Panthera R&D Program for Hematto-Oncology

High-risk Multiple Myeloma patients are missed without gene expression profiling

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Introduction

Multiple Myeloma (MM) is a rare and heterogeneous blood cancer of the plasma cells. Various new therapies have been introduced and are used in combination to combat the heterogeneity. Despite ongoing research, improvements for the fast progressing (high-risk) patients have been limited. Innovative clinical trials are set up to find new therapies that investigate benefit for this specific patient group. In order to select highrisk patients for these trials, it is important to have a conclusive assessment of the patient's risk profile, including their Gene Expression Profile (GEP). Aim: To show that GEP is an important contributor in selecting high-risk MM patients.

Methods

SkylineDx

Six datasets were combined: MRC-IX (n=180), HOVON87/NMSG-18 (n=148), EMN-02/HOVON-95 (n=249), GIMEMAMMY-3006 (n=112), a Czech cohort (n=27 E-MTAB-1038) and the MMpredict non-trial cohort (n=89, [2]). Pooled, a total of n=805 MM patient samples were available including corresponding GEP data, iFISH and ISS annotation and Overall Survival (OS). Patients were risk classified in three strata comparable as proposed by Kuiper [1]: Low Risk (LR) as SKY92 standard risk + ISS I; Intermediate Risk (IR) as SKY92 standard risk + ISS II or III; and High Risk (HR) as SKY92 high risk. Subsequently, each stratum was further refined into: patients with high-risk iFISH t(4;14) and/or del(17p) (iFISH); and patients without these markers (non-iFISH). The Cox proportional Hazards model was applied to estimate survival.

Results

The combination of SKY92+ISS identified three risk strata in the cohort: n=188 for LR (23%), n=448 for IR (56%), n=169 for HR (21%). The OS of the HR stratum was significantly shorter than the LR stratum (hazard ratio=6.0, p <0.001), see Figure 1. Similarly, patients with iFISH (n=179) had a shorter survival than the non-iFISH patients, but with a less prominent effect size (n=626; hazard ratio = 1.8; p<0.001). For all three SKY92+ISS strata, the comparison of iFISH versus non-iFISH patients for OS resulted in a non-significant OS: hazard ratio=1.4 and p=0.44 for LR, Figure 1B; hazard ratio=1.2 and p=0.41 for IR, Figure 1C; and hazard ratio=1.4 and p=0.061 for HR, Figure 1D. Our analyses showed that for 44% (79 out of 179) of iFISH patients, the traditional high-risk classification was correct. However, GEP identified another 90 out of 169 (53%) patients with comparable poor outcomes that were missed since they belonged to the non-iFISH group, Figure 1D. Lastly, 30 out of 179 (17%) iFISH patients (considered high-risk), showed an intermediate survival (median survival not reached at 80 months), Figure 1B. To summarize, without SKY92+ISS, many high-risk and low-risk patients remain unidentified. Image: Figure 1: Kaplan Meier plots for the SKY92 + ISS LR, IR and HR strata and their respective splits based on presence of iFISH markers t(4;14) and/or del(17)p or absence of both.

Conclusion

When designing a clinical trial, currently used risk stratification methods are sub-optimal and might influence the conclusion on effectiveness of the investigational therapeutic treatment. GEP, here SKY92+ISS, distinctively contributes to further refine risk groups, as we have shown that true high-risk patients are missed. SKY92 should therefore be added as risk stratification method for a holistic view on a patient's course of disease.

Abstract at EMN 2021