Tracking clonal evolution in large b-cell lymphoma using ctdna sequencing

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Abstract

Background

Despite novel treatments like chimeric antigen receptor (CAR)-T-cell therapy, prognosis for relapsed/refractory large B-cell lymphoma (rrLBCL) remains poor. Circulating tumor (ct)DNA is a promising biomarker for minimal residual disease (MRD) but integrating clonal evolution under treatment might further improve risk stratification.

Objective

We aimed to evaluate ctDNA for MRD assessment in rrLBCL and identify clonal evolution patterns to enable early detection of relapse or progression.

Methods

We applied our ultrasensitive ctDNA sequencing pipeline (Heger, Blood, 2024) to 326 blood samples from 88 rrLBCL patients receiving 131 treatment lines at two German academic centers. For clonal deconvolution, we developed an in-house pipeline integrating mutation provenance analysis, absolute copy number estimation, PyClone Bayesian Clustering and CONIPHER phylogenetic reconstruction, with mutational signatures assigned using SigProfiler.

Results

ctDNA log-fold reduction at 14–21 days after treatment as well as MRD-negativity (below detection limit <5.93 $\times 10^{-6}$) at any timepoint independently predict overall survival (OS) and progression-free survival (PFS) in multivariate cox regression (ctDNA log-fold reduction: OS [HR 2.14, p<0.01], PFS [HR 1.79, p<0.01]; MRD-negativity: OS [HR 4.79, p<0.01], [PFS HR 4.45, p<0.01]). Pre-treatment mutational signatures were identified, with SBS1, SBS5, SBS39, and SBS84 being the most frequent. Exploratory K-means clustering identified two subgroups: Cluster 1 shows high activity of Activation-Induced-Cytidine-Deaminase (AID) and somatic hypermutation, while Cluster 2 has lower levels of both (SBS84: mean 68% vs 23% mutations/sample assigned, p<0.001). Cluster 2 showed a trend towards shorter PFS with 12-months PFS of 13% compared to 44% for Cluster 1 (p=0.056). Most frequent emerging mutations under treatment included KMT2D (n=15), PCLO (n=15), and PDE4DIP (n=14). Common clonal hematopoesis of unknown potential variants such as DNMT3A (n=6), TET2 (n=2) or ASXL1 (n=0) were less frequent. In axicabtagene-ciloleucel CAR-T recipients, a CD28 point mutation from the CAR vector enabled CAR detection and potentially quantification. Phylogenetic analysis revealed diverse clonal and subclonal populations, with some subclones resembling clonal populations and others driving relapse.

Conclusion

These findings highlight the potential of ctDNA-based MRD monitoring to guide treatment decisions in rrLBCL patients. We identified distinct trajectories of clonal evolution, which, integrated into prognostic models, could enhance treatment strategies and outcomes.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.