Differentiating asymptomatic monoclonal gammopathy (AMG including MGUS and AMM) from clinical multiple myeloma (CMM) by gene expression profiling of purified plasma cells

Rashid Khan[1], Christoph Heuck[1], Adam Rosenthal[3], Scott Miller[1], Donald Johann[1], Madhav Dhodapkar[2], Pingping Qu[3],Frits van Rhee[1], Joshua Epstein[1], Shmuel Yaccoby[1], Yogesh Jethava[1], Maurizio Zangari[1], Monica Grazziutti[1], Philip Farmer[1], Antje Hoering[3], John Crowley[3], and Bart Barlogie[1]

[1] Myeloma Institute for Research and Therapy and Department of Radiology, University of Arkansas for Medical Sciences, Little Rock AR; [2] Division of Hematology, Yale School of Medicine; [3] Cancer Research And Biostatistics, Seattle WA

INTRODUCTION

Previous research indicated that plasma cells (PC) from AMG and CMM could not be distinguished at the gene expression profile (GEP) level.(1) We reported that a GEP70 risk score could identify a subset of AMG patients at high risk for progression to CMM requiring therapy.(2) We now re-address this issue in a larger population of patients (pts) in order to contribute to a better understanding of the genetics of this progression event from clinically benign to malignant disease.

MATERIALS AND METHODS

We identified baseline GEPs of 89 pts with AMG and 38 pts with MGUS in our observational study and compared them to 785 GEPs of previously untreated pts with MM who were enrolled in Total Therapy 2 and 3. GEPs were separated into training and test sets of 60 and 29 pts for AMM, 26 and 12 pts for MGUS and 524 and 261 pts for CMM respectively. We performed t-tests to identify differentially expressed probe-sets between AMM and CMM, MGUS and CMM and AMM and MGUS. Results adjusted for multiple testing and probe-sets were ranked by q-value for each comparison.

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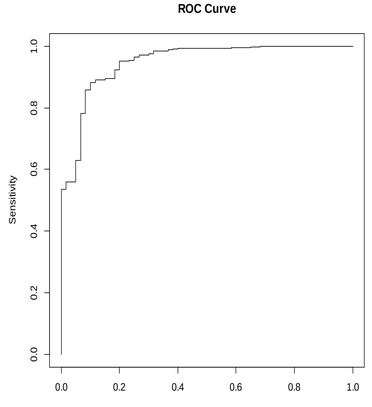
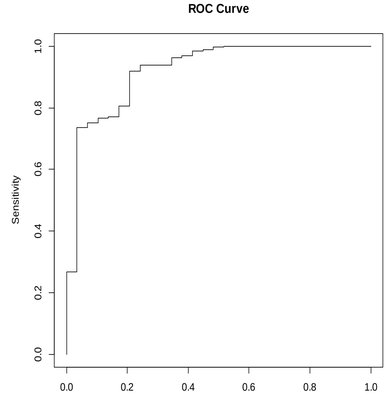
RESULTS

- In the comparison between AMM and CMM we identified 74 probe-sets significantly differentially expressed with a q-value <1 X 10^{-6}.
- Using a class predictor approach the $\log^2$ transformed expression values for each gene were summed. An optimal cut-point was identified in the training set and validated in the test set.
- Performance was satisfactory with a sensitivity of 79.3%, a specificity of 92.0% and a positive predictive (PPV) value of 90.7%.
- AMM samples classified as CMM had a significantly shorter time to progression to CMM than those classified as AMM.



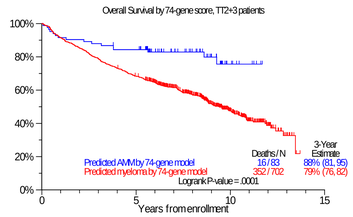
Training set

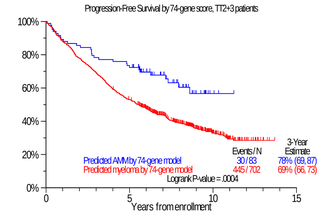


Test Set

RESULTS continued

- Conversely patients with CMM who were classified as AMM had a better PFS and OS than those classified as CMM.





- 206 genes were differentially expressed between MGUS and CMM and a predictive model based on these genes showed a sensitivity of 83%, specificity of 92.3% and PPV of 91.9%.
- 11 probe-sets were common between the AMM/CMM and MGUS CMM gene lists.

CONCLUSIONS

Gene expression profiling can readily differentiate between MGUS or AMM and CMM. More importantly pts with AMM who have a CMM-like GEP signature have a significantly shorter time to progression to CMM while AMM-like signature in CMM predicts better outcome.

BIBLIOGRAPHY

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