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

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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 (TAA-T) specific for WT1, PRAME, and Survivin (REST trial, NCT02789228) 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 (Hont 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 TAA-T 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 TAA-T than in those who received standard chemotherapy or radiation therapy.

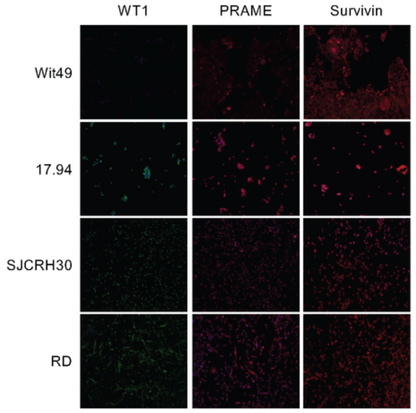
METHODS

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 relapsed/refractory (r/r) patients who received TAA-T infusion. Peripheral blood samples were taken prior to therapy, during therapy, and off therapy if available. Samples were evaluated using IFN-γ ELISPOT for the presence of T cells specific to 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 TAA-T 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



Wit49, 17.94: Wilms Tumor, SJCRH30, RD: Rhabdomyosarcoma.

TABLE 1: Patient Characteristics of Standard Chemotherapy/Radiation Arm

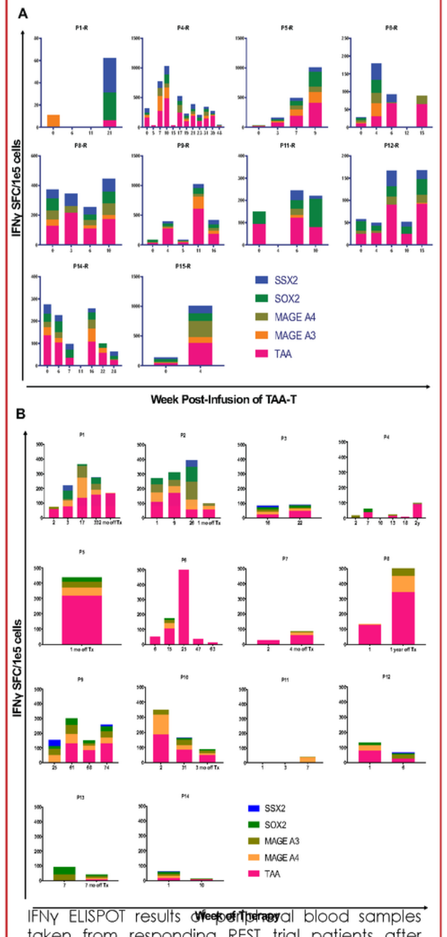
A

Characteristic	Enrolled (n = 14)
Median age, years (range)	4 (1-17)
Sex	
Female	8 (57%)
Male	6 (43%)
Diagnosis	
Wilms Tumor	11 (79%)
Embryonal Rhabdomyosarcoma	1 (7%)
Ewing Sarcoma	1 (7%)
Neuroblastoma	1 (7%)

B

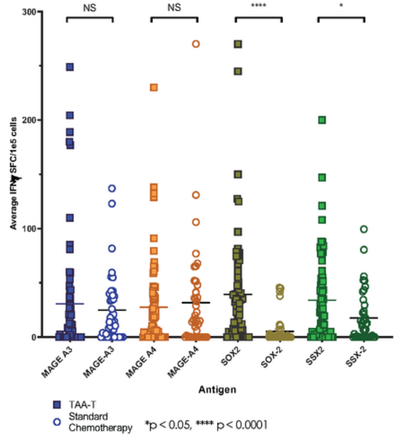
Patient ID	Disease	Age at Enrollment (Years/Sex)	Disease Characteristics	Outcome to date
P1	WT	5/F	Stage III, anaplastic histology	Remission
P2	WT	2/M	Stage III, favorable histology	Remission
P3	WT	4/F	Stage IV, favorable histology, metastatic	Remission
P4	WT	2/M	Stage I, favorable histology	Remission
P5	WT	2/M	Stage IV, favorable histology, metastatic	Remission
P6	eRMS	2/F	Botryoid subtype, metastatic	Deceased
P7	WT	8/F	Stage III, favorable histology	Remission
P8	WT	6/F	Stage II, favorable histology	Remission
P9	NB	17/M	High-risk, MYC-N nonamplified, metastatic	Relapsed disease, ongoing treatment
P10	WT	2/F	Stage III, favorable histology	Remission
P11	ES	15/F	EWSR1 translocation positive	Remission
P12	WT	10/M	Stage III, favorable histology	Deceased
P13	WT	4/M	Stage IV, favorable histology	Remission
P14	WT	1/F	Stage IV, favorable histology	Remission

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



IFNγ ELISPOT results of peripheral blood samples taken from responding REST trial patients after infusion of TAA-T (A) and from standard chemotherapy arm patients (B) while on treatment.

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



CONCLUSIONS

- Pediatric solid tumor cell lines demonstrate surface expression of WT1, PRAME, and Survivin
- Similar levels of antigen spreading as demonstrated by T cell responses to MAGE-A3 and MAGE-A4 were observed in responding patients who received TAA-T for r/r disease or standard of care chemotherapy.
- Significantly more T cell responses against SOX-2 and SSX-2 were observed in patients who received TAA-T 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 TAA-T products to broaden specificity.

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