Prognostic Impact of Lymphopenia in Myelodysplastic Neoplasms (MDS)

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INTRODUCTION

- In addition to MDS somatic mutations, both **adaptive and innate immunity** play an important role in the disease genesis and progression[1]
- Molecular International Prognostic Scoring System (IPSS-M) better stratifies patients for survival than IPSS-R[2], however, its predictive power for response to available treatments remains limited[3]
- **Lymphopenia is not captured** by current prognostic scores
- Associations of MDS **genetic lesions and lymphopenic phenotype** are poorly characterized

METHODS

- **Lymphopenia was defined as <1.5 G/l according to local laboratory threshold**
- Molecular profiling was performed using next-generation sequencing targeting a panel of 80 genes
- Cox proportional hazard regression model was applied for multivariate analysis

PATIENT COHORT

Primary MDS patients (n=372) treated at Saint Louis Hospital in Paris (France) were retrospectively included if absolute lymphocyte count (ALC) was available at diagnosis

Low Risk (LR):	**Intermediate Risk (IR):**	**High Risk (HR):**
IPSS-M Low and Very Low, scores < -0.5 ; **n=230 (62%)**	IPSS-M Moderate Low and Moderate High, scores -0.5 to 0.5 ; **n=70 (19%)**	IPSS-M High and Very High, scores > 0.5 ; **n=72 (19%)**

RESULTS

Lymphopenia is highly prevalent in MDS

The median ALC in our whole cohort was 1.20 G/l (IQR, 0.87-1.60), and there was no difference according to age or gender. Lymphopenia was highly prevalent in all MDS subgroups (68%, 79% and 75% respectively) (**A**).

Associations with MDS mutational landscape

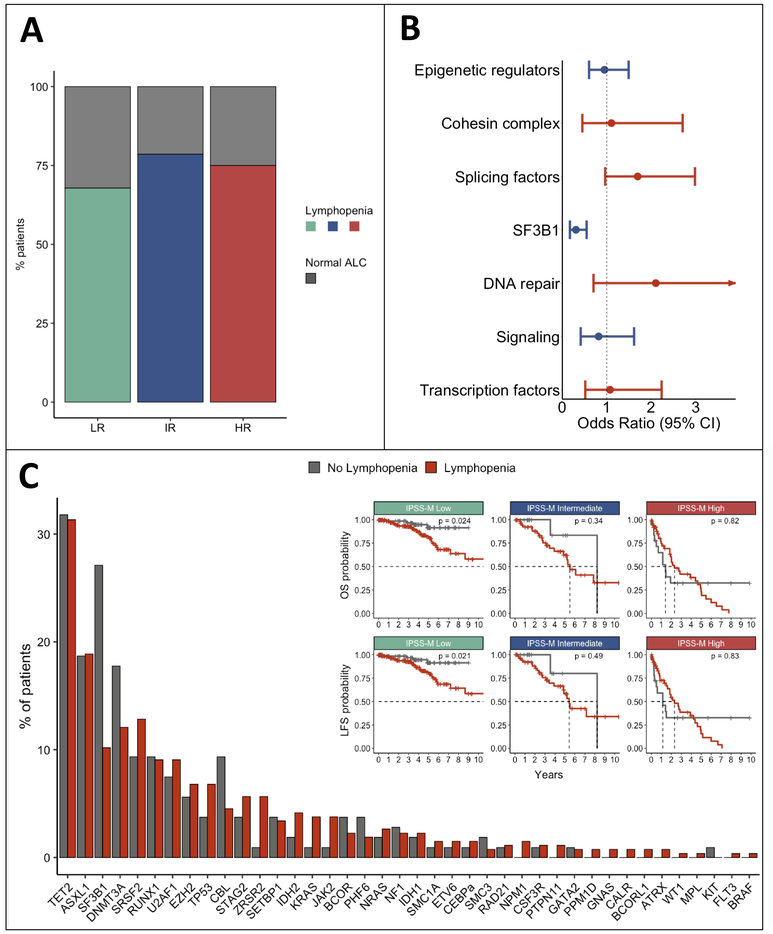
In our whole cohort, 305/372 (82%) of patients had at least one molecular abnormality. The frequencies of recurrent somatic mutations were consistent with recent data from large, international MDS cohorts[2,3]. Lymphopenia was not significantly associated with any recurrently mutated pathways (**B**).

SF3B1 mutations were more prevalent in MDS patients without lymphopenia (29/107 (27%) versus 27/265 (10%), p<0.01), while the rest of the somatic mutational landscape did not differ between the 2 groups (**C**).

Lymphopenia confers poorer prognosis in LR-MDS

Lymphopenia at MDS diagnosis was associated with poorer overall survival (OS, median 73.0 vs. 98.9 months, p=0.05) and Leukemia Free Survival (LFS, median 80.2 vs. 98.9 months, p=0.05). In a subgroup analysis, this adverse impact was restricted to LR-MDS patients with a median OS of 128.4 months (p=0.024) and median LFS of 147.6 months (p=0.021) versus not reached in patients without lymphopenia (**C**).

In the LR-MDS subgroup, the further inclusion of sex, age at MDS diagnosis and thrombocytopenia (variables significantly impacting OS and LFS in univariate analysis) in a multivariate model resulted in borderline p-values regarding the impact of lymphopenia on OS (p=0.06) and LFS (p=0.05).



CONCLUSIONS

- High prevalence of lymphopenia in MDS suggests a specific effect of MDS on ALC:
  - Relative bone marrow failure and increased myeloid bias secondary to specific MDS-related somatic mutations in hematopoietic stem cells likely contribute to this phenotype
- Of note, *SF3B1*-mutated MDS patients had a decreased prevalence of lymphopenia, however we did not detect other associations with the MDS mutational landscape
- Prognostic impact of lymphopenia on OS was **only significant in LR patients**, but not in IR and HR patients, suggesting a protective role of host immunity mostly prevalent at disease onset
- Characterization of lymphocyte subtypes' phenotype and numbers, and the power for prediction of response to hypomethylating agents and immune checkpoint inhibitors remains to be elucidated

REFERENCES

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