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Blood 142 (2023) 2989–2990

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Prognostic Value of Tumor Mutational Burden in Follicular Lymphoma Patients Treated with Immunochemotherapy

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INTRODUCTION: Follicular lymphoma (FL) is the most prevalent indolent non-Hodgkin lymphoma subtype. It is characterized by frequent relapses, and patients who progress or relapse within 24 months (POD24) of front-line immunochemotherapy (ICT) have a poor outcome. Several prognostic indices have been proposed to identify high-risk patients, but none of them are currently used in clinical practice to guide treatment. Tumor mutational burden (TMB), defined as the number of somatic mutations/megabase (mut/Mb), has been proposed as a biomarker for predicting response to immune checkpoint inhibitors in several types of cancer. Therefore, this study aimed to explore the role of TMB in FL patients treated with frontline ICT.
METHODS: The study included a total of 103 patients with FL grade 1-3a treated with frontline ICT. TMB was determined by Next Generation Sequencing (NGS) in 98 diagnostic lymph node biopsies with enough material available, with the Oncomine Tumor Mutational Load Assay (Thermo Fisher). This assay covers 1.65Mb across 409 genes frequently mutated in cancer, allowing an accurate estimation of TMB. Sequencing was performed on the Ion GeneStudio S5 system with >300X mean read depth. Only exonic non-synonymous variants remaining after manual variant refinement to exclude artefacts were considered. In addition, the mutational profile of 56 of the 98 patients was analyzed using a QIAgen custom DNA panel which covered 64 genes frequently mutated in FL. Sequencing was performed using NextSeq (Illumina) with >3000X mean read depth. Variants were analyzed and interpreted for pathogenicity using several databases, and only pathogenic or presumed pathogenic variants (P/PP) were considered. Statistical analysis was performed using SPSS and R.
RESULTS: The final cohort included 94 patients, as in 4/98 patients (4%) TMB could not be accurately estimated due to a high frequency of artefacts caused by cytosine deamination. Median age at diagnosis of 61 years (range 24-86), 51% males and 49% females. Patients with advanced disease stage at diagnosis represented 87% of the cohort. Median TMB was 5.08mut/Mb (range 1.69-13.80 mut/Mb), and all cases genetically profiled presented at least one P/PP variant. The number of P/PP mutations correlated with TMB at diagnosis (p=0.004). TMB did not correlate with clinical parameters, such as age at diagnosis (p=0.891), histologic grade (p=0.243), Ann Arbor stage (p=0.200), ECOG (p=0.190), FLIPI (p=0.363), FLIPI2 (p=0.693), or LDH levels (p=0.483). However, lower TMB at diagnosis was associated with the absence of the t(14;18)(q32;q21) translocation (mean 3.93 vs 5.42 mut/Mb, p=0.006). The analysis of the mutational status of the 64 genes frequently mutated in FL revealed that mutations in genes involved in cellular migration (*GNA13, GNAI2*) were associated with higher TMB values (4.50 vs 7.56 mut/Mb, p=0.001).
An statistically significant association between low TMB and shorter progression-free survival (PFS) (p=0.011) was found when stratifying patients into two groups: high basal TMB (>2.55mut/Mb) and low basal TMB (≤2.55mut/Mb) (Figure 1). 2-year PFS was 54.5% (95%CI: 33.2-89.5%) in low-TMB patients and 84.9% (95%CI: 77.3-93.7%) in high-TMB patients. 5-year PFS was 39.0% (95%CI: 19.7-77.0%) in low-TMB patients and 70.5% (95%CI: 60.0-82.9%) in high-TMB patients. The proportion of POD24 cases was higher in the low-TMB group (46.1% vs 16.9%, p=0.039), none of them being refractory to treatment (7/70 in the high-TMB group). Genetically, the low-TMB group was enriched in patients with mutations affecting genes involved in the mTOR signaling pathway (*ATP6AP1, ATP6AP2, ATP6V1B2, RRAGC*) (50.0% vs 8.7%, p=0.006).
CONCLUSIONS: FL patients harboring t(14;18) or mutations in genes involved in migration have higher TMB values at diagnosis. Patient stratification based on TMB values allows the identification of a subgroup of FL patients with ≤2.55 mut/Mb with shorter PFS after treatment with frontline ICT. The prognostic usefulness of TMB should also be explored at relapse, in

particular in patients receiving novel immunotherapies such as bispecific antibodies and CAR T-cell therapies, that are being approved for relapsed/refractory FL.

ACKNOWLEDGMENTS: Work supported by Institut de Salud Carlos III-Federación Española de Enfermedades Raras (ISCIII-FEDER) grant PI19/00034, GLD18/00117, 2017SGR205, PT20/00023, and Xarxa de Banc de Tumors de Catalunya.

Disclosures Bellosillo: *ThermoFisher:* Research Funding, Speakers Bureau. **Salar:** *BMS/Celgene:* Speakers Bureau; *Roche:* Speakers Bureau; *Janssen:* Speakers Bureau.

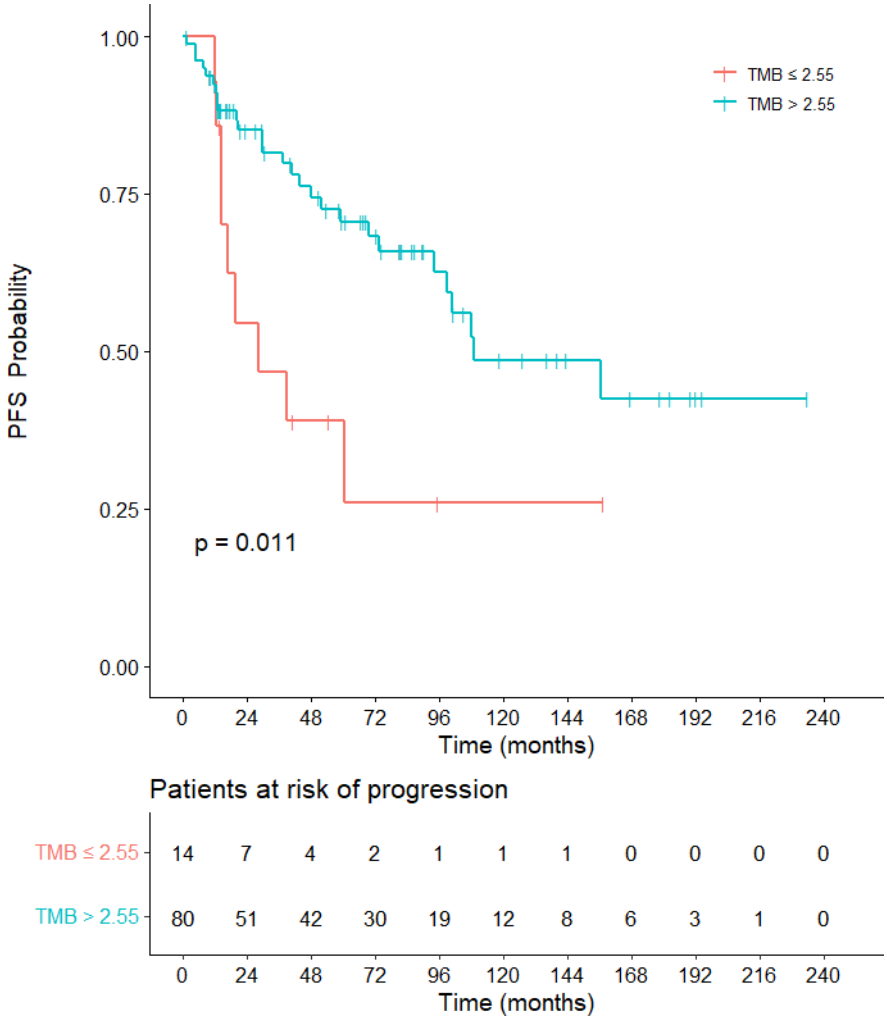

Figure 1

https://doi.org/10.1182/blood-2023-180622