Panthera R&D Program for Hematto-Oncology

A high-risk survival signature for multiple myeloma

R Kuiper[1], A Broyl[1], Y de Knegt[1], M van Vliet[2], E van Beers[2], B van der Holt[3], L el Jarari[3], G Mulligan[4], W Gregory[5], G Morgan[6], H Goldschmidt[7], H Lokhorst[8], M van Duin[1], P Sonneveld[1]

[1] Erasmus Medical Center, Rotterdam, Netherlands
[2] Skyline Diagnostics, Rotterdam, Netherlands
[3] HOVON Data Center, Rotterdam, Netherlands
[4] Millennium Pharmaceuticals, Cambridge, United States of America
[5] University of Leeds, Leeds, United Kingdom
[6] Royal Marsden, London, United Kingdom
[7] University Hospital Heidelberg, Heidelberg, Germany
[8] University Medical Center Utrecht, Utrecht, Netherlands

Introduction

Survival of patients with newly diagnosed multiple myeloma is highly variable and there is a strong need to improve current prognostic markers. Gene expression profiles reflect the biology of MM in individual patients and have potential to be of prognostic value.

Aims

We aimed to establish and evaluate a prognostic signature based on gene expression profiling

Methods

The HOVON65/GMMG-HD4 trial compared the efficacy of bortezomib induction and maintenance treatment with standard induction and maintenance regimes.1 For 290 patients, both gene expression

SkylineDx

and survival data were available. These were selected for training. Supervised principal components analysis was applied to generate a signature of 92 probe sets. High-risk disease within the training set was defined to be the proportion of patients with an overall survival of less than two years. Four independent datasets were available for validation, including newly diagnosed patients (TT2, n=351; TT3, n=142; MRC-IX, n=247) and relapsed patients (APEX, n=264)

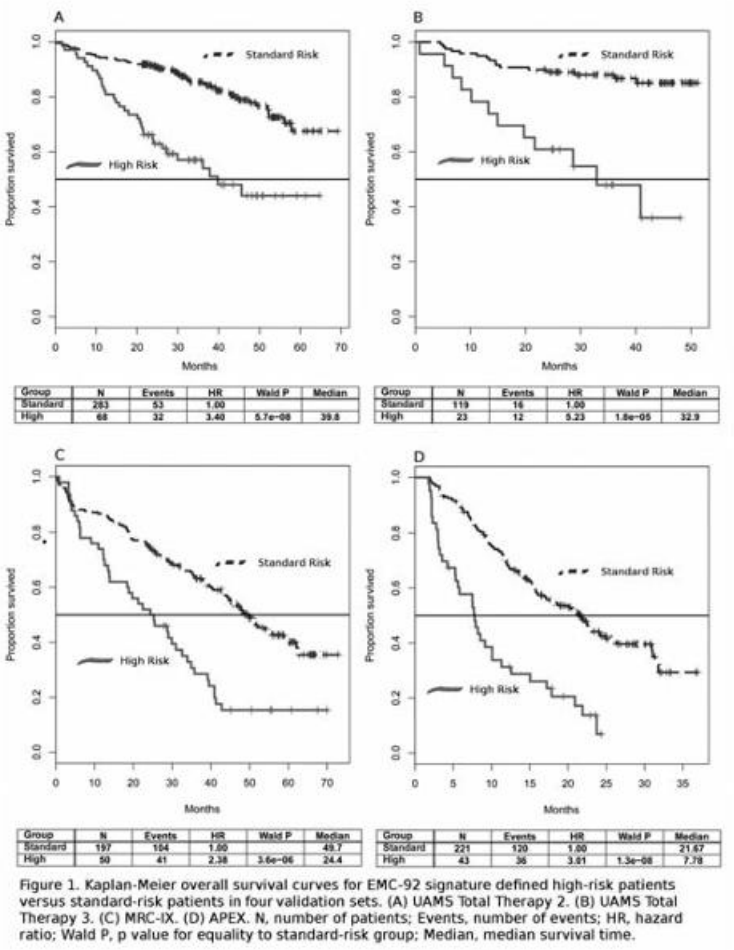
Results

In all validation sets, patients defined as high-risk by the EMC-92-gene signature show a clearly reduced overall survival. A hazard-ratio (HR) of 3.4 (95%CI:2.19-5.29) was found for the TT2 study, HR:5.23 (2.46-11.13) for the TT3, HR:2.38 (1.65-3.43) for the MRCIX and HR:3.01 (2.06-4.39) for the APEX ($p<0.0001$ in all studies; Figure 1). In multivariate analyses, the EMC-92-gene signature proved an independent and superior predictor compared with clinical variables such as the International Staging System and cytogenetic aberrations including del(17p). Furthermore, in standard-risk classified patients in the MRC-IX validation set, no survival difference was found between patients with or without at least one poor risk FISH marker, confirming the strength of the EMC-92 gene signature in relation to cytogenetics. In addition the performance of the EMC-92 is independent of existing signatures like the UAMS-17,70 and 80. Likelihood-ratio tests for pair-wise comparison showed that the increase in likelihood on addition of the EMC-92 was consistently higher than when another signature was added to EMC-92. For instance, the adjusted p-value for the addition of the EMC-92 to UAMS-80 and vice versa were 7.6x10-7and 2.2x10-3 respectively. The genes in the EMC92 signature had little overlap to other signatures and was limited to genes such as BIRC5 and ITM2B. Within the HOVON-65/GMMG-HD4 high-risk patients, bortezomib treated patients survived longer than patients treated with vincristine based chemotherapy (30 months compared to 19 months, respectively), albeit not significant (p=0.06).

Conclusion

The EMC92-gene signature has a strong and highly significant predicting ability in multiple myeloma patients irrespective of age and setting, newly diagnosed or relapse. Use of this signature will contribute to risk assessment in clinical trials and could ultimately provide a tool for treatment choices in high-risk multiple myeloma patients.

Abstract at EHA 2012



Group	N	Events	HR	Wald P	Median
Standard	283	53	1.00		
High	68	32	3.40	5.7e-08	39.8

Group	N	Events	HR	Wald P	Median
Standard	119	16	1.00		
High	23	12	9.23	1.8e-05	32.9

Group	N	Events	HR	Wald P	Median
Standard	197	104	1.00		49.7
High	50	41	2.38	3.6e-06	24.4

Group	N	Events	HR	Wald P	Median
Standard	221	120	1.00		21.67
High	43	36	3.01	1.3e-08	7.78

Figure 1. Kaplan-Meier overall survival curves for EMC-92 signature defined high-risk patients versus standard-risk patients in four validation sets. (A) UAMS Total Therapy 2. (B) UAMS Total Therapy 3. (C) MRC-IX. (D) APEX. N, number of patients; Events, number of events; HR, hazard ratio; Wald P, p value for equality to standard-risk group; Median, median survival time.