3. RELAPSED/REFRACTORY MULTIPLE MYELOMA

HEPTA-REFRACTORY MULTIPLE MYELOMA: BIOLOGY, PROGNOSIS, AND TREATMENT

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Introduction. Despite major therapeutic advances, including T-cell–engaging therapies, most patients with multiple myeloma (MM) eventually relapse. An increasing number of patients are presenting with disease refractory to CD38-targeting antibodies, two immunomodulatory drugs (IMiDs), two proteasome inhibitors (PIs), as well as BCMA- and GPRC5D-directed immunotherapies. This disease state can be termed “hepta-refractory“ MM, representing a newly emerging end-stage entity. In this study, we characterize the clinical outcomes and underlying genomic landscape of hepta-refractory MM.

Methods. We analyzed a multicenter cohort of 44 patients with hepta-refractory MM. Whole genome sequencing (WGS) was performed in 17 patients, including 3 with sequential samples and 8 with extramedullary biopsies. WGS (depth 107x) was performed with purified CD138+ cells on NovaSeq instruments. Variants were called with Strelka2, Manta, GATK4 and HadoopCNV. Immunohistochemical (IHC) staining for BCMA was performed in 12 patients using an anti-BCMA antibody (E6D7B, Cell Signaling; 1:100).

Results. Median overall survival was 12.8 months, and median progression-free survival (PFS) across subsequent lines of therapy ranged from 2.7 to 3.2 months. WGS revealed frequent biallelic inactivation of tumor suppressor genes, most notably TP53 and CDKN2C (each 6/17, 35%). Genomic alterations associated with resistance to IMiDs, BCMA-, GPRC5D-, and CD38-directed therapies were identified in 71%, 41%, 35%, and 12% of patients, respectively. Notably, nearly one-third of patients (5/17) harbored biallelic alterations affecting both BCMA and GPRC5D. Sequential WGS available in three patients demonstrated branching evolutionary patterns with multiple distinct TNFRSF17 and GPRC5D variants within individual patients, suggesting ongoing mutational processes in persistent clones even after deep remissions. IHC confirmed loss of BCMA expression due to biallelic TNFRSF17 genomic events but also revealed loss of expression mediated by alternative mechanisms. The optimal therapeutic strategy in the hepta-refractory setting remains challenging. To address this, we evaluated PFS across subsequent treatment regimens. Patients received a median of 2 lines of therapy after entering the hepta-refractory state (range 0–8). Re-treatment with BCMA-directed CAR T-cell therapy (n=6) resulted in the longest median PFS (6.9 months). BCMA status was predictive of response: All four patients without TNFRSF17 alterations by WGS responded to cilta-cel (n=3) or ide-cel (n=1). In contrast, both patients harboring biallelic TNFRSF17 deletions were refractory. Re-treatment with bispecific antibodies (n=13) yielded a median PFS of 3.0 months. Regimens based on polychemotherapy or high-dose melphalan (n=17), combinations incorporating IMiDs, PIs, anti-CD38 antibodies, and/or monochemotherapy (n=10), belantamab mafodotin (n=11), mezigdomide (n=6), selinexor (n=9), and targeted therapies such as BRAF/MEK inhibitors or venetoclax (n=5) were associated with median PFS values of 4.4, 3.2, 2.5, 2.5, 1.5 months, and not reached, respectively.

Conclusions. Hepta-refractory MM, genomically defined by the accumulation of high-risk features and multidrug resistance, represents a newly emerging and highly challenging therapeutic setting. Within the limitations of the small sample size, re-treatment with CAR T-cell therapy appeared to be the most effective option in our cohort for patients with preserved TNFRSF17 by WGS.