

Chemotherapy exposure is associated with genome wide somatic events and ultra-high risk double-hit *TP53* alterations in previously treated Waldenström macroglobulinemia.

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Purpose: BTK-inhibitors, proteasome-inhibitors and chemoimmunotherapy (CT) are mainstays of treatment in Waldenström macroglobulinemia (WM). However, the genomic impact of prior therapy on the malignant clone, and its impact on WM disease outcomes remain unknown. As such, we performed to our knowledge, the largest whole-exome (WES) and RNA sequencing effort in CD19-selected bone marrow lymphoplasmacytic cells from previously treated WM patients and evaluated the relationship between prior CT-exposure, genome-wide somatic damage, and *TP53*^{ALT} within the malignant clone, as well as their impact on overall survival (OS) and cancer-specific survival (CSS).

Methods: We performed whole exome (WES) on CD19+ bone marrow lymphoplasmacytic cells and matched germline tissue for 247 WM patients previously treated with and without CT. To ensure adequate tumor content, we restricted analysis to 164 patients with a *MYD88*^{L265P} variant allele frequency of >5% and performed tumor RNA sequencing in 137 patients.

Results: Prior CT-exposure was associated with more somatic variants (median 35.5 vs. 30; $p=0.012$), copy number alterations (CNAs; median 2 vs. 1; $p=0.036$), inclusive of *TP53* alterations (*TP53*^{ALT}) that included Chr17p deletions and *TP53* mutations (*TP53*^{MUT} $p=0.088$). Double-hit *TP53*^{ALT} were greater in those exposed to both alkylators and nucleoside analogues (18.8%) versus either alone (6.1%) or none (3.7%) ($p=0.069$). The number of CT-exposures was associated with a stepwise increase in the number of somatic variants and CNAs, with patients treated with ≥ 2 CT-containing lines of therapy having an increased number of somatic variants (median 43.5 vs. 31; $p=0.001$) and CNAs (median 3 vs. 1; $p=0.022$) compared to those with single or non-CT exposures. RNA sequencing confirmed *TP53*^{MUT} expression and lower gene expression in *TP53*^{ALT} samples ($p=0.01$). Double-hit *TP53*^{ALT} conferred inferior overall (adjHR 3.61; $p=0.004$) and cancer specific (adjHR 8.06; $p<0.001$) survival, while single-hit *TP53*^{ALT} resembled *TP53* wild-type outcomes. Chr8p deletions (adjHR 3.39; $p=0.018$) and Trisomy Chr18 (HR: 5.45; $p=0.002$) emerged as novel, adverse CSS markers that enriched among CT-exposed patients. By Boruta analysis, double-hit *TP53*^{ALT} ranked as the leading predictor of CSS. Many somatic variants and CNAs which could impact subsequent treatments were also enriched among CT-exposed patients, including mutations in *MS4A1* (11% vs. 0%; $p=0.003$), *TRAF2*, *UBR4*, and *MUC17* (7.3% vs. 0%; $p=0.028$),

and Chr7 trisomy (10.1% vs. 0%; $p=0.007$). Somatic variants in *SPI1* and *HMCN2* (26.3% vs. 1.4%; $p<0.001$), *IGFN1*, *MUC17*, and *NF1* (15.8% vs. 2.1%; $p=0.021$), and CNAs including Chr8p deletions (33.3% vs. 5%; $p<0.001$), Chr6q deletions (77.8% vs. 38.8%; $p=0.002$), Trisomy Chr4 (22.2% vs. 5.8%; $p=0.034$), Monosomy ChrX (22.2% vs. 5.8%; $p=0.035$), and Chr8q amplifications (16.7% vs. 3.6%; $p=0.049$) were enriched in *TP53*^{ALT} samples.

Conclusions: Prior CT-exposure is associated with enhanced tumor genome wide somatic events, including *TP53*^{ALT} as well as somatic variants and CNAs that can impact subsequent therapies. Double hit *TP53*^{ALT} emerged as the leading determinant of CSS in previously treated WM. Our findings provide a genomic basis for informing risks associated with upfront CT-exposure.

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