Background

NY-ESO-1 is highly expressed in the majority of synovial sarcomas as well as other solid tumors and may be an effective target for T-cell-based therapies. We conducted a clinical study of adoptive transfer of lymphocytes transduced with NY-ESO-1-specific TCR in refractory cancer patients with preexisting TBI (12). High-dose of S4/10 autologous peptides and expanded lymphocytes, consisting of 560 T cells, was transferred into 6 patients, three of whom had synovial sarcoma. Three out of 6 patients experienced an objective clinical response (PR) and had cytokine-release syndrome (CRS) with high levels of IL-6 and MCP-1 that could be managed with tocilizumab. Longitudinal PBMC samples were obtained for immunomonitoring. We used high-dimensional mass cytometry and combined a 36-antibody panel with a multiplexed combination peptide-MHC tetramer staining approach to longitudinally track and phenotypically characterize adaptively transferred HLA-A*02:01 NY-ESO-1-specific T cells from TBI-CRS patients in 14, 28, and 56 days after treatment.

Methods: Simultaneous identification and profiling of antigen-specific T cells (targetiSCAPE™)

Sample labeling with 36 heavy metal tagged antibodies

Combination tetramer coding to probe 10 T cell specificities

Cell subset frequency analysis

Phenotypic profiling

High-dimensional visualization

Characterization of manufactured product

(1) CD69+ T cells

(2) Longitudinal tracking and differentiation of NY-ESO-1-specific CD69+ T cells in patients

(3) Phenotypic characterization of NY-ESO-1 and virus-specific T cells

(4) Distribution of NY-ESO-1-specific T cells in high-dimensional space

Summary

• Objectives This pilot study aimed to assess feasibility of longitudinally tracking and phenotypically adapted T cells in 6 cancer patients who underwent adoptive transfer of high-dose autologous T cells transduced to express HLA-A*02:01 NY-ESO-1-specific TCR TCR.

• Results The infusion products had variable percentages of naive, TEMRA and EM CD4+ T cells, with the three patients developing CRS having the highest proportion of EM T cells. NY-ESO-1 TCR transgenic T cells could be detected in the circulation in 5 out of 6 treated patients, with frequencies peaking at day 14 and day 28, specific T cells were undetectable in all patients by day 50. The differentiation status of circulating NY-ESO-1-specific CD69+ T cells varied across patients and due to the small cohort size, a robust association between T cell repertoire and clinical response could not be drawn; however, a general tendency for increased differentiation during time was measured in all patients. In addition, in the three patients presenting with CRS, close to 100% of circulating NY-ESO-1-specific CD69+ T cells developed an activated late-differentiated phenotype (CD30+; CD45RO+; CD244+; KLG1+; HLA-Dt+), similar to that of CMV-specific T cells and consistent with antigen experience, in proliferation and effector function.

• Conclusions Adoptive transfer of NY-ESO-1 TCR-transgenic T cells has shown signs of efficacy in patients with high NY-ESO-1 tumor expression, with manageable adverse events. Our study shows feasibility of tracking evolution of phenotypic profiles of adoptively transferred tumor-antigen-specific T cells in patients and defines association between adoptive T cell status and clinical outcomes, and should be extended to a larger patient cohort.

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