

NOVEL ANALYSIS STRATEGY OF T-CELL RECEPTOR NGS DATA TO DEVELOP PATIENT-SPECIFIC CLONOTYPE PANELS AND DETECT MINIMAL RESIDUAL DISEASE (MRD) IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (T-ALL)

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Background Minimal residual disease (MRD) detection in leukemias is characterized by identification of pathologic biomarkers despite lack of leukemic cell detection by light microscopy. The diagnostic armamentarium to assess MRD in T and B cell-derived hematological malignancies includes multiparametric flow cytometry (mpFC), real-time quantitative PCR, and NGS of hypervariable T/B-cell receptor junctions to indiscriminately assess clonal frequencies. Of these diagnostic tools, NGS-MRD is 10–100-fold more sensitive and provides distinct clinical value. Specifically, MRD levels in acute lymphoblastic leukemia (ALL) are associated with significantly improved overall survival and event free survival after induction treatment. While there are clinically approved NGS-MRD tests for B-cell derived malignancies, a standardized biostatistical analysis in T-cell derived leukemias has yet to be approved. The objective of this work was to use a pilot training set of retrospective data from T-cell (T)-ALL patients to propose a putative clinical test for MRD detection.

Methods NGS of T-cell receptor (TCR) β and TCR γ clonotypes was obtained via Adaptive Biotechnologies immuneACCESS[®] database and analyzed on the immunoSEQ Analyzer[®] platform. T-ALL samples included bone marrow aspirates before treatment and after induction therapy (N=43); control samples were from healthy adults aged 18–35.

Results Pre-treatment analysis of TCR β and TCR γ clonotypes revealed expansion of multiple clones as putative biomarkers for an individualized panel. These candidate TCR β and TCR γ clones were not expressed at a frequency greater than 0.08% in the healthy control cohort and represented putative neoplastic lymphoblasts. Using all productive rearrangements that were expressed more than 3% of the total TCR β or TCR γ sequences in the treatment-naïve sample, 43/43 samples qualified for longitudinal MRD testing. These panels were used to evaluate the corresponding post-induction treatment samples and positive MRD detection was defined as identification of at least one of the pre-treatment neoplastic clones in the top 50 TCR β or TCR γ rearrangements. This strategy identified MRD in post-induction treatment samples that were both mpFC positive and negative, which suggests enhanced sensitivity of MRD detection.

Conclusions Collectively, these data establish a novel MRD analysis strategy for T-ALL using NGS of TCR β and TCR γ clonotypes that is potentially translatable to all T-cell derived hematological malignancies. More sensitive MRD assessments could impact therapeutic decisions for maintenance therapy or candidacy for hematopoietic cell transplant in patients with a higher risk of relapse. Future efforts will evaluate a longitudinal patient cohort of T-cell derived leukemias prospectively for comparison to matched whole blood samples to facilitate less invasive longitudinal testing.

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