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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Genomic Landscape of Ccus Compared to MDS Indicates a Potential Applicability of the IPSS-M

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Background: The 5 th edition of the WHO classification newly included myeloid precursor lesions introducing CCUS as an entity. CCUS is defined as clonal hematopoiesis (CH) in the presence of unexplained, persistent cytopenia requiring detection of either somatic mutation in certain CH associated genes or clonal chromosomal abnormalities.
Aim: Characterize a large CCUS cohort with respect to cytogenetics and molecular genetics and compare the findings to an MDS cohort to evaluate differences in the genomic landscape.
Methods: The CCUS cohort comprised 222 cases (median age: 76 y; female: 33%), the MDS cohort 698 cases (median age: 73 y; female: 43%). The diagnoses were established following WHO 2022. All samples were analyzed by cytomorphology, cytogenetics, targeted NGS panel (median coverage 1500x) and whole genome (median coverage 100x) sequencing. Mutation (MUT) status of 59 genes associated with myeloid malignancies were analyzed in detail (54 CH associated; 5 relevant for IPSS-M).
Results: Significant differences in age, gender, BM blasts, blood parameters and number and types of cytopenias were detected. CCUS patients (pts) were older, had more WBC, less PLT, harbored a higher HB, less BM blasts and were even more predominantly male compared to MDS pts (all $p<0.05$). Within the CCUS cohort 29 pts (13%) showed cytogenetic abnormalities (CA) only (thereof 69% loss of chromosome Y (Y-loss)), while the remaining 193 pts (87%) showed at least one MUT (VAF $\geq$2%) in any of the 54 CH associated genes (thereof 84% MUT only; 16% MUT+CA).
Regarding cytogenetics 162 CCUS pts (73%) harbored normal karyotypes while CA were detected in 27% (MDS: 43%; $p<0.001$) with Y-loss being most frequent (39/60; 65%). Y-loss was more frequently found in CCUS than in MDS (17% vs. 5%; $p<0.001$), while complex karyotypes and del(5q) were more frequent in MDS (11% and 16% vs. 1% and 0%; both $p<0.001$). Based on WGS data additional pts with Y-loss (n=7; confirmed by FISH) and recurrent CN-LOH (4q: n=4; 7q: n=5) were observed.
With respect to somatic MUTs, 356 MUTs were found within the entire CCUS cohort (in 28 CH genes, 3 non-CH genes). Overall, CCUS pts showed less MUTs (median: 1 [0-6]) compared to MDS (median: 2 [0-12]; $p<0.001$). CCUS pts most frequently harbored MUTs in *DNMT3A* (32%), *TET2* (28%) and *ASXL1* (14%) followed by MUTs in splicing genes and *TP53* (Fig. 1A). MUTs in *DNMT3A* and *PPM1D* were more frequent in CCUS than MDS while MUTs in *ASXL1, TP53, SF3B1, STAG2, RUNX1, NRAS, CUX1* were less frequent in CCUS (each $p<0.05$). Notably, biallelic *TP53* MUTs were less frequent in CCUS compared to MDS (*TP53*bi of mutated: 14% vs. 55% $p=0.008$). Within the 15 most frequently mutated genes in CCUS, MUTs in 6 genes (*DNMT3A, SF3B1, TP53, CBL, STAG2, PPM1D)* showed a median VAF <10%. Nine of the top 15 genes showed significantly lower median VAFs than in MDS (*DNMT3A, TET2, ASXL1, SRSF2, U2AF1, SF3B1, TP53, PPM1D, IDH2;* each $p<0.05$). Thus, the frequency and VAF of *ASXL1*, *TP53, SF3B1* MUTs were significantly lower in CCUS than in MDS, while *DNMT3A* and *PPM1D* MUTs were significantly more often detected in CCUS but at a lower VAF than in MDS.
Combining cytogenetics and mutational analysis we calculated the IPSS-M, a patient-specific risk score for MDS resulting in six risk categories, and detected a clear skewing towards low risk categories in CCUS (Fig. 1B). The frequency of categories very low (VL) and low (L) were significantly higher in CCUS than in MDS (30% vs. 15%; 50% vs. 40%; both $p<0.013$), while high and very high categories were more rare (1% vs. 13%; 1% vs. 14%; both $p<0.001$). Although CCUS follow-up data were short (median: 1.5 y), no differences in overall survival were observed between CCUS VL+L and MDS VL+L, while within CCUS survival differed between VL+L and the remaining cases ($p=0.05$).
Conclusions: Our data confirm the comparable mutational spectrum between CCUS and MDS but clearly show major differences in the frequency and VAF of distinct gene mutations. These biological differences hint towards different subgroups within CCUS with cases closer to MDS than others. A combined risk score for MDS and CCUS would reflect this continuous

spectrum and has the potential to derive an objective risk assessment irrespective of observer-dependent grading of dysplasia. Our study indicates plausible short term results for CCUS patients stratified according to the IPSS-M. However, the definite applicability of the IPSS-M needs to be confirmed in larger CCUS studies with longer follow-up.

Disclosures Huber: *MLL Munich Leukemia Laboratory:* Current Employment. **Baer:** *MLL Munich Leukemia Laboratory:* Current Employment. **Hutter:** *MLL Munich Leukemia Laboratory:* Current Employment. **Hoermann:** *MLL Munich Leukemia Laboratory:* Current Employment. **Pohlkamp:** *MLL Munich Leukemia Laboratory:* Current Employment. **Walter:** *MLL Munich Leukemia Laboratory:* Current Employment. **Meggendorfer:** *MLL Munich Leukemia Laboratory:* Current Employment. **Kern:** *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership. **Haferlach:** *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership. **Haferlach:** *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership.

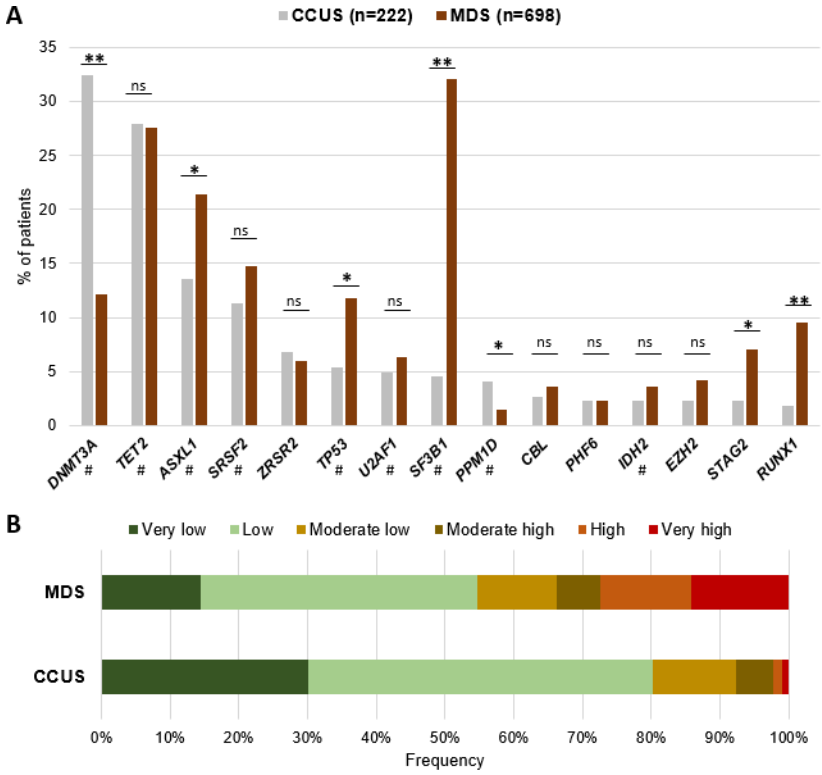

Figure 1 (A) Frequency of mutated genes in CCUS (grey) or MDS (brown) patients depicting the 15 most frequently mutated genes in CCUS (found at least in 4 patients). ** p<0.001; *p<0.05; ns: not significant; # significant lower variant allelic frequency in CCUS. **(B)** Distribution of IPSS-M risk categories within CCUS and MDS patients.

Figure 1

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