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636.MYELODYSPLASTIC SYNDROMES-BASIC AND TRANSLATIONAL

Impact of Somatic Second Hit and Comutations in Myeloid Neoplasms with Germline DDX41 Mutations

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Background: Germline *DDX41* mutations are the most common genetic predisposition to myeloid neoplasms (MN) and have been suggested to represent a distinct MN subtype. A second somatic *DDX41* mutation (second hit) is known to occur in most patients, with a clear predominance for R525H. However, its impact on disease progression and survival remains elusive. Additionally, comutation patterns are not well defined across all MN subtypes, with limited evidence regarding their prognostic significance.

Methods: We performed a retrospective cohort study to evaluate outcomes of *DDX41*-mutant MN, focusing on the impact of co-occurring mutations, including second hit *DDX41* lesions. We included 100 patients with at least 1 *DDX41* variant and a MN or precursor condition. *DDX41* mutation was identified by an in-house NGS myeloid gene panel. Skin biopsy was the most frequent DNA source for germline testing. When this was not available, we applied a validated model to predict the nature of *DDX41* variants based on VAF, public germline databases and known hotspot somatic mutations. Kaplan-Meier analysis and Cox models were used for survival analyses. Observations were censored for transplant.

Results: Overall, the median age at diagnosis was 71 years (IQR 65-79) and 66% were male. The underlying diagnosis was MDS in 43% of cases, AML in 47% and other MN in 10% (including chronic myelomonocytic leukemia, myeloproliferative neoplasms and clonal cytopenia of undetermined significance). Most patients had a normal karyotype (77%, 72/93). In the MDS cohort 36% (14/39) had higher-risk (HR) disease (IPSS-R>3.5) and 30% of AML patients (14/46) had adverse risk disease (ELN 2022). Median overall survival (OS) for patients with HR-MDS or AML was 24.6 months (95% CI 7.7-37.4).

Out of 169 identified *DDX41* variants, 51% were predicted as germline, corresponding to 86% of all patients carrying a germline variant. Twenty-one patients had a *DDX41* mutation confirmed in germline DNA, and all would have been predicted by the model. In our cohort, most MN patients carrying a germline *DDX41* mutation had a somatic second hit (71%, 61/86) but the presence of a second hit did not impact OS (logrank p=0.72) and its prevalence was not significantly different in patients with lower-risk (LR)-MDS, HR-MDS or AML (p=0.45). This suggests that, albeit the occurrence of a second hit seems related to developing a MN, its presence is not necessarily associated with progression nor worse survival. There was a numerically worse median OS in those harboring the R525H second hit (33 vs 89 months), but the survival distribution was not significantly different (logrank p=0.28). However, an increasing R525H prevalence was noted from LR-MDS to HR-MDS to AML (33%, 67%, 77%; p=0.004).

Among patients with germline DDX41 variants, the presence of at least one somatic mutation beyond DDX41 (comutation) was associated with significantly worse OS in univariate analysis (HR 4.26, 95% CI 1.16-15.67, p=0.03) but did not retain significance when diagnosis was added to the model (HR 2.43, 95% CI 0.57-10.36, p=0.23). Yet, the distribution of the proportion of patients with at least one comutation between LR-MDS, HR-MDS and AML was significantly different (p=0.03), with an increase from LR-MDS to the other 2 categories. The same results held true for the presence of 2 or more mutations. The top 5 comutations were *TET2* (14%), *ASXL1* (13%), *SRSF2* (11%), *DNMT3A* (10%) and *CUX1* (10%). Interestingly, there was a significantly lower prevalence of *CUX1* in MDS than in AML (2% vs 17%, p=0.02) and a tendency for increased frequency from LR-MDS to HR-MDS to AML (0% vs 7% vs 17%, p=0.07), highlighting a potential role in disease progression. There was no significant difference when comparing the clone sizes of second hit *DDX41* mutations and comutations (median VAF 14% vs 14%, p= 0.78).

Conclusions: While most patients with germline *DDX41* MN harbor a somatic second hit, its presence was not predictive of survival and its frequency was not differently distributed across the MDS-AML continuum. The presence of additional comutations equally lacked survival impact. However, the frequency of patients with any somatic comutation, the frequency

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of R525H second hit, and the occurrence of *CUX1* mutation increased from MDS to AML, placing these as candidate drivers of leukemic progression in germline *DDX41* MN. Moreover, similar clone sizes of somatic *DDX41* mutations and comutations favors co-occurrence of these events.

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