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Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

Validation and Improvement Opportunities of the Revised International Staging System for Multiple Myeloma: An Analysis on Mature Data from European Clinical Trials Within the HARMONY Big Data Platform

Mattia D'Agostino, Hovon, Juan José Lahuerta, GMMG, Elena Zamagni, Lars Bullinger, Alessandra Larocca, Maria-Victoria Mateos, Hovon, GMMG, Bruno Costa, Joan Blade, Hovon, Paola Tacchetti, Giovannino Ciccone, Sonja Zweegman, Hartmut Goldschmidt, Michele Cavo, Jesus San Miguel, Pieter Sonneveld, Mario Boccadoro, Jesus Maria Hernandez

On behalf of HARMONY, EMN, data owners

The clinical outcome of multiple myeloma (MM) patients (pts) is heterogeneous. In 2015, analyzing 4445 newly diagnosed MM (NDMM) pts enrolled into 11 clinical trials after a median follow-up of 46 months (mos), a risk stratification algorithm named Revised-ISS (R-ISS) was developed combining International Staging System (ISS), chromosomal abnormalities (CA) detected by interphase fluorescent in situ hybridization (FISH) and serum lactate dehydrogenase (LDH) (Palumbo et al., JCO 2015). Here we report a mature follow-up of 5584 pts enrolled in 14 clinical trials, providing an updated report on the R-ISS prognostic role and highlighting potential improvements.

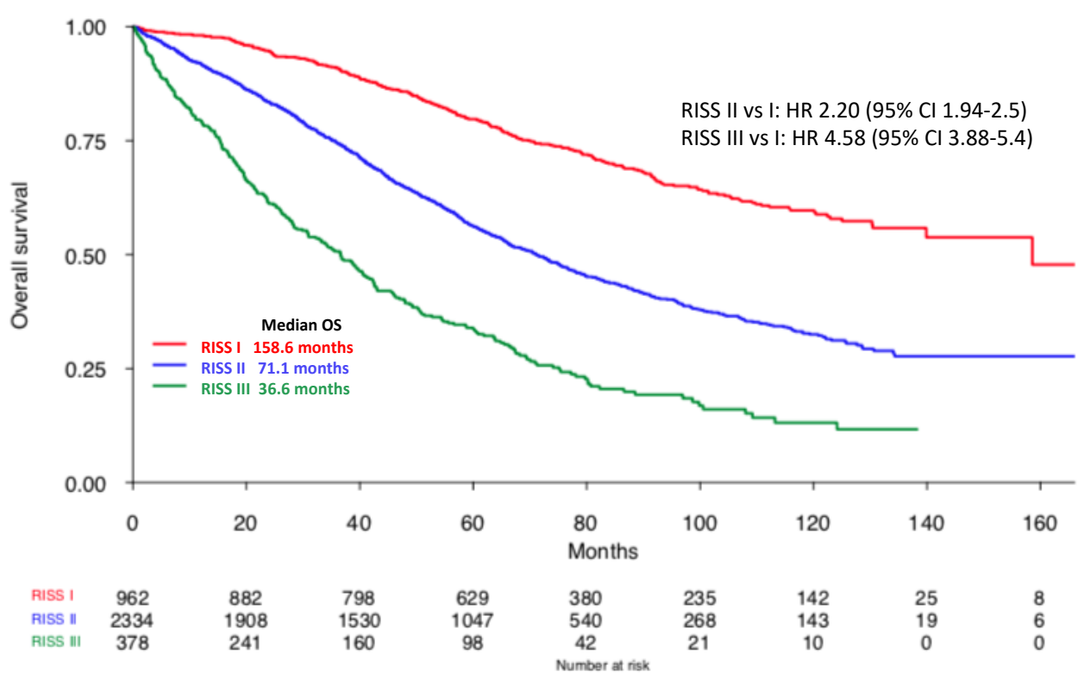
Methods — Data from different European cooperative groups were collected through the European Myeloma Network (EMN) and registered in a big data platform developed by HARMONY, which is a European public-private partnership focusing on hematologic malignancies with unmet medical needs and providing a legal-ethical framework for international data sharing and analysis. The primary end point of this analysis was overall survival (OS) according to R-ISS. All NDMM pts received immunomodulatory agents (IMiDs) or proteasome inhibitors (PIs) as part of their upfront treatment.

Conclusion — We confirmed the prognostic role of R-ISS within the largest cohort of NDMM pts analyzed so far. Moreover, we detected other independent OS predictors that can help us to further refine the current prognostic method. The addition of new datasets is planned; the improvement of the current R-ISS may foster a worldwide

Results — 5584 NDMM pts with a median age of 65 years were analyzed after a median follow-up of 74 mos. 35% of evaluable pts had ISS I disease, 40% ISS II and 25% ISS III. LDH was ≤ the upper limit of normal (ULN) in 87% of evaluable pts, >ULN in 13%. To define high-risk CA, we performed a multivariate Cox model for OS individually evaluating del(17p), t(4;14) and t(14;16) positivity. Del(17p) (HR 1.78, p< 0.001) and t(4;14) (HR 1.67, p<0.001) confirmed their role as independent risk factors, while t(14;16) (HR 1.19, p=0.16) did not. We therefore defined high-risk CA as del(17p) and/or t(4;14) positivity. High-risk CA were present in 23% of evaluable pts, while low-risk CA in 77%. Overall, 3674 pts (66%) had complete ISS, CA and LDH data and were thus eligible for R-ISS analysis. Baseline characteristics and OS of pts with complete vs incomplete data (median OS 80.6 vs 80.2 mos, p=0.95) were similar, thus excluding a selection bias. R-ISS I was calculated as ISS I, no high-risk CA [del(17p) and/or t(4;14)] and normal LDH level; R-ISS III was calculated as ISS III and high-risk CA or high LDH level; R-ISS II included all the other possible combinations. 962 (26.2%) pts had R-ISS I disease, 2334 (63.5%) R-ISS II and 378 (10.3%) R-ISS III. Median OS was 158.6 mos for R-ISS I pts, 71.1 mos for R-ISS II pts, and 36.6 mos for R-ISS III pts (Figure 1). 5-year OS rates were 80%, 56% and 34%, while 10-year OS rates were 60%, 33% and 13% for R-ISS I, II and III respectively.

In a multivariate Cox model, R-ISS II vs I (HR 2.20, 95% CI 1.94-2.5), R-ISS III vs I (HR 4.58, 95% CI 3.88-5.4), male sex (HR 1.20 vs female sex, 95% CI 1.09-1.31) and age >65 years (HR 1.62 vs ≤65 years, 95% CI 1.47-1.78) significantly increased the risk of death (p<0.001).
The prognostic role of R-ISS was also confirmed in the 1244 pts that were not included in the original R-ISS report (R-ISS II vs I HR 2.38, R-ISS III vs I HR 4.40, p<0.001), validating it. The prognostic role of R-ISS was also confirmed by subgroup analyses on: transplant-eligible pts [2161, 58.8%; both receiving (1611, 43.8%) or not receiving (550, 15.0%) transplant]; transplant-ineligible pts (1513, 41.2%); and pts receiving PIs (874, 23.8%), IMiDs (1669, 45.4%) or both (1131, 30.8%). We next identified prognostic factors that predicted OS independently from R-ISS, age and sex. NDMM pts with an IgA monoclonal component showed a worse OS compared to non-IgA pts (HR 1.21, p<0.001). A baseline creatinine clearance ≤45 ml/min independently predicted OS, as compared to a normal (>60 ml/min) renal function (HR 1.24, p<0.001). The amp(1q) effect on OS was solid (HR 1.45, p<0.001), although data were only available in 1231 pts due to many missing values. Pts with a poor prognostic performance status (ECOG >1 or Karnofsky <80) were at higher risk of death independently from R-ISS, age and sex (HR 1.36, p<0.001).
collaboration.

Figure 1.
OS in NDMM patients stratified by R-ISS



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