Identification of misclassified multiple myeloma patient risk subgroups with a novel biological disease stratifier

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Background

The outcome of high-risk MM patients classified by ISS, R-ISS or adverse risk cytogenetics is not uniform and patients show heterogeneous survival. Recent insights into the pathogenesis of MM highlighted APOBEC cytidine deaminase enzyme as well as inflammation are involved in MM progression. We hypothesized that inclusion of these molecular features into risk stratification could potentially resolve the challenge of identifying unrecognized patient subgroups, who have been previously misclassified by current risk stratifiers.

Method

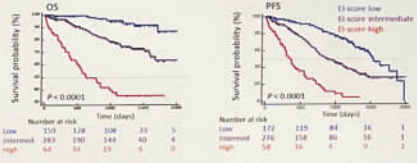
The Multiple Myeloma Research Foundation CoMMpass study genomics dataset, combining mRNA Seq and clinical data from more than 700 MM patients, allowed us to define an accurate weighted OS/PFS risk score (Editor-Inflammation (EI) score) based on mRNA expression of *APOBEC2, APOBEC3B, IL11, TGFB1, TGFB3*, as well as ß2-microglobulin and LDH serum levels. The novel EI-score applied to different ISS, R-ISS and cytogenetic risk subgroups to see whether EI-score can identify misclassified patient subgroups by current MM risk stratifiers.

Results

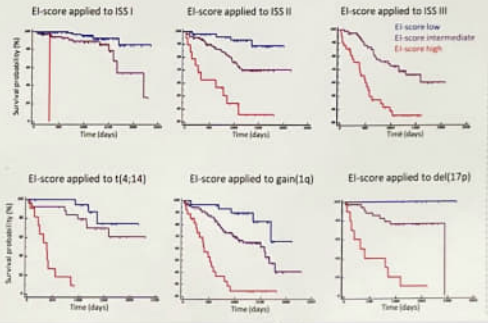
Defining the Editor / Inflammation (EI) score

PFS	OS
(*APOBEC2*; ≤0.19=0, >0.19=4)	(*APOBEC2*; ≤0.20=0, >0.20=3)
+ (*APOBEC3B*; ≤6.91=0, >6.91=3)	+ (*APOBEC3B*; ≤3.79=0, >3.79=3)
+ (*IL11*; ≤0.56=0, >0.56 =2)	+ (*IL11*; ≤0.48=0, >0.48 =2.5)
+ (*TGFB1*, ≤0.43=0, >0.43 =1)	+ (*TGFB1*, ≤0.11=0, >0.11 =1)
+ (*TGFB3*; ≤0.03=0, >0.03=1)	+ (*TGFB3*; ≤0.10=0, >0.10=2)
+ (ß2- microglobulin; ≤3.33=0, >3.33=4)	+ (ß2- microglobulin; ≤4.22=0, >4.22=4)
+ (LDH; ≤3.08=0, >3.08=2)= Risk score Low-risk cf High-risk cf	+ (LDH; ≤3.18=0, >3.18=2)= Risk score Low-risk cf High-risk cf

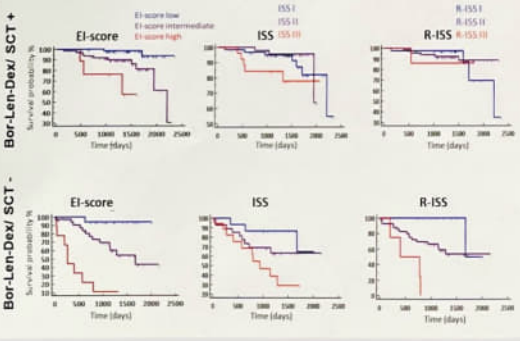
APOBEC2, APOBEC3B, IL11, TGFB1, TGFB3 (mRNA expression level, TPM); ß2- macroglobulin (Serum level µg/mL), LDH (Serum level ukat/L).



The EI-score precisely identifies misclassified MM patients in different high-risk cytogenetic and ISS risk subgroups



EI-score outperforms ISS and R-ISS to predict the prognosis of patients who received induction regimen Bor-Len-Dex (VRd)



Conclusion

Although MM is considered as an incurable disease, an improved risk stratification could help to identify previously unrecognized low- and high-risk patient subgroups that are over- or undertreated and lead to improved outcomes. Our EI-score is a simple score that is based on recent insights into MM biology and accurately identifies high-risk and low-risk newly diagnosed MM patients as well as misclassified MM patients in different cytogenetic and ISS risk subgroups.

References

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