

P890 COMBINING SKY92 GENE EXPRESSION PROFILING WITH CYTOGENETICS ACCORDING TO R2-ISS FOR MULTIPLE MYELOMA RISK CLASSIFICATION: THE FIRST PROSPECTIVE EVIDENCE

Topic: 14. Myeloma and other monoclonal gammopathies - Clinical

Xiang Zhou^{*1}, Benedict Engel¹, Annika Hofmann¹, Cornelia Vogt¹, Silvia Nerreter¹, Eva Teufel¹, Emilia Stanojkovska¹, Marietta Truger², Philipp Weis¹, Xianghui Xiao¹, Florian Eisele¹, Christine Riedhammer¹, Maximilian Johannes Steinhardt¹, Umair Munawar¹, Seungbin Han¹, Larissa Haertle¹, Claudia Haerlach², Hermann Einsele¹, K Martin Kortum¹, Leo Rasche¹

¹Würzburg, Würzburg, Germany; ²Munich, Munich, Germany

Background:

The definition of high-risk (HR) multiple myeloma (MM) is controversial. Currently, FISH is the most commonly used tool for risk stratification in MM. According to the R2-ISS, HR cytogenetics is defined as presence of del(17p), t(4;14), and/or 1q CNA. On the other hand, SKY92 gene expression profiling has been developed for detection of HR MM in clinical trials. However, data on risk stratification combining SKY92 with FISH according to R2-ISS is still missing.

Aims:

The aim of this study was to evaluate the HR detection using SKY92 in combination with FISH according to R2-ISS in MM.

Methods:

We prospectively collected bone marrow (BM) and clinical data of 258 MM patients. Cytogenetics were analyzed on purified CD138 positive MM cells by FISH, and HR cytogenetics was defined as per the current R2-ISS classification. SKY92 risk status was determined with MMprofiler gene expression assay. Whole genome sequencing (WGS) was performed to compare SKY92 and FISH.

Results:

In total, 258 patients were included in our study (NDMM: n=109; RRMM: n=149). SKY92 status was available for 216 (83.7%) patients. However, samples of 26 (17.7%) patients, who showed significantly lower bone marrow infiltration than the remaining patients (median: 20% vs 50%, $P=0.006$), did not meet the SKY92 quality control criteria. HR SKY92 was significantly enriched in RRMM (57/121, 47.1%) compared with NDMM (17/95, 17.9%) ($P<0.0001$). The percentage of patients suffering from extramedullary disease (EMD) was significantly higher in HR SKY92 (12/74, 16.2%) compared to (SR) SKY92 (8/142, 5.6%) ($P=0.01$). In RRMM, HR SKY92 was significantly more frequent in patients with ≥ 4 prior lines of therapies (32/52, 61.5%) compared to those with < 4 therapy lines (25/65, 36.2%) ($P=0.009$). Moreover, HR SKY92 was significantly more common in patients who received autologous SCT (48/89, 53.9%) than the remaining patients (9/32, 28.1%) ($P=0.01$), suggesting that MM-therapy including SCT may influence the expression level of different genes and, in turn, the SKY92 status. RRMM patients with HR SKY92 showed significantly shorter progression free survival (PFS) ($P<0.0001$) and overall survival (OS) ($P<0.0001$) than standard-risk (SR). In NDMM, HR SKY92 also indicated a significantly inferior PFS ($P<0.0001$) in comparison with SR.

We then combined SKY92 with FISH according to R2-ISS in 181 patients (NDMM: n=79; RRMM: n=102). We found a discrepancy between the both risk stratification systems, with 67 (37.0%) and 99 (54.7%) patients being defined as HR by SKY92 and FISH, respectively. Overall, 13 (16.4%) NDMM and 36 (35.3%) RRMM patients

Copyright Information: (Online) ISSN: 2572-9241

© 2023 the Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the European Hematology Association. This is an open access Abstract Book distributed under the Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) which allows third parties to download the articles and share them with others as long as they credit the author and the Abstract Book, but they cannot change the content in any way or use them commercially.

Abstract Book Citations: Authors, Title, HemaSphere, 2023;7(S3):pages. The individual abstract DOIs can be found at <https://journals.lww.com/hemasphere/pages/default.aspx>.

Disclaimer: Articles published in the journal HemaSphere exclusively reflect the opinions of the authors. The authors are responsible for all content in their abstracts including accuracy of the facts, statements, citing resources, etc.

showed HR in both SKY92 and FISH (“double-HR”). After a median follow up of 10.2 months, double-HR presented a negative prognostic factor for PFS in both NDMM ($P=0.0003$) and RRMM ($P<0.0001$). Furthermore, “double-HR” patients showed the worst OS ($P=0.0002$) in RRMM.

To elucidate the discrepancy between FISH and SKY92, we performed WGS in 16 patients who exhibited either only HR SKY92 ($n=7$) or only HR FISH ($n=9$). Interestingly, 1 patient with bi-allelic *TP53* inactivation (del + mut) and 6 patients harbouring 1q CNA were determined as SR by SKY92 but as HR by FISH. The median PFS was not reached after a median follow up of 11.3 months in these 9 patients. Vice versa, 4 out of 7 patients with only HR SKY92 but SR FISH displayed 1q CNA, which was detected only by WGS, and del1p32 was found in 1 patients. Interestingly, we found *CRBN* mutation in 3 out of 7 patients with only HR SKY92 but SR FISH. The remaining 2 patients did not show any known HR genomic alterations, suggesting that HR MM may be associated with other factors, e.g. epigenetic modifications.

Conclusion:

We provide the first prospective evidence that “double-HR” (SKY92 + FISH according to R2-ISS) indicates the highest-risk MM.

Copyright Information: (Online) ISSN: 2572-9241

© 2023 the Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the European Hematology Association. This is an open access Abstract Book distributed under the Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) which allows third parties to download the articles and share them with others as long as they credit the author and the Abstract Book, but they cannot change the content in any way or use them commercially.

Abstract Book Citations: Authors, Title, HemaSphere, 2023;7(S3):pages. The individual abstract DOIs can be found at <https://journals.lww.com/hemasphere/pages/default.aspx>.

Disclaimer: Articles published in the journal HemaSphere exclusively reflect the opinions of the authors. The authors are responsible for all content in their abstracts including accuracy of the facts, statements, citing resources, etc.