Panthera R&D Program for Hemato-Oncology

SKY92 GEP, iFISH and ISS comparison for risk stratification in multiple myeloma

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Introduction

Prognostic biomarkers are valuable for risk assessment in clinical settings in Multiple Myeloma which is a heterogeneous disease with variable outcome. Markers that have extensively and consistently been related to prognosis are t(4;14), del(17), ISS, and GEP signatures. Ideally a prognostic marker is robust across datasets, identifies a relevant fraction of patients and captures as much of the risk as possible. We evaluated four risk models for their clinical performance in two large datasets, HOVON65/GMMG-HD4 and MRC-IX. We compare HR, p-value, proportion of high risk cases and concordance between high risk models. Importantly, we show how individual patients may or may not be high risk depending on the model used.

Aims

To provide insight in the prognostic value of four different high risk models A) iFISH t(4;14) and/or del(17); B) SKY92 [1]; C) iFISH+ISS [2] and D) SKY92+ISS [3] in 2 different datasets.

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Methods

230 cases from HOVON-65/GMMG-HD4 (GSE19784) and 169 from MRC-IX (GSE15695) having GEP, iFISH, ISS data were analyzed. Kaplan Meier analyses were used to calculate Cox proportional hazard ratios and pvalues. Venn diagrams visualize the overlap between the high risk models. Note that HOVON65/GMMG-HD4 data is the trainingset for EMC92/SKY92 [3]

Results

iFISH high risk (A) and SKY92 high risk (B) were compared for hazard ratio (p-value), proportion and overlap in two clinical cohorts. All hazard ratios except for iFISH (A) in MRC-IX were significant with $p<0.05$. The largest HR was observed for SKY92+ISS (D) for the highest risk category in comparison to the lowest risk category of SKY92, namely HR=13,6 in HOVON-65/GMMGHD4 (Figure 1D) and HR=5,9 in MRC-IX (Figure 1). The two cohorts HOVON65 and MRC-IX have similar overlap of patients positive for iFISH, SKY92 or both (14/12/12% and 12/10/10% respectively) suggesting the robustness of these categories.

Conclusion

SKY92 (model B) is a better prognostic marker than iFISH (model A) or FISH+ISS (model C) with twofold higher HR. Besides, addition of ISS to SKY92 (model D) is relatively easy to perform and is powerful for the identification of a group of patients with favorable prognosis as judged by the median OS which is not reached at 60 months in both cohorts.

References

1. Kuiper, R (2012) Leukemia, 26(11), 2406-2413.
2. Avet-Loiseau, H et al. (2013) Leukemia, 27(3), 711-717.
3. Kuiper R et al. ASH 2013 abstract 3092.

Abstract at EHA 2015

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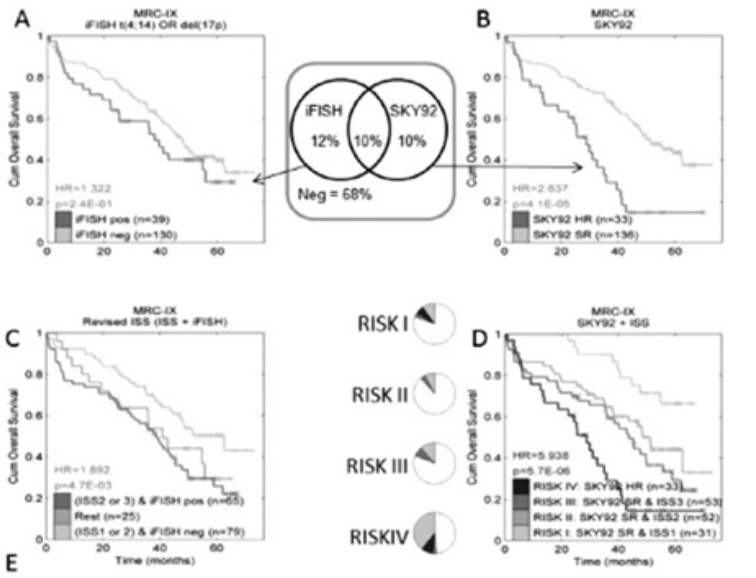

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Cohort	Size	Risk model	HR	p-value	group size
HOVON-65/GMMG-HD4	N=230	A	2.505	**4.6E-05**	27%
		B	4.674	**6.4E-12**	25%
		C	2.989	**6.6E-05**	27%
		D	13.557	**2.4E-10**	25%
MRC-IX	N=169	A	1.322	2.4E-01	23%
		B	2.637	**4.1E-05**	20%
		C	1.892	**4.7E-03**	38%
		D	5.938	**5.7E-06**	20%

Figure 1. Shows four prognostic models applied to the (n=169) MRC-IX dataset. OS Kaplan Meier analyses were performed using risk model A, B, C or D (see aim). The overlap between high risk cases in model A and B is given in the Venn diagram. The pie charts visualize - for model D - the enrichment of iFISH t(4;14) (light grey) and del(17) (dark grey), or both (black) in each of the four strata. E) table with hazard ratios between for the extreme strata in each model.

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