Panthera R&D Program for Hemato-Oncology

Proteasome inhibitor treatment response can be predicted by gene expression profiling in Multiple Myeloma

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Introduction

Multiple Myeloma (MM) is a heterogeneous disease in terms of genetic background, survival and treatment response for which more and more 'novel agents' become available. However, there is a large diversity between subgroups of patients in treatment response and survival. This signifies an ever increasing need for predictive markers for MM that may allow identification of such subgroups at time of diagnosis. Gene Expression Profiling (GEP) studies have resulted in several markers, such as the EMC92/SKY92 high risk signature, virtual karyotyping (t(4;14), t(11;14), etc.), and the GEP clusters (MS, MF, etc.).

Aims

To identify predictive GEP based markers capable of distinguishing patients that benefit from proteasome inhibitor based treatment.

Methods

The data from the HOVON-65/GMMG-HD4 phase 3 trial was used, in which bortezomib, doxorubicin, and dexamethasone (PAD), followed by high dose melphalan (HDM)/autologous stem cell

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transplantation (ASCT) and bortezomib maintenance was compared with vincristine, doxorubicin, and dexamethasone (VAD) followed by HDM/ASCT and thalidomide maintenance. GEP was performed (Affymetrix U133 Plus 2.0 GeneChip; algorithms: MMprofiler assay) for 329 MM patients. A subset of this dataset was previously used as a training set for the EMC92/SKY92 signature (290 patients), for the signatures of the 12 clusters (320 patients), as well as for the signatures for chromosomal aberrations (virtual karyotyping of t(4;14), t(11;14), t(14;16)/t(14;20), add1q, add9q. del13, and del17, number of patients depending on the FISH). The predictive power for Overall Survival (OS) of those markers in relation to the PAD/VAD treatment arms was assessed. For each marker, a Cox Proportional Hazards model was fit on the patients that are positive for that marker, with samples split into PAD/VAD as covariate. A Hazard Ratio (HR) larger than 1 indicates that PAD patients had longer OS than those treated with VAD (uncorrected p values also reported).

Results

The predictive power of the EMC92/SKY92 signature, markers for the various chromosomal aberrations and GEP clusters was assessed by comparing VAD with PAD. Five markers, EMC92/SKY92, t(14;16)/t(14;20), add1q21, MF and CD2 cluster, were found to have longer OS when treated with PAD (HR ranging from 2.2 to 12.9, $p<0.05$, Figure 1A). t(4;14) shows improved survival when treated with PAD (HR=1.8), but is not significant ($p=0.15$). These markers capture different biological mechanisms, and therefore different sets of patients. For example, the EMC92/SKY92 (23.1% of patients) and cluster MF (6.4% of patients) together identify 26.1% of patients with an HR of 2.7 (Figure 1A and B). These results indicate that GEP markers may provide a good predictive marker for proteasome inhibition therapy.

Conclusion

Five GEP markers have been found that can predict longer OS in subsets of MM patients when treated with proteasome inhibitors (PAD/Bortezomib), suggesting that they may serve as a predictive marker. The predictive power of these markers must be validated in the EMN02/HOVON-95 clinical trial which will include a bortezomib based induction regimen, and consolidation regimen.

Abstract at EHA 2014

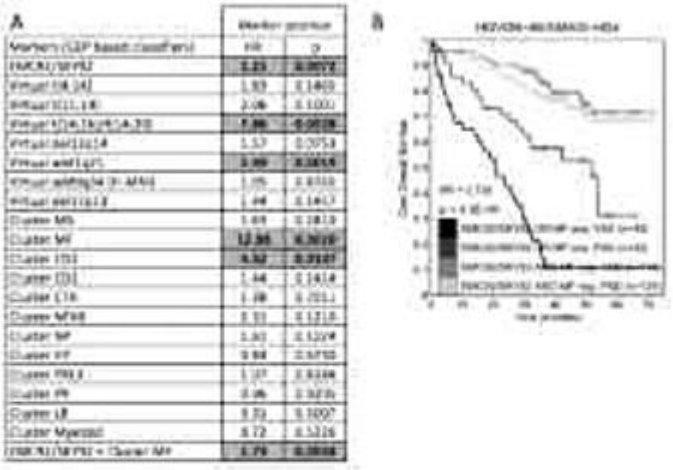

Figure 1. A) Predictive hazards ratios of all MMprofiler markers and one marker combination (VAD *versus* PAD treatments arms). Bold text indicates p<0.05. B) Kaplan-Meier curve for the combination of EMC92/SKY92 and MF cluster split out for the two treatment arms. The Hazard Ratio compares the treatment arms within the "EMC92/SKY92 positive OR MF cluster positive" group.