Panthera R&D Program for Hemato-Oncology

Combining FISH and GEP signatures in multiple myeloma towards a more robus and meaningful high risk definition

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Introduction

Multiple Myeloma (MM) is a heterogeneous disease with different recurring chromosomal aberrations that have been associated with prognosis for survival (e.g. t(4;14), t(14;16)/t(14;20), del13, del17p, add1q). Strategies for combining these markers are emerging [1] and are being evaluated [2]. More recently, gene expression profiling (GEP) studies have identified signatures that distinguish groups of high risk patients, such as the SKY-92 and UAMS-70 signatures [3,4]. Although collectively referred to as high risk signatures they employ different genes and are independent risk markers, similar to how the chromosomal aberrations represent different biological risk markers. It is currently unclear what the best high risk definition is for MM. Here we compare GEP signatures and fluorescent in situ hybridization (FISH) markers for this purpose.

Aims

SkylineDx

We explore the evidence to combine chromosomal aberrations and high risk GEP signatures towards a more robust and meaningful definition of high risk in MM.

Methods

GEP and FISH data (if available) were analyzed for five clinical cohorts (Table 1). Five high risk GEP signatures (SKY-92, UAMS-70, UAMS-17, UAMS80, MRCIX-6) have been applied to all five datasets. Associations between markers and overall survival (OS) were investigated in Kaplan-Meier plots with the logrank test $P \leq 0.05$ considered as significant.

Results

Univariate associations with survival are shown in Figure 1A. The prognostic value of these FISH markers all failed to reproduce across cohorts while five published GEP signatures did. Figure 1B shows the Kaplan-Meier curves for FISH, GEP, and their combination on the MRC-IX cohort. This analysis indicated that GEP alone offers superior OS prognosis compared to FISH markers currently used. The same results were obtained when using the other high risk signatures, and when applied to the HOVON-65/GMMG-HD4 cohort.

Conclusion

GEP signatures are superior to FISH markers for high risk stratification in MM. Combining GEP and FISH does not result in better identification of a high-risk group in the MRC-IX and the HOVON-65/GMMG-HD4 cohorts. Our results are perhaps not surprising given the fact that some would classify e.g. t(4;14) as standard risk [1] while others still consider it to predict for worse survival [2].

Reference

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2. Morgan GJ, and Kaiser MF. How to use new biology to guide therapy in multiple myeloma. Hematology Am Soc Hematol Educ Program, 2012, 342-9.
3. Kuiper R, et al. A gene expression signature for high-risk multiple myeloma. Leukemia, 2012, 26:2406–13.
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Abstract at EHA 2013

A

Cohort	Marker significant on given cohort (Yes: p<=0.05; No: p>0.05; NA: Not Available; *training cohort)										
	t(4;14)	t(11;14)	t(14;16) t(14;20)	add1q	del13	del17	SKY-92	UAMS-70	UAMS-17	UAMS-80	MRCIX-6
HOVON-65/GMMG-HD4 (n=290)	Yes	No	No	No	Yes	Yes	Yes*	Yes	Yes	Yes	Yes
MRC-IX (n=247)	No	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes*
TT2 (n=351)	NA	NA	NA	NA	NA	NA	Yes	Yes*	Yes*	Yes	Yes
TT3 (n=142)	NA	NA	NA	NA	NA	NA	Yes	Yes	Yes	Yes*	Yes
APEX (n=264)	NA	NA	NA	NA	NA	NA	Yes	Yes	Yes	Yes	Yes

B

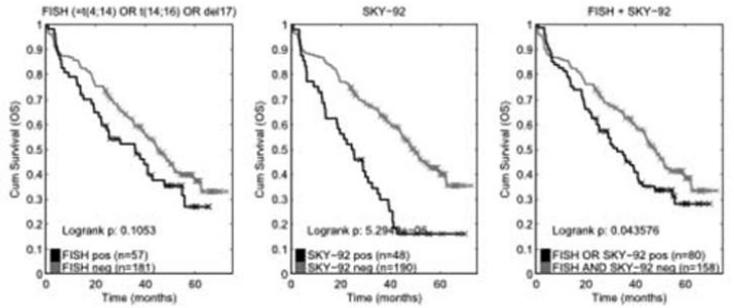

Figure 1. (A) Overview of univariate associations with overall survial; B) Kaplan Meier curves of the independent MRC-IX cohort showing the FISH high risk stratification (left), the SKY-92 GEP high risk signature (middle), and combination of the two (right).