GENOMIC AND CLINICAL CHARACTERIZATION OF THE ROLE OF MYD88 MUTATION STATUS IN WALDENSTROM’S MACROGLOBULINEMIA

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Background

Waldenström’s Macroglobulinemia (WM) is characterized by bone marrow (BM) involvement of IgM secreting lymphoplasmacytic lymphoma and somatic activating mutations in MYD88 and CXCR4 in 95% and 35-40% of patients, respectively. Deletions in chromosome 6q were also observed in half of MYD88 mutated (MYD88MUT) patients. Patients with wild-type MYD88 (MYD88WT) have an increased mortality risk compared to their MYD88MUT counterparts (Treon et al, BJH 2017) and demonstrate inferior response to the BTK inhibitor, brutinib (Treon et al, NEJM 2015). These findings point to fundamental genomic differences in tumor biology between MYD88 mutated and wild-type patients.

Aim

To improve the care and clinical management of all WM patients we sought to study the clinical characteristics and genetic lesions that differ in WM patients based on MYD88 mutation status.

Patients and Methods

We identified 46 MYD88WT and 262 MYD88MUT patients diagnosed during the same time period. Clinical characteristics were compared at time of diagnosis and patients were followed for disease transformation and overall survival. Bone marrow (BM) CD19+ WM cells were isolated from 18 MYD88WT patients following informed consent. DNA and RNA from these cells were submitted for next generation whole exome and RNA sequencing. Findings were compared to our existing whole genome and RNA sequencing data of 57 WM patients (Hunter et al, Blood 2014; 2016). A cohort of 9 CD19+CD27+ memory B-cells (MB), 9 CD19+CD27- peripheral blood B-cells, and 16 CD138+ plasma cells from healthy donors (HD) were also included.

Results

Whole exome sequencing analysis of the MYD88WT patients revealed somatic mutations in TBL1XR1 (28%), PTPN13 (22%), KMT2D (17%), CXCR4 (17%), MALT1 (11%), NFKB2 (11%), TP53 (11%) and with BCL10, NFKB1, NFKB2, NFKBIZ, NOTCH1, ATM, IGF1R, KDM6A, and KMT2D each observed once (6%). No deletions were observed in chromosome 6q in MYD88WT WM.

The median follow-up for all patients was 64.1 and 73.7 months for MYD88WT and MYD88MUT patients, respectively (p=N.S.). To date 11 (23.9%) and 15 (5.7%) deaths have been recorded among the MYD88WT and MYD88MUT patients, respectively (p=0.003). The estimated 10-year survival was 73% (95% CI 52-84%) for MYD88WT and 90% (95% CI 82-95%) for MYD88MUT patients (Log-rank p<0.001). Transformation to diffuse large B-cell lymphoma occurred in 7 (15.2%) of MYD88WT and 2 (0.76%) of MYD88MUT patients (p<0.0001), with an odds ratio of transformation of 23.3 (95% CI 4.2-233.8; p<0.001).

Conclusions

Our findings confirm the prognostic significance for MYD88 mutation status as an important determinant of overall survival and risk of disease transformation. While genomic drivers differ between the two populations, the overall transcriptional profile seems largely comparable with the overall MYD88MUT gene expression signature. Additional studies and comparisons to related lymphomas are planned.