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Comprehensive Genomic Characterization of Refractory Multiple Myeloma Reveals a Complex Mutational and Structural Landscape Associated with Drug Resistance

Nicola Lehnert, MD,^{*,1,2} Umut H Toprak,^{*,3} Jing Xu,^{*,2} Nagarajan Paramasivam,^{*,3,4}
Daniel Hübschmann,^{*,3,5,6} Martina Fröhlich,^{*,7} Nur H Md Hanafiah,^{*,2} Sadaf Mughal,^{*,7} Elias
K Mai, MD,^{*,1} Anna Jauch,^{*,8} Jens Hillengass, MD,¹ Roland Eils,^{*,3,5} Carsten Müller-Tidow,^{*,9}
Benedikt Brors,^{*,7} Hartmut Goldschmidt, MD,^{10,11} Matthias Schlesner,^{*,3} Marc S Raab, MD PhD^{*,1,2}

¹Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany

²Max-Eder-Group "Experimental Therapies for Hematologic Malignancies", German Cancer Research Center, Heidelberg, Germany

³Division of Theoretical Bioinformatics, German Cancer Research Center, Heidelberg, Germany

⁴Medical Faculty, University of Heidelberg, Heidelberg, Germany

⁵Institute for Pharmacy and Molecular Biotechnology and BioQuant, University of Heidelberg, Heidelberg, Germany

⁶Department of Pediatric Immunology, Hematology and Oncology, Heidelberg University Hospital, Heidelberg, Germany

⁷Division of Applied Bioinformatics, German Cancer Research Center, Heidelberg, Germany

⁸Institute for Human Genetics, Heidelberg University Hospital, Heidelberg, Germany

⁹Department of Internal Medicine V, University Hospital Heidelberg, Heidelberg, Germany

¹⁰Heidelberg University Hospital, Heidelberg, Germany

¹¹National Center for Tumor Diseases, Heidelberg, Germany

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Abstract

Introduction: Despite the improvement in prognosis of multiple myeloma (MM), patients refractory to immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs) still experience a very poor outcome. While sequencing endeavors in recent years have comprehensively described the genetic composition of newly diagnosed and relapsed MM, the mutational landscape of refractory MM (rMM) remains elusive.

Methods: In order to elucidate the genetic landscape of rMM we have recently initiated a program including whole genome (WGS) and transcriptome sequencing of rMM patients. We here report data on 38 rMM tumor/germline pairs with a median coverage of 77x for WGS, including 9 patients with consecutive tumor samples. Patients had received a median of 5 prior lines of therapies (range 2 - 13), all had relapsed after PIs and IMiDs, 90% had received an autologous transplant. They were refractory to carfilzomib (72%), pomalidomide (79%), or were quadruple refractory (48%). FISH cytogenetics revealed high-risk features in 62% of patients with del(17p) present in 48%, gain(1q21) (> 3 copies) in 28%, and t(4;14) in 14%.

Results: In the entire rMM cohort, we found a median number of 110 single nucleotide variants (SNVs, range 36-239) and 5 small insertions/deletions (indels, range 0-16) in exonic regions that might affect protein function.

Supervised analysis of mutational signatures detected nine different signatures in our rMM cohort. In contrast to previous reports from newly diagnosed MM, a major impact was seen of signature 3 (defect in DNA double-strand break repair by homologous recombination, '*BRCAness*'). Deficient DNA mismatch repair as well as the APOBEC signature contributed to a lesser extent. Presence of mutational signature 3 coincided with highly recurrent mutations in genes known to confer PARP inhibitor sensitivity with potential therapeutic implications for rMM.

Analysis of somatic SNVs and small indels confirmed the enrichment of mutations affecting NRAS/KRAS/BRAF (76%) and TP53 (31%) at a higher prevalence than commonly reported in newly diagnosed patients. In addition, a surprisingly high number of recurrently mutated genes could be found in this rMM cohort involving well-known pathways and cellular functional networks, such as signaling regulators, histone demethylases and methyltransferases, E3 ubiquitin-protein ligases and ubiquitin specific peptidases. Affected gene families of interest comprised proteasomal subunits (14%) and genes belonging to the spliceosomal complex SF3B (14%) or the NOTCH family (21%). Significantly mutated single genes also included EWSR1 (7%), KMT2C (7%), UBR5 (7%) and CUL4B (7%).

Analysis of structural variants confirmed the MM hallmarks t(11;14), t(4;14) as well as rearrangements of c-Myc, mainly involving FAM46C as a translocation partner, all found in similar prevalences compared to newly diagnosed patients. However, we detected a median of 110 structural rearrangements per patient. Remarkably, 31% of rMM patients had simultaneous combinations of immunoglobulin rearrangements potentially representing "multi-hit" rMM. Regarding fusion gene candidates, RB1 and TRAF3 were among the most frequent non-hallmark targets of structural rearrangements.

Recurrent Kataegis-like clusters were identified in our cohort, located in known targets of aberrant somatic hypermutation (aSHM) and co-localized with breakpoints of translocations, thus possibly indicating a functional relationship.

In the subset of rMM patients with available consecutive tumor samples, we could find evidence of both linear and branching clonal evolution. Mutations occurring only in the later sample of a tumor pair, obtained at emerging resistance to second generation IMiDs/Pis, affected amongst others KMT2D, UBR4 and NOTCH4.

Conclusions: Comprehensive genomic characterization of rMM samples from double- to quadruple-refractory patients reveals striking differences in the mutational and structural landscape compared to what has been reported in newly diagnosed patients. A higher than expected number of recurrently mutated genes mainly in pathways regulating protein homeostasis, gene transcription, DNA integrity and cellular signaling, a major impact of the *BRCAness* mutational signature, and complex structural aberrations strongly suggest multifactorial mechanisms of drug resistance in rMM and provide the rationale for novel treatment approaches.

Disclosures

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Author notes

*Asterisk with author names denotes non-ASH members.