreading response, evaluating the expression of non-target antigens on patient tumor tissue and gene engineering TAAT1 products to broaden specificity.

ACKNOWLEDGEMENTS
The project was supported by Award Numbers P30CA76161 and P30CA051008 from the National Cancer Institute. Children’s National accepts the contributions of all stakeholders and it is the policy of Children’s National to share all research documents that it receives representing the official views of the Children’s National Research Institute.