Panthera R&D Program for Hematto-Oncology

Prognosis in elderly Multiple Myeloma patients in the HOVON-87 NMSG-18 study based on revised ISS and SKY92-ISS

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Introduction

The incidence of multiple myeloma (MM) increases with age with a median at diagnosis of 69 years. Patients older than 65 years old are often considered to be ineligible for stem-cell transplantation. Treatment for older patients is lenalidomide and dexamethasone, or melphalan/prednisone with thalidomide or bortezomib. The HOVON-87/NMSG-18 trial showed that replacing thalidomide with lenalidomide, followed by maintenance therapy until disease progression, i.e. MPR-R vs MPT-T, did not result in improved progression free and overall survival (PFS and OS) of MPR-R treated patients compared to MPT-T treated patients (Zweegman *et al.* Blood 2016;127(9):1109-1116). MPR-R treated patients did demonstrate significantly lower grade 3/4 neuropathy.

Aims

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The aim of this analysis was to evaluate the SKY92 gene expression classifier in comparison to revised-ISS (R-ISS) in elderly, non-transplant eligible patients included in the HOVON-87/NMSG-18 trial using updated survival data.

Methods

For 190 patients, CD138 purified plasma cells were available to determine the SKY92 risk score (median age 72 years, inter-quartile range: 69 – 76). SKY92 scores were determined using the MMprofiler™ CE IVD assay. In addition, treatment arm, FISH and R-ISS were analyzed by survival analysis for both PFS and OS. Hazard ratios (HR) are given with 95% confidence intervals in brackets. Likelihood ratio (LR) tests were used to evaluate the significance of each prognostic model.

Results

At the time of analysis the median follow up was 6 yrs. The SKY92 classifier identified 14% of patients as high-risk. The median PFS and OS of the high-risk patients was 12 months and 19 months, respectively, compared to 23 (PFS) and 61 months (OS) for standard risk patients (OS, HR=2.6 [1.6–4.1]; LR $p=7x10^{-5}$; PFS, HR=2.4 [1.6–3.7]; LR $p=7x\ 10^{-5}$).

Based on ISS (n ISS I/ II/ III = 48/ 92/ 46) and SKY92, 186 patients were classed into four risk groups: SKY92 high-risk combined with any ISS stage (13%), SKY92 standard-risk and ISS III (21%), SKY92 standard-risk and ISS II (45%) and SKY92 standard risk and ISS I (21%; Kuiper et al., 2015; Blood, 126: 1996-2004). The median PFS of these respective groups was 11, 21, 22 and 25 months and the median OS was 18, 49, 56 and 88 mo (PFS: LR p-value=$5x10^{-3}$; OS: LR p-value =$2x10^{-4}$).

Classifying in R-ISS stages (n R-ISS I/II/III = 12/129/28) demonstrated a median PFS of 13, 20 and 30 months (LR p-value=$5x10^{-3}$) and a median OS of 25, 54 and 78 months (LR p-value=$1x10^{-3}$).

Factors independently associated with OS in the multivariate analysis were SKY92-ISS, R-ISS and del17p, whereas only SKY92-ISS and R-ISS remained independently associated with PFS.

Eleven SKY92 high-risk patients were treated with lenalidomide and demonstrated a median OS of 55 months compared to 17 months for thalidomide treated high-risk patients (n=15). The median OS in standard-risk patients was 59 months (lenalidomide) vs 61 months (thalidomide). Using an interaction term in the Cox regression model, a significant difference in OS (p=0.04) was found between the treatment arms conditional on SKY92 risk status.

Conclusion

Also in non-transplant eligible MM patients, the SKY92 classifier is a robust marker to identify high-risk patients. The SKY92-ISS has prognostic value independent of the revised ISS. In addition, SKY92 high-risk patients appear to have a survival benefit of lenalidomide treatment over thalidomide treatment, which is not found for SKY92 standard risk patients.

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