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Large-Scale Analysis of Relapsed/Refractory Multiple Myeloma Genome Reveals Increased Prevalence of High-Risk Molecular Features and Oncogenic Drivers

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Introduction

Multiple myeloma (MM) is a heterogeneous disease defined by genetic lesions including translocations, chromosomal copy number aberrations (CNA), and mutations. Large-scale analyses of genomic data from newly-diagnosed patients (ndMM) have defined key oncogenic drivers beyond previously known primary events. In relapsed/refractory MM (rrMM), analyses have been completed on small numbers of patient samples for mutational profiles; however, a large-scale analysis of genomic and transcriptomic data has not been performed. In this initial analysis, we describe the rrMM genomic landscape including prevalence of key translocations, oncogenic/tumor suppressor mutational drivers, and chromosomal CNA.

Methods

We generated whole genome sequencing (WGS) and whole transcriptome expression (RNA-seq) from 485 rrMM patient samples derived from clinical trials: NCT01712789/CC-4047-MM-010 (N=236),

NCT02045017/CC-4047-MM-013 (N=17), NCT02773030/CC-220-MM-001 (N=45) and NCT01421524/ CC-122-ST-001MM2 (N=10). Somatic single nucleotide variants (SNVs) and indels were derived from WGS from 308 samples using GATK/MuTect2 and annotated using ANNOVAR. Clonal and subclonal CNA were identified using Sclust. Translocations were determined using Manta. Oncogenic/tumor suppressor drivers were identified using cDriver, which utilizes recurrence and functional consequence and cancer cell fraction (CCF) of each mutation.

Results

Key translocations included: t(11;14) [76/308 (25%)], t(8;14) [79/308 (25%)], t(4;14) [44/308 (14%)], t(14;16) [24/308 (8%)], t(6;14) *CCND3* [18/308 *(*6%)], t(14;20) [17/308 (5.5%)], and t(6;14) [*IRF4* 17/308 (5.5%)]. Hyperdiploidy was detected in 140/308 (46%) patients. Key chromosomal CNA included del14q 134/308 (44%), del13q 131/308 (43%), del8p 113/308 (37%), del17p 53/308 (17%), amplification of 1q (≥4 copies) 45/308 (15%), and del1q 31/308 (10%). Compared to samples from ndMM patients, we saw an increase of del17p (17% vs. 8%) and t(11;14) (25% vs. 15%) in rrMM. Further, out of the 53 del17p patients, 45 (85%) were high CCF (>0.55) versus 63/107 (59%) reported in ndMM (Thakurta et al, *Blood*. 2019) Double Hit patients (biallelic inactivation of TP53 or amplification of 1q on a background of ISS3) was detected in 12% patients which is significantly higher than ndMM (6%, $p < 0.05$) (Walker et al, *Leukemia*. 2018)

We identified a total of 107 driver genes (FDR<0.05). Of these, 23 were known cancer genes according to the COSMIC Cancer Gene Census (CGC) of which 19 were Tier1 such as *TP53*, *DNMT3A* and *SETD2*. Further, 19/107 driver genes were previously identified in ndMM from the Myeloma Genome Project including IRF4, *TRAF3*, NFKB2 and FGFR3. The top ten ranking driver genes in rrMM were *DIS3*, *FAM46C*, *IGLL5*, *KMT2B*, *TRAF3*, *SP140*, *MALRD1*, *TP53*, *L1TD1* and *PRKCD*. Among these, novel driver genes such as *IGLL5* (N=19, 6.2%; medianCCF=1; Immunoglobulin Lambda-Like Polypeptide 5) were also identified. We examined if loss-of-function (LOF) and gain-of-function (GOF) variants result in different sets of drivers, thus identifying putative tumor suppressor genes (TSG) and oncogenes (ONC) respectively. We identified a total of 72 and 43 ONCs and TSGs, respectively (FDR < 0.05). The top ten ranking ONCs included driver genes such as *UBR4* and *IRF4*. Among the top ten ranking TSGs were novel driver genes such as *TDG* and *SMARCA4* as well as known ndMM driver genes such as *UBR5* and *CDKN1B*. We confirmed that *FGFR3* driver mutations were associated with t(4;14) and *IRF4* were associated with t(11;14) ($p < 0.05$) in our rrMM population. Further analysis will be focused on association of significant mutations with CNA and translocation groups, impact on clinical outcomes in genetic subsets, delineating the effect of multiple lines of therapy on tumor clonality, genetic architecture of resistance patterns, and the role of oncogenic drivers.

Conclusions

We have established and analyzed the largest molecular rrMM dataset with associated clinical outcome data. These analyses are revealing the evolution of genetic drivers of resistance to therapy and will assist in identification of subsets of poor prognostic groups (eg, Double Hit) and new molecular subsets of rrMM where novel targeted therapies could be developed.

Disclosures

Towfic: *Celgene Corporation:* Employment, Equity Ownership. **Ansari-Pour:** *Celgene Corporation:* Consultancy. **Ortiz:** *Celgene Corporation:* Employment, Equity Ownership. **Gooding:** *Celgene Corporation:* Research Funding. **Rozelle:** *Celgene Corporation:* Other: Contractor for Celgene. **Zadorozhny:** *Celgene Corporation:* Other: Contractor for Celgene. **Mavrommatis:** *Celgene Corporation:* Employment, Equity Ownership. **Lata:** *Celgene Corporation:* Employment, Equity Ownership. **Stong:** *Celgene Corporation:* Employment, Equity Ownership. **Kamalakaran:** *Celgene Corporation:* Employment, Equity Ownership. **Tsai:** *Celgene Corporation:* Employment, Equity Ownership. **Flynt:** *Celgene Corporation:* Employment, Equity Ownership. **Thakurta:** *Celgene:* Employment, Equity Ownership.

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