Noninvasive, dynamic risk profiling of aggressive B-cell lymphomas by peripheral blood circulating tumor DNA sequencing

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Background & objectives

Despite the use of intensive immunochemotherapeutic regimens in aggressive B-cell malignancies, relapsed/refractory disease (r/r) occurs frequently and is difficult to treat. Current strategies for risk stratification rely on scores composed of clinical features and imaging techniques to assess response to therapy. However, since these strategies lack discriminatory power and fail to detect patients at high risk before relapses eventually occur, there is a high unmet need for the development of novel risk stratifications incorporating baseline biological features and the assessment of minimal residual disease (MRD).

Thus, our objective is to develop dynamic risk stratification tools for aggressive B-cell lymphomas based on sequencing of circulating tumor (ct)DNA obtained from peripheral blood.

Methods

We applied ctDNA-sequencing to n=67 patients with Primary Central Nervous System lymphoma (PCNSL), n=165 patients with Hodgkin lymphoma (HL), and n=86 patients with r/r diffuse large B-cell lymphoma (DLBCL) and included both baseline and follow up samples into our study. Targeted gene panels were separately optimized for HL and DLBCL/PCNSL. Sample collection, DNA extraction, sequencing and data analysis was performed with a previously published workflow (Sobesky et al., 2021, Med) and with the addition of duplex barcodes for improved sensitivity and specificity.

Results

Genotyping and measurement of minimal residual disease (MRD) was possible in almost every patient, irrespective of the type of aggressive B-cell lymphoma.

In PCNSL, higher peripheral mean mutated allele frequencies at baseline were associated with impaired outcomes. Based on this finding and the detection of MRD, we developed a dynamic risk model that was highly predictive of progression-free-survival (PFS, $p = 0.00012$).

In HL, we integrated our findings from this and our previous study (Sobesky et al., 2021, Med) and focused on genotyping, which is particularly challenging in this disease. We were able to describe three distinct genetic clusters of HL with different clinical and tumor microenvironmental features solely by ctDNA sequencing: Inflammatory immune escape HL; EBV/EBV-like HL and Oncogene-driven HL.

In DLBCL, we identified a high correlation between the ctDNA concentration, lactate dehydrogenase, and the international prognostic index (IPI) at baseline. Interestingly, none of these factors was associated with outcome measures. In contrast, assessment of MRD was highly predictive of PFS in the setting of r/r DLBCL.

Conclusion

We present a ctDNA-sequencing approach for genotyping and MRD detection usable across aggressive B-cell lymphomas. Depending on the disease, we focused on the detection of biological features in patient subgroups by ctDNA-based genotyping (HL) or detection of baseline risk factors and using MRD during treatment as a response biomarker (DLBCL and PCNSL). Our platform might thus ultimately improve therapeutic guidance across aggressive B-cell lymphomas.