Abstract Title

Impact of testing for genetic markers on treatment selection and clinical outcomes among patients with chronic lymphocytic leukemia

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Background

Genetic markers like 17p deletion (del17p), *TP53* mutation (*TP53m*), and immunoglobulin heavy variable chain (IGHV) mutation are prognostic and predictive in chronic lymphocytic leukemia (CLL). Evidence is limited on how genetic testing influences front-line (1L) treatment (tx) choices and clinical outcomes in CLL.

Methods

This retrospective cohort study utilized the US electronic health record-derived de-identified Flatiron Health Research Database; 80% of the data were from community practices. Eligible patients (pts) included adults with CLL diagnosis who started 1L tx 01/01/2020-11/30/2024. Primary exposures included testing any time before 1L initiation. Tests included fluorescence in situ hybridization (FISH) for del17p, DNA sequencing for *TP53m*, and IGHV. Descriptive statistics were summarized by each test and by combining del17p and *TP53m*. The reference group was pts tested before 1L. Outcomes included real-world time to next tx or death (rwTTNT) and overall survival (rwOS) from 1L initiation. Landmark tx and survival probabilities were estimated using Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models, adjusting for age, sex, race/ethnicity, insurance, comorbidity, socioeconomic status, practice type, Rai stage, year of 1L initiation, and Eastern Cooperative Oncology Group performance status (ECOG PS). Stratified analysis was performed by 1L tx, including chemoimmunotherapy (CIT), ibrutinib (ibr), and National Comprehensive Cancer Network (NCCN) guideline-preferred novel therapies (NTs; acalabrutinib, zanubrutinib, venetoclax-based therapies). Interaction analysis between testing and 1L tx was assessed for each outcome. In exploratory analyses, proportion of pts with 1L tx by test result was summarized.

Results

Among 5481 pts, 81.9% had FISH, 26.5% had *TP53m* testing, and 51.9% were tested for IGHV before tx. Compared with pts not tested before tx, tested pts were younger (median age: 71 vs 75 [del17p/*TP53*], 70 vs 73 [IGHV]), more likely to be male (65 vs 61% [*TP53*], 64 vs 59% [IGHV]), non-Hispanic White (74 vs 72% [del17p/*TP53* and IGHV]), and had ECOG PS 0 (42 vs

33% [del17p/*TP53*], 44 vs 37% [IGHV]). Pts tested by FISH were more likely to be treated at community than academic practices (80 vs 75%), in contrast to pts with *TP53* tests (20 vs 23%). Tested pts were also more likely to have commercial insurance (17 vs 13% [del17p/*TP53*], 19 vs 14% [IGHV]), and less likely to have Medicare (63 vs 73% [del17p/*TP53*], 60 vs 68% [IGHV]), than untested pts.

Survival outcomes were worse in pts not tested before tx versus those tested. Median (95% CI) rwTTNT was 30.0 (26.5-36.4) mo for pts without del17p/*TP53* testing versus 41.7 (39.1-44.1) mo for pts tested (adjusted HR [aHR] 1.10; 95% CI 0.99-1.22). Pts without IGHV testing had lower median (95% CI) rwTTNT of 34.0 (31.1-37.8) mo versus 45.3 (41.6-49.3) mo for pts tested (aHR 1.12; 95% CI 1.03-1.22). Median rwOS was not reached (NR) for any group. After adjusting for demographic and clinical factors, pts without IGHV or del17p/*TP53* testing had 27% and 28% higher hazards of death than pts with IGHV testing (aHR 1.27; 95% CI 1.11-1.44) and del17p/*TP53* testing (aHR 1.28; 95% CI 1.10-1.49), respectively.

Pts not tested before tx were less likely to receive NCCN guideline–preferred NTs (del17p/*TP53*: 35 vs 48%; IGHV: 41 vs 50%) and more likely to receive CIT (del17p/*TP53*: 28 vs 22%; IGHV: 26 vs 20%). Pts with del17p/*TP53*m were less likely to receive 1L CIT (15 vs 23%) or 1L venetoclax+obinutuzumab (9 vs 14%) than pts without del17p/*TP53m*. Among all pts, median (95% CI) rwTTNT was longest for those who received NCCN guideline-preferred NTs (60.2 mo; 55.9-NR), followed by ibr (38.7 mo; 34.9-42.3) and CIT (9.9 mo; 8.4-12.1). Among pts who received 1L NTs, landmark probabilities of staying on current tx or not dying were numerically lower in pts without than with IGHV testing (12 mo: 82 vs 85%; 24 mo: 71 vs 76%) or del17p/*TP53* testing (81 vs 84%; 70 vs 74%). There was a statistically significant interaction between testing and 1L tx on rwTTNT ($P<.0001$) but not on rwOS ($P>.5$), indicating the effect of test status on rwTTNT.

Conclusion

This large, real-world study suggests pts who received pre-tx prognostic genetic marker testing for CLL were more likely to have better clinical outcomes, further emphasizing the need to test before 1L tx as a proxy for optimal care management in CLL.