Fragmentomics analysis to enhance ctDNA based risk stratification in aggressive B-cell lymphoma

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Abstract

1. Background

Current clinical challenges in aggressive B-cell lymphoma include treatment-related toxicities and relapsed/refractory disease. Up to now risk stratification tools mainly rely on clinical characteristics and lack sensitivity. Recent studies, including ours, show that circulating tumor (ct)DNA sequencing offers the potential to overcome this limitation (Sobesky, Med, 2021; Heger, JCO, 2024).

2. Objective
We aim to increase sensitivity to distinguish tumor (ctDNA) from non-tumor derived cell-free (cf)DNA and refine our minimal residual disease (MRD) assay (Heger, JCO, 2024) by incorporating fragmentomics analysis.

3. Methods
We developed a software package to extract advanced fragmentomics data at the read level and incorporate mutational information. The tool was applied to 154 plasma samples from 71 patients with Hodgkin lymphoma (HL) and 10 healthy controls.

4. Results
We found significant differences in fragment length distribution between pre-treatment HL samples and healthy controls (mean 180 vs. 197bp, Mann-Whitney U test, $p<0.01$). Interestingly, fragment length increased with more treatment applied, ultimately approximating healthy controls (healthy control=197bp; pre-treatment=180bp; mid-treatment=184bp; end-of-treatment=187bp). Shorter mean fragment length (<182bp) in pre-treatment HL samples was associated with shorter progression free survival (PFS) (5-year PFS 48.3% vs 88.4%. Log-Rank-test $p<0.01$).

Compared with healthy controls, we observed significant depletion of “TC”, “CC”, “GC” (3’ end) and “TC”, “GC”, “GG” (5’ end) end motif frequency (Mann-Whitney U test, multiple-testing corrected, $q<0.01$) in pre-treatment samples. Additionally, we found enrichment in “AG”, “TG”, “CT” (3’ end) and “AG”, “CT”, “AA, “AT” (5’ end) end motif frequency (Mann-Whitney U test, multiple-testing corrected, $q<0.01$) in pre-treatment samples. Similarly, we observed significant differences in 3-mer end motifs on both the 3’ end and the 5’ end between pre-treatment samples and healthy controls.

The analysis of a large B-cell lymphoma cohort (88 patients, 326 samples) is ongoing and will be presented at the meeting.

5. Conclusion
Fragmentomics analysis in our HL cohort showed shorter mean pre-treatment fragment length compared to healthy controls, with shorter mean length associated with inferior PFS. These findings suggest a potential use of fragment size and motif patterns for dynamic risk stratification in patients with HL.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.