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Blood 142 (2023) 2996–2997

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Early Identification of Refractory/Relapsed Diffuse Large B Cell Lymphoma with Serial Ctdna Sampling

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Background: Diffuse Large B Cell Lymphoma (DLBCL) is an aggressive lymphoma that is curable in 60% of patients with chemoimmunotherapy. Outcomes are poor for those experiencing relapsed or refractory disease (rrDLBCL), particularly for patients with primary refractory disease (REFR, < 9 months from diagnosis) and early relapse (ER, 9 months to 2 years from diagnosis). Some of these patients would be candidates for chimeric antigen receptor T cell therapy (CART) in second line, where outcomes are superior when the disease burden is low. Therefore, exploring strategies to identify these high-risk patients early is important. Plasma circulating tumor DNA has been shown to be prognostic in various DLBCL cohorts.
Method: We developed a custom panel of 170 genes to identify early treatment failure in a cohort of 171 patients that had profiling performed on 323 plasma samples. Plasma samples were taken serially starting at diagnosis and as patients progressed through frontline treatment. All plasma samples underwent DNA extraction, library preparation and subsequent sequencing using a panel of DLBCL related genes at high read depth (~1000x). Single nucleotide variant (SNV) calling was carried out using a custom pipeline including paired normal DNA for improved somatic variant detection. ctDNA fraction was estimated based on the highest variant allele fraction detected, using a loss of heterozygosity somatic model. Our ctDNA analysis focused on samples at diagnosis, cycle 2 of therapy, and end of treatment in order to identify early determinants of refractory disease. Changes in ctDNA levels between time points were represented as log2 ratio of ctDNA fraction.
Results: rrDLBCL cases were separated into 3 categories based on the time between diagnosis and progressive disease (PD): 47 REFR, 34 ER, and 31 late relapse (LR, >24 months). The remaining patients were disease free after frontline therapy for over 24 months (CR, n=59), resulting in a cohort enriched for rrDLBCL (65% of cases). The average international prognostic index (IPI) of each group at diagnosis was REFR=3.38, ER=2.87, LR=2.81, and CR=2.41. Cell of Origin, as determined by Hans algorithm, showed a higher number of non-GCB samples in ER and LR groups (53% and 60%, respectively) while REFR and CR displayed increased GCB cases (63% and 66%, respectively).
The REFR patients were significantly more likely to be of a 4/5 IPI score at diagnosis than other groups (p=0.0203). Progression-free survival (PFS2) at relapse therapy for REFR (median=0.29 years) was shorter when compared to both ER (p=0.0104, median=0.44 years) and LR (p=0.0012, median=0.80 years). Using the diagnostic plasma sample, there was no significant difference in ctDNA fraction in any of the three groups. When the sample with the highest ctDNA fraction was compared between patients, REFR had significantly higher levels than LR and CR, consistent with a higher overall tumor burden (p=0.001 and 0.026, respectively). There was a trend towards higher ctDNA fraction at the end of treatment in both REFR and ER groups. As ctDNA dynamics are known to be informative of molecular response, we compared patients using the change in ctDNA fraction at cycle 2 of therapy (log2 ratio). This value was significantly different in REFR patients (p=0.0073 vs ER), consistent with a lower rate of molecular response to treatment.
Conclusions: While refractory and later relapsed DLBCL have similar ctDNA features at diagnosis, we find they have distinct ctDNA dynamics during treatment. REFR had higher maximal ctDNA levels across time points and both REFR and ER patients exhibited higher levels of ctDNA at end of treatment. Moreover, patients with minimal change in ctDNA levels at cycle 2 of therapy are at a high risk of treatment failure and refractory disease. Further exploration of the specific mutational patterns

is ongoing. These results could enable the earlier identification of rrDLBCL and facilitate the prioritization of approaches for therapeutic intervention in rrDLBCL.

Disclosures Rushton: *SAGA Diagnostics:* Current Employment. **Steidl:** *Seattle Genetics, AbbVie, and Bayer:* Consultancy; *Bristol Myers Squibb, Epizyme and Trillium Therapeutics Inc.:* Research Funding. **Scott:** *Abbvie, AstraZeneca, Incyte:* Consultancy; *Janssen and Roche:* Research Funding. **Johnson:** *Abbvie:* Consultancy; *Merck:* Consultancy, Honoraria; *Gilead:* Consultancy; *Roche:* Consultancy, Honoraria.

https://doi.org/10.1182/blood-2023-190649