

IMMUNE ACTIVATION BY ANTIGEN-SPECIFIC T CELLS ELICITED IN PATIENTS RECEIVING STANDARD THERAPY FOR PEDIATRIC SOLID TUMORS

Jillian Smith*, Amy Hont, Catherine Bollard. *Children's National Hospital, Washington, DC, USA*

Background Immunotherapy in the form of immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cells has revolutionized the treatment of select malignancies.¹⁻² However, beyond CD19+ cancers, clinical responses to CAR-T have been modest in pediatric cancers, likely due to lower mutational burden. Antigen spreading, an expanded anti-tumor immune response through exposure to neoantigens, has been observed in patients following treatment with immunotherapy agents or chemotherapy for malignancies with typically higher mutational burdens.³⁻⁶ However, this has not been observed in pediatric patients with solid tumors after standard treatment. We demonstrated the safety of autologous tumor-associated antigen-specific T lymphocytes (TAA-T) specific for WT1, PRAME, and Survivin in Phase I studies.⁷ We also identified antigen spreading post-infusion with increased T cells specific for non-targeted antigens MAGE-A3, MAGE-A4, SSX-2, and SOX-2, all expressed on solid tumors.⁸⁻¹² 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 Fourteen patients with pediatric solid tumors who received standard-of-care therapy were enrolled on the standard chemotherapy arm and compared to fourteen relapsed/refractory patients who received TAA-T infusion. Peripheral blood samples were taken prior to therapy, during therapy, and off therapy if available, and these were evaluated for the presence of T cells specific to MAGE-A3, MAGE-A4, SSX-2, and SOX-2 as measured by IFN- γ ELISPOT.

Results Our results demonstrate the presence of antigen spreading in newly diagnosed patients who receive standard therapy as evidenced by T cells specific for MAGE-A3 (mean: 28.2, range: 0–137 IFN- γ SFC/1e5 cells (SFC)), MAGE-A4 (mean: 31.8, range: 0–270 SFC), SSX-2 (mean: 22.8, range: 0–100 SFC) and SOX-2 (mean: 7.2, range: 0–46 SFC). Similar levels of antigen spreading were also identified in relapsed/refractory patients post TAA-T infusion detecting T cells specific for MAGE-A3 (mean: 30.7, range: 0–249 SFC), MAGE-A4 (mean: 27.6, range: 0–230 SFC), SSX-2 (mean: 33.9, range: 0–200 SFC) and SOX-2 (mean: 39.5, range: 0–270 SFC).

Conclusions These results demonstrate immune activation as evidenced by antigen spreading in newly diagnosed pediatric patients with solid tumors receiving standard-of-care chemotherapy and radiation therapy, the majority of which remain in remission following treatment. Similar levels of antigen spreading were also observed in responding patients who received TAA-T for relapsed/refractory disease. This data provides further support for the role of immunotherapy in the treatment of pediatric solid tumors and the strong anti-tumor response these therapies can potentiate.

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