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CLINICAL AND GENOMIC PATTERNS OF DISEASE PROGRESSION IN CLL PATIENTS TREATED WITH FIXED-DURATION VERSUS CONTINUOUS TARGETED THERAPIES

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Introduction: Bruton tyrosine kinase inhibitors (BTKi) and venetoclax (VEN) display their effects on distinct subpopulations of chronic lymphocytic leukemia (CLL) cells: BTKi primarily target proliferating nodal cells, which are killed after mobilization into the circulation, whereas VEN eliminates resting CLL cells. Such divergent mechanisms may influence both the pattern of relapse and the emergence of genomic evolution, including cytogenetic and TP53 changes, which remain poorly characterized.

Aims: To evaluate clinical and biological features of CLL progression according to treatment modality, comparing fixed--duration (FD) versus continuous targeted therapies.

Methods: We retrospectively analyzed 135 patients with progressive disease (PD) after target therapy with BTKi (continuous) or fixed duration VEN±anti-CD20 or BTKi+VEN (FD). Clinical presentation at PD was classified as nodal, peripheral blood (PB), or both. Cytogenetic and molecular evolution were assessed through paired analyses comparing pre- and post-treatment FISH, karyotype complexity, and TP53 status. Karyotype evolution was defined as the appearance of ≥1 novel cytogenetic abnormalitiy at progression, either as a new subclone or as an unrelated clone, in at least two metaphases compared with baseline.

Results: Median follow-up was 52 months. Median age was 67 years, 76% had unmutated IGHV, TP53 disruption was present in 30%, and a complex karyotype (CK) in 42% at baseline. Forty-eight (35%) patients were treatment-naïve (T-N) and 87 (65%) relapsed/refractory (RR). Overall, 22% of RR and 13% of TN patients received FD therapy, while 43% and 22% received continuous regimens, respectively.

At PD, the clinical pattern differed significantly by regimen (p 0.004): BTKi-treated patients more often progressed in PB (58%), while nodal PD was more frequent after FD therapy. Of note 40% of nodal relapses after BTKi corresponded to Richter transformation.

Paired cytogenetic analysis were available in 71 cases. Both among TN and RR patients, the number of cytogenetic abnormalities increased significantly under continuous therapy (TN p 0.009, RR p 0.005) but remained stable with FD regimens (TN p 0.336, RR p 0.481). Cytogenetic evolution occurred more frequently in those with baseline CK (p 0.027) and del(17p) (p 0.041).

Paired FISH and TP53 data were available in 86 and 72 cases, respectively; new FISH lesions were detected in 33% and TP53 mutations in 13%, without significant differences between FD and continuous regimens or between TN and RR settings.

Conclusions: Continuous therapy was associated with higher PB progression and greater cytogenetic evolution. Although limited by sample size and heterogeneous follow-up, these findings suggest that continuous exposure may impose stronger selective pressure on CLL clonal architecture.