P846 EXPRESSION SIGNATURE OF TP53 BIALLELIC INACTIVATION IDENTIFIES A GROUP OF MULTIPLE MYELOMA PATIENTS WITHOUT THIS GENETIC CONDITION BUT WITH DISMAL OUTCOME.

Topic: 13. Myeloma and other monoclonal gammopathies - Biology & Translational Research

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Background:

Cytogenetic abnormalities remain the most relevant prognostic factors, especially those related to TP53 gene. Biallelic inactivation of TP53, included in the definition of double-hit (DH) MM, entails an ominous prognosis, although is present in less than 5% of newly diagnosed MM (NDMM). However, ultra-high-risk MM, defined as those patients with a median survival less than 24 months, represents 15-20% of the MM population. While other high-risk cytogenetic abnormalities may account for this adverse prognosis, these kind of cytogenetic alterations are not present in all patients with such an unfavorable outcome. On the other hand, p53 can be deregulated by other mechanisms different from changes in DNA gene sequence, such as epigenetic regulation or altered expression of its regulators.

Aims:

To define the transcriptional signature of DH-TP53 and to find out if it was present in other patients who did not have biallelic inactivation of TP53.

Methods:

We analyzed RNA-seq, whole-genome and whole-exome sequencing data from 660 newly diagnosed MM (NDMM) patients from the MMRF (Multiple Myeloma Research Foundation) CoMMpass study to characterize the transcriptional signature of DH-TP53 MM. This gene signature was used to build a score based on a Spearman correlation coefficient and a scaled GINI index. Survival data were retrieved from the IA16 release and the analysis was performed using the Kaplan-Meier estimator and log-rank test. Multivariable Cox models were fitted in R. GSE4581 and GSE136400 gene expression series from GEO were used as validation cohorts.

Results:

TP53 biallelic inactivation, defined in this work as DH-TP53 group, was found in 23 out of 660 patients (3.5%) and was associated with an exclusive gene expression signature consisted of 78 genes. Based on these genes, we calculated the DH-TP53 score, which identified a subgroup of 50 patients that shared the same transcriptional profile (DH-TP53-like group). The prognosis of this group was particularly unfavorable with a median overall survival (OS) of 23 months; and a progression-free survival (PFS) of 15 months, even worse than that described for DH-TP53 patients (HR = 1.83 [95% CI, 1.00-3.35], p = 0.046). The prognostic value of the DH-TP53 was confirmed as an independent prognostic factor for PFS (HR 3.84 [95% CI 2.51-5.88], p < 0.001) and OS (HR 3.32 [95% CI, 2.31-4.77], p < 0.001) in the multivariable analysis. We also observed that survival for any of the cytogenetic abnormalities was significantly shortened in the DH-TP53-like group (p < 0.05). Furthermore, the prognostic value of the DH-TP53 score was externally validated using gene expression data obtained by microarray analysis.

Image:
Summary/Conclusion:

The expression signature of DH-TP53 MM was shared by other MM patients without TP53 biallelic inactivation (DH-TP53-like group). The DH-TP53 score identified an ultra-high-risk group of MM patients with a median overall survival below 24 months. In addition, this score refined the prognostic stratification of cytogenetic abnormalities, and was externally validated using expression data analyzed by microarrays.

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