

Title: Understanding clonal evolution through bilateral bone marrow biopsies in patients with Waldenstrom macroglobulinemia: a study in progress

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Background

Although patterns of clonal evolution in Waldenström macroglobulinemia (WM) are increasingly described, little is known about whether clonal dynamics differ in subregions of the same patient's bone marrow. In patients with other types of indolent non-Hodgkin lymphoma, heterogeneity has been observed in the subclonal composition of concurrent biopsies obtained from different lymph nodes. To evaluate site-specific sampling differences and clonal heterogeneity among marrow-resident lymphoplasmacytic (LPL) cells, we perform contralateral bone marrow biopsies in WM patients with previously untreated (PU) or relapsed/refractory (RR) disease. We aim to investigate the tumor-microenvironment and clonal trajectories using biopsies acquired at a single timepoint from different marrow sites.

Methods

We conduct bilateral bone marrow biopsies from contralateral iliac crests in patients with a known history of PU or R/R WM, enrolled on an observational clinical study (NCT00923507, compliant with the Declaration of Helsinki). These biopsies are currently evaluated side-by-side using flow cytometry, next-generation sequencing (NGS), and droplet digital PCR (ddPCR). We plan to employ whole exome sequencing and single cell sequencing in the future.

Results

To date, we have obtained biopsies from 6 patients, 4 with PU WM, and 2 with R/R disease approaching re-treatment. Median values among PU patients included: age 69 years, hemoglobin 12.8 g/dL, platelets 238 K/mcL, IgM 1551 mg/dL, and beta-2 microglobulin (B2M) 1.75 mg/L. Median values among R/R patients included: age 72.5 years, hemoglobin 11.5 g/dL, platelets 269 K/mcL, IgM 2762 mg/dL, and B2M 3.0 mg/L. Flow cytometry results were not significantly different between right and left aspirates. All samples demonstrated positivity for CD19 and CD22 (often dim). Despite no recent rituximab exposure, one R/R patient was negative for CD20 on both the right and left sides. CD38 and CD138 expression were also similar between right and left biopsies. The median percentage of LPL cells representing lymphocytes was 22.5% on the right and 25% on the left (median inpatient difference 1%). With regard to total cellularity, as assessed on an aspirate smear or touch

prep, the median inpatient difference in lymphocyte and plasma cell populations between sides was 3.75% and 0.75%, respectively.

NGS analysis is ongoing and was performed on one side in 3 patients. Only one patient demonstrated MYD88 L265P with a variant allele frequency (VAF) of 19%. Other mutations of clinical or pathologic significance among the 3 patients assessed included CHEK2 (VAF 44%), DDX41 (VAF 50%), CREBBP (VAF 15%), and ASXL1 (VAF 5%). NGS was performed on both sides in one R/R patient: LPL cells accounted for 2% of total cells on the right and NGS showed MYD88 (VAF 2.2%), BCOR (VAF 4.6%) and ATM (VAF 2.6%); LPL cells accounted for 3% of total cells on the left but NGS detected only the ATM mutation (VAF 3.1%).

Conclusions

Not surprisingly, we demonstrate similar findings in right and left bone marrow biopsies assessed for cellularity and subjected to flow cytometry, NGS and ddPCR. To investigate clonal evolution, we are now moving to exome sequencing of CD19+ selected LPL cells from the contralateral biopsies.

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