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A gene signature to predict risk of transformation in patients with follicular lymphoma

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Background

Follicular lymphoma (FL) is an indolent but mainly incurable disease. Histological transformation to diffuse large B cell lymphoma is associated with rapid progression, treatment resistance and poor prognosis. Prospective identification of transformation-potential would also serve for guiding treatment and monitoring of patients. We aimed to validate a prognostic signature previously identified by our group (González-Rincón *et al.*, 2019) to stratify patients according to their risk of transformation.

Methods

We conducted targeted massive parallel sequencing on new diagnostic samples from 21 pre-transformed (pre-tFL) and 30 non-transformed FL (ntFL) patients. Additionally, our previously published cohort of 42 samples (22 pre-tFL and 20 ntFL) was included to enable risk analysis. Cox proportional hazards regression and Kaplan-Meier analysis were performed joining both cohorts to develop risk models.

Results

Comparative analysis revealed that pre-tFL showed more mutations than ntFL samples (9.5 vs. 8). The variant allele frequency (VAF) in pre-tFL samples was lower than in ntFL (pre-tFL: 24% vs. ntFL: 30%; t-test $p<0.001$), resulting in a higher proportion of subclonal mutations (<20% VAF) per sample (pre-tFL: 38% vs. ntFL: 24%; t-test $p=0.034$). The detection of mutations in *HIST1H1E*, *NOTCH2*, *IRF8* and *UBE2A* were statistically ($p<0.05$) associated with transformation by the multivariate Cox analysis. Inclusion of the Follicular Lymphoma International Prognostic Index (FLIPI) with alterations in *HIST1H1E*, *NOTCH2*, *IRF8* and *UBE2A* into the multivariate Cox model rendered a classification of the samples into three risk groups, with distinct transformation probabilities at 5 years (85%, 46% and 22% for the high-risk, intermediate-risk and low-risk group; $p<0.001$) by the Kaplan-Meier analysis.

Conclusions

In summary, genomic analysis on FL samples have enabled the association of mutated genes with higher risk of transformation. We have also demonstrated that mutations below 20% VAF in FL samples at diagnosis are associated with transformation. Integration of the mutational status with clinical risk factors into a predictive model improves the risk stratification and could be useful for identifying patients at higher risk of transformation.

Legal entity responsible for the study

Lymphoma Research Group of the Instituto de Investigación Sanitaria Puerta de Hierro-Segovia de Arana.

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Disclosure

All authors have declared no conflicts of interest.