



LYMPHOMAS

## THE IMPACT OF TP53 ABERRATION IN RICHTER TRANSFORMATION IN THE TARGET THERAPIES ERA: A REAL-LIFE CASE SERIES

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**Background.** Richter Transformation (RT), the evolution of chronic lymphocytic leukemia (CLL) into an aggressive lymphoma, remains a major therapeutic challenge, particularly in patients previously exposed to targeted agents. This study reports clinical and molecular features, treatment approaches, and outcomes of RT cases treated in our institution, with specific focus on TP53 aberrations.

**Methods:** A retrospective analysis was conducted on 12 consecutive patients, diagnosed with RT following CLL diagnosis (2012-2025), confirmed by histopathology and immunophenotyping. Data collected included demographics, prior CLL therapies, RT subtype, and molecular/genetic profile (IGHV status, del17p, TP53 mutation, complex karyotype). Response to RT therapy was evaluated per Lugano 2014 criteria; survival was estimated from RT diagnosis to death or last follow-up.

**Results:** Median age at RT was 66 years (range 56-86); 11 patients (91.7%) had received prior CLL therapy, including BTK inhibitors in seven cases. Adverse molecular features

were frequent: TP53 mutation in 5/12 (41.7%), del17p in 4/12 (33.3%), and complex karyotype in 3/12 (25%). RT histology was DLBCL-type in 8/12 (66.7%), Hodgkin-like in 3/12 (25%), and mixed in 1/12 (8.3%). First-line RT treatment included chemoimmunotherapy (n=6), targeted combinations (n=4), and cellular therapies (n=2). The overall response rate was 41.7% (5/12). Patients with TP53 aberrations showed markedly inferior outcomes, with median overall survival of 5.2 months compared to 13.8 months in wild-type cases. Among deceased or lost to follow-up patients (n=6), all belonged to the DLBCL subgroup with high-risk molecular features.

**Conclusions:** This real-life case series highlights the aggressive nature of RT in heavily pretreated CLL patients, where TP53 aberration remains the strongest adverse prognostic factor. Despite the introduction of targeted therapies, outcomes remain unsatisfactory, supporting the need for early identification of high-risk cases and integration of innovative, non-chemotherapeutic strategies.