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ORAL ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Molecular Taxonomy of Myelodysplastic Syndromes and Its Clinical Implications

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Background
Recurrent genetic abnormalities are responsible for the pathogenesis of myelodysplastic syndromes (MDS) and their biologic heterogeneity, however current classifications of MDS are still largely based on morphology.Here, we propose a molecular taxonomy of MDS and describe its clinical relevance.
Methods
We assembled a cohort of 3,233 diagnostic MDS or related myeloid neoplasm samples from the International Working Group for the Prognosis of MDS. Gene mutations, copy-number alterations (CNAs) and copy-neutral loss of heterozygosity (cnLOH) events were derived from targeted sequencing of a 152-gene panel. Molecular features were used for unsupervised clustering analysis using Bayesian Dirichlet processes, and the results were manually curated into a rule-based hierarchical classification tree.
Results
We detected oncogenic mutations, CNAs, and cnLOH events in 91, 43, and 11% of patients, respectively. We validated and extended patterns of co-occurrence and mutual exclusivity between gene mutations and CNAs, and further described (i) specific occurrences in *cis* between gene mutations and cnLOH events, (ii) distinct patterns of co-mutation between the allelic state of a same locus (haploid LOH or cnLOH associated with -7/del(7q)), or of the same mutated gene (*TP53*, *TET2*), and (iii) distinct patterns of co-mutation between hotspots of the same gene (*U2AF1*). These patterns informed feature definition for clustering analysis.
We characterized 18 distinct MDS molecular subgroups. The first 16 groups encompassed 86% (n=2,769) of patients and were based on the presence or absence of mutations in 21 genes (*ASXL1*, *BCOR, BCORL1, DDX41, DNMT3A, EZH2, FLT3, IDH1, IDH2, MLL, MYC, NPM1, SETBP1, SF3B1, SRSF2, STAG2, TET2, TP53, U2AF1, WT1, ZRSR2*), and 6 cytogenetic events (inv(3), complex karyotype, der(1;7), -7, del(5q), -Y), as well as LOH at the *TP53* and *TET2* locus. The *molecularly not-otherwise specified (mNOS)* group(8%, n=254) corresponded to the presence of other cytogenetic abnormalities and/or mutations in 51 other recurrently mutated genes (>0.5%). The *No-event* category (6%, n=210) was characterized by the absence of any recurrent drivers in our assay.
Groups ranged in size from 0.5% to 14% of patients and were associated with distinct clinical phenotypes (**Fig 1A**) and outcomes (**Fig 1B**). The median bone marrow blast percentage across groups ranged from 1.5 to 10%, the median overall survival (OS) from 0.9 to 8.2 years, and the 2-year rate of leukemic transformation from 0 to 40%. The representation of molecular groups within blast strata (<5%, 5-9%, 10-19% blast percentages) was highly heterogeneous: 7, 8, and 9 different groups accounted for more than 5% of patients within each blast stratum, respectively. The prognostic impact of blast counts on outcomes depended on the molecular subgroups. Among the 12 molecular groups with at least 10 patients with outcome data in all 3 blast strata, blast count was prognostically significant in 8 of those groups (*SF3B1, CCUS-like, del(5q), bi-TET2, mNOS, BCOR/L1, IDH-STAG2, TP53-complex*) and was not significant in 4 groups (*EZH2-ASXL1, -7/SETBP1, DDX41, AML-like*). The molecular groups validated established (*TP53-complex, del(5q), SF3B1*) and well characterized entities (*DDX41, AML-like*), added further evidence to support previously reported subsets (*bi-TET2, der(1;7), CCUS-like*), and described novel genetic subsets (-7/ *SETBP1, EZH2-ASXL1, IDH-STAG2, BCOR/L1, U2AF 157 , U2AF1 34 , SRSF2, ZRSR2*).

Finally, the MDS molecular groups were used to investigate the genetic heterogeneity of secondary/therapy-related MDS (s/t-MDS) and of myelodysplastic/myeloproliferative neoplasms (MDS/MPN). There were 7 and 6 distinct groups that accounted for more that 5% of patients with s/t-MDS or MDS/MPN, respectively. Within each genetic subgroup, s/t-MDS and MDS/MPN had similar clinical and outcome profiles to primary MDS.

Conclusions

The genetic complexity of MDS can be organized into 18 molecular groups that reflect the underlying genetic basis of the disease. The prognostic influence of bone marrow blasts varied in the individual genetic subgroups, suggesting that the clinical impact of increased blasts depends on the genetic context. The molecular taxonomy derived in this study is clinically relevant and will inform future classification schemas.

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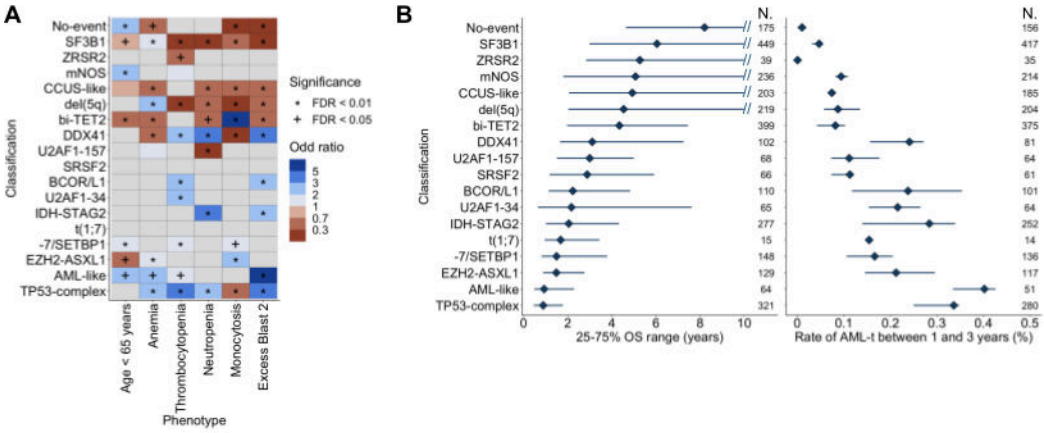

Figure 1. Associations between MDS molecular groups, clinical phenotypes, and outcomes. A. Association between molecular groups and clinical phenotypes. **B.** Association between molecular groups and outcomes, for overall survival (OS, left) and acute myeloid leukemia transformation (AML-t, right). Left: dots indicate median survival and lines extend to the interquartile (IQR) range. Right: dots indicate the 2-year incidence of AML-t and lines extend to the 1 year and 3rd years incidences. **C.** Cumulative incidence curves of AML transformation stratified with the range of blast percentages within the *DDX41* and *AML-like* subgroups (0-5, 5-10, and 10-20% in shades of green). P-values are from the Gray's test. **D.** Kaplan-Meier probability estimates of OS stratified with the range of blast percentages within the *EZH2-ASXL1* and *-7/SETBP1* subgroups. P-values are from the log rank test.

Figure 1

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