Abstract: P766

Title: EXPLORING SEX-DIVERSITY OF GENE MUTATIONS AND RESPONSE TO ESA TREATMENT IN LOW-RISK MYELODYSPLASTIC NEOPLASMS

Abstract Type: Poster Presentation

Topic: Myelodysplastic syndromes - Clinical

Background:

Low-risk myelodysplastic neoplasms (LR-MDS) are clonal myeloid disorders mainly manifesting with anemia whose first line treatment are erythropoiesis stimulating agents (ESAs). LR-MDS are chronic disorders with a low tendency to progress into acute myeloid leukemia (AML) and calculation of the risk of evolution is based on IPSS-R. Recently, a new score that takes into account MDS-related mutations, named IPSS-M, has been developed. MDS incidence is known to be higher among men and recent data have shown that MDS male and female patients display different incidence of specific somatic gene mutations as well as different pattern of comutations.

Aims:

Given the observed sex-based differences in MDS genotype, we evaluated the possible correlations of IPSS-M risk score and of number/type of recurrently mutated genes with ESA response in LR-MDS patients stratified by sex.

Methods:

A cohort of 589 LR-MDS patients diagnosed in 15 European Centers and subsequently treated with ESAs was evaluated. Erythroid response was assessed at 12 weeks of treatment, based on 2018 IWG criteria. Baseline t-NGS data were used to calculate IPSS-M score. Known predictors of ESA response like baseline serum erythropoietin levels (sEPO) and transfusion-dependency (TD, ≥ 4 red blood cell units/8 weeks), along with IPSS-M score and type of somatic mutations, were correlated with ESA response in uni- and multivariate logistic regression analysis (**Fig. 1A**).

Results:

Median age was 74 years (19 – 96 years) with a mean sEPO of 99.5 U/L (4 – 849 U/L) and a TD rate of 46%. As expected, there was a male preponderance (53%). Response rate (RR) was 59% with no significant difference between sexes. Lower sEPO levels, IPSS-M score and TD rate were found in ESA responders and were predictive of response in multivariate analysis (OR 0.99, p=0.0005; 0.58, p=0.018 and 0.55, p=0.0004, respectively). No difference between males and females was observed among these parameters.

When stratifying per sex, we found that *SRSF2*, *ZRSR2* and *STAG2* mutations were enriched in males (**Fig. 1B**), who also harbored more mutations than females (mean 2.22 vs 1,71 respectively, p=0.003).

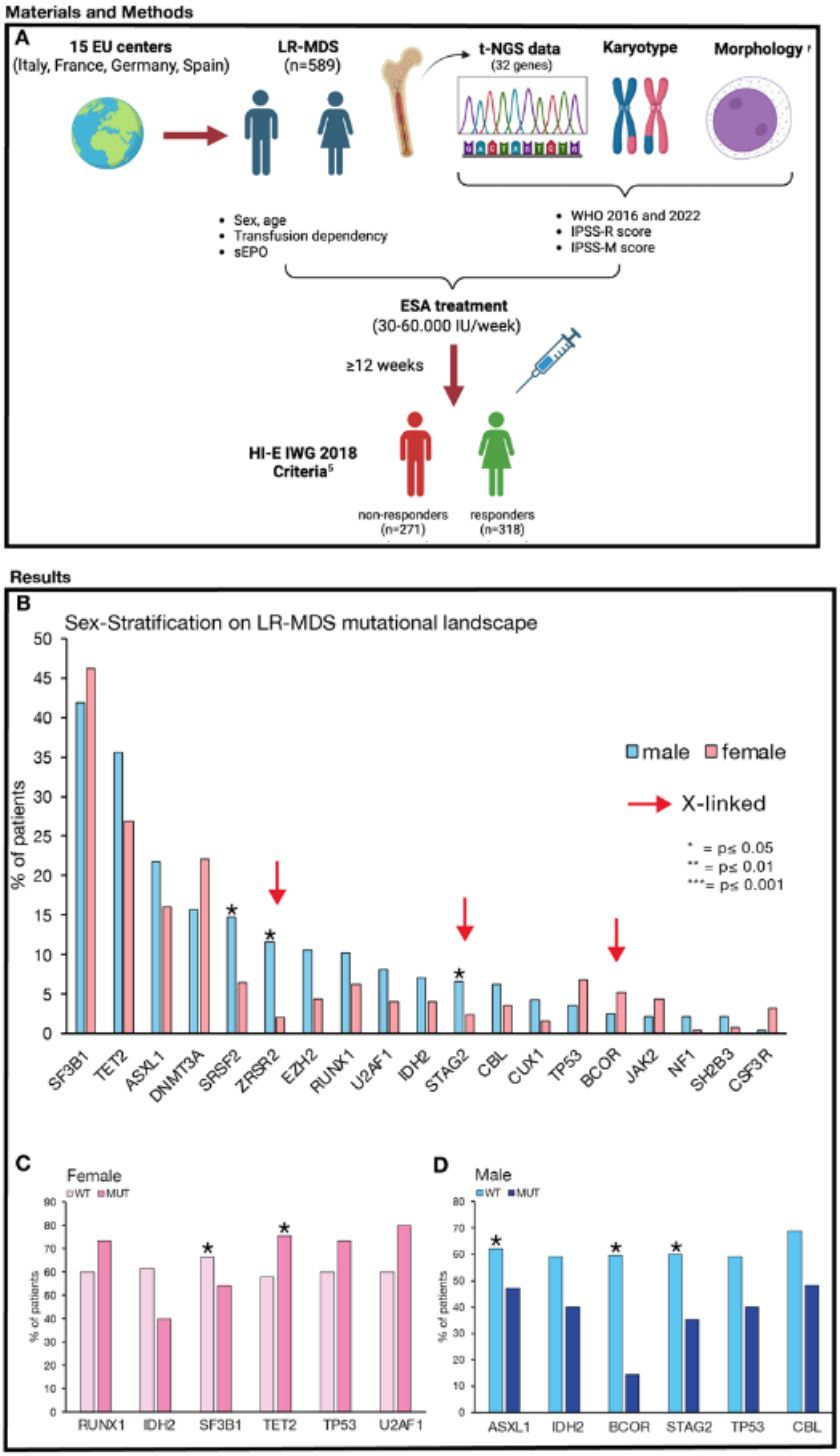
Next, we evaluated the correlation of single mutations with ESA response based on sex and observed that mutations in *ASXL1*, *BCOR* and *STAG2* in males (**Fig. 1C**) and *SF3B1* in females were associated with reduced RR compared to patients with wild type (WT) genes, whereas only MDS female patients with *TET2MUT* had higher RR compared with ones with TET2WT(**Fig. 1D**).

Multivariate analysis comprising sEPO, TD and IPSS-M score, together with the sex-specific somatic mutations found previously, showed that sEPO (OR 0.99, p=0.0007), TD (OR 0.48, p=0.03) and *STAG2* mutation (OR 0.13, p=0.003) predicted for ESA response in males, while sEPO (OR 0.55, p=0.03) and IPSS-M score (OR 0.53, p=0.01) were predictive for response in females.

Summary/Conclusion:

We showed that IPSS-M risk score is predictive of ESA response in LR-MDS female patients in addition to sEPO. Some of the prognostically relevant MDS mutations are enriched in males and can affect ESA response differently according to sex. In particular, we observed that mutation in the X-linked *STAG2* gene is a negative predictor of ESA response only in males, in whom is more frequent.

In conclusion, our data indicate the need for future MDS prognostic models to include among variables also sex at birth. The sex-dependent effect of single mutations in disease course and response to MDS treatments warrants further investigations to improve personalized precision medicine.



Keywords: Somatic mutation, Myelodysplastic syndrome, Erythropoieisis, Gender