P1274 EARLY DETECTION OF NON-HODGKIN LYMPHOMA IN PREDISPOSED PATIENT GROUPS THROUGH IMMUNOGENETIC SEQUENCING

Topic: 20. Lymphoma Biology & Translational Research

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Background:

Since chronic lymphocytic leukemia development can be detected up to 16 years prior to diagnosis through immunogenetic sequencing, we aim to evaluate whether early detection through immunogenetic sequencing translates to other types of non-Hodgkin lymphoma (NHL). A particularly interesting group with potential clinical utility consists of patients with underlying conditions that confer an increased risk of lymphoma and leukemia. Generally, this group is characterized by dysregulation of the immune system, in the form of autoimmune diseases, primary immunodeficiencies, immunosuppressive treatment and several infectious diseases.

Aims:

To evaluate the capacity of immunogenetic sequencing for early detection of NHL and leukemia in patient groups at increased risk.

Methods:

We selected two patient groups with an increased risk of NHL and leukemia: solid organ transplant recipients and patients with auto-immune disease. For each group, we selected patients who had developed NHL and controls with the same underlying condition matched on sex, age and sampling window. Currently, we have included 16 cardiac and 10 renal transplant recipients and 10 primary Sjögren’s syndrome (SjS) patients (in total 18 cases and 18 controls). A total of 114 longitudinal pre-diagnostic samples were included in the study, taken a median of 1.2 years before diagnosis (IQR 3.5 years). Genomic DNA was isolated from the PBMC samples of the participants and the immunoglobulin heavy chain (IGH) was sequenced on the Illumina Miseq platform. All PBMC samples were taken after SjS diagnosis or solid organ transplantation and prior to NHL diagnosis.

Results:

In 7 out of 18 NHL patients we identified clonotypes in prediagnostic PBMC samples that were present at an abnormal frequency compared to the healthy background clonotypes. Notably, distribution of IGH gene repertoire in controls was normal. Prevalence of IGH gene repertoire skewing was particularly pronounced among SjS patients (3 out of 5 patients) and cardiac transplant recipients (4 out of 8 patients) compared to renal transplant recipients (1 out of 5 patients). IGH gene repertoire skewing was restricted to samples taken within 5 months to two years before diagnosis for the majority of the cases. In solid organ transplant recipients with an abnormal clonotype, the degree of skewing of the IGH gene repertoire increased over time towards the moment of NHL diagnosis or remained stable at elevated levels.

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For the SjS patients, two out of the three abnormal clonotypes utilized the IGHV1-69/IGHJ4 or IGHV4-59/IGHJ5 rearrangements stereotypic for rheumatoid factors, which have previously been associated with MALT lymphoma development in SjS. Unbiased marker identification has yielded putative prediagnostic lymphoma markers for 7 out of 18 patients.

**Summary/Conclusion:**

We conducted a pilot study investigating a novel method of early detection of NHL development in 36 patients at increased risk of hematological malignancy. In total, we observed an abnormal distribution of the IGH repertoire between 5 months to 2 years prior to NHL diagnosis in 7 out of 18 patients, compared to 0 out of 18 of the matched controls. While our results suggest potential merit for early detection of NHL development through immunogenetic sequencing, the current cohort size does not yet permit drawing definitive conclusions. Therefore, inclusion of additional patients will be a priority during the continuation of the study.