Panthera R&D Program for Hemato-Oncology

Prognostic and predictive performance of SKY92 combined with R-ISS in elderly multiple myeloma patients in the HOVON-87 NMSG-18 study

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Introduction

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SkylineDx

The prognosis of multiple myeloma (MM) is highly dependent on cytogenetic abnormalities and gene expression. Currently, evidence to either start or withhold therapy is insufficient. Especially, in the eldest patient such a predictive tool is eagerly awaited as side effects of treatment are more pronounced and might be irreversible. In the HOVON-87/NMSG-18 trial elderly patients were treated with either thalidomide or lenalidomide, followed by maintenance therapy until progression, i.e. MPR-R vs MPT-T. In this cohort, we assessed the prognostic and predictive performance of the previously described SKY92-ISS and the revised ISS (R-ISS).

Methods

Purified assay were available for n=190 patients. This gene expression profiling (GEP) assay delivers the SKY92 risk score, as well as GEP derived IGH translocation status. ISS (n=186), treatment arm and R-ISS (n=176) were included in Cox survival analyses for progression free survival (PFS) and overall survival (OS) and assessed by the likelihood ratio test.

Results

The 186 newly diagnosed patients analyzed had a median age of 72 years (inter-quartile range: 69 76). At the time of analysis the median follow up was 6 years; 25% of patients had ISS I, 49% ISS II and 26% ISS III. Classification into the four-tier SKY92-ISS was applied dividing the patients into high- to low-risk categories: SKY92 high-risk (HR)-ISSI/II/III (13% of patients), SKY92-standard risk (SR)/ISS III (45%), SKY92-SR/ISS II (21%) and SKY92-SR/ISS I (21%). The median PFS of these groups from high- to low-risk was 11, 21, 22 and 25 months (p=6.8x10-3) and median OS 18, 49, 56 and 88 months (p=1.7x10-4). R-ISS classification resulted in 7% R-ISS III, 74% R-ISS II and 18% R-ISS I patients with a median PFS of 12, 20 and 30 months (p=0.09); median OS of 25, 53 and 88 months (p=4x10-4). In a multivariate analysis (n=176), SKY92-ISS and RISS both remain independently related to PFS (p=1.6x10-3 and 4.7x10-2) and to OS (p=2.4x10-4 and 1.1x10-2). As the ISS term in SKY92-ISS was redundant when combined with R-ISS, the SKY92 and R-ISS were combined as follows from high- to low-risk: 11% SKY92 HR/R-ISS II/III, 73% SKY92 HR/R-ISS I or SKY92 SR with R-ISS II/III, 16% SKY92 SR and R-ISS I. Combining SKY92 with RISS suggests that high-risk patients (SKY92 HR and R-ISS II/III) may benefit from MPR-R as compared with MPT-T with median OS of 55 versus 13 months respectively. This is supported by a significant interaction term for OS between riskgroup and treatment (p=0.01).

Conclusion

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The SKY92-ISS and R-ISS are robust markers to identify HR patients, also in non-transplant eligible MM patients. Both markers have independent prognostic value in relation to OS and PFS. In addition, the SKY92-R-ISS combination demonstrates predictive value for treatment in this trial. This finding requires validation in independent datasets.

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