Chronic Lymphocytic Leukemia: Update on Management and Therapeutic Algorithms

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The management of chronic lymphocytic leukemia (CLL) has undergone a fundamental paradigm shift over the last decade, moving rapidly from chemoimmunotherapy to targeted agents that interfere with B-cell receptor signaling or apoptosis regulation. This educational session provides an updated, evidence-based algorithm to guide diagnostic and therapeutic decisions in daily practice, integrating the latest clinical data and guidelines.

Current diagnosis relies on established immunophenotyping criteria, while risk stratification has evolved to prioritize genetic markers that dictate therapeutic choices. Specifically, the status of *TP53* (deletion 17p or mutation) and *IGHV* mutation are critical factors; *TP53* dysfunction precludes the use of chemoimmunotherapy, necessitating targeted approaches.

In the first-line setting, chemoimmunotherapy has been largely replaced by two main therapeutic strategies: continuous monotherapy with Bruton tyrosine kinase (BTK) inhibitors (e.g., acalabrutinib, zanubrutinib) or fixed-duration combination therapy with the BCL2 inhibitor venetoclax and obinutuzumab. Both strategies offer improved outcomes regardless of patient fitness, making comorbidities less central to decision-making than in the chemotherapy era.

For relapsed or refractory disease, optimal sequencing is crucial. Patients progressing on BTK inhibitors may switch to venetoclax-based regimens, while those relapsing after fixed-duration venetoclax can be successfully treated with BTK inhibitors. A major emerging challenge is "double-refractory" CLL—disease resistant to both covalent BTK inhibitors and BCL2 inhibitors. This session will discuss the management of these complex cases, including the use of non-covalent BTK inhibitors like pirtobrutinib, which retains efficacy in the presence of *C481S* resistance mutations. Finally, we will review the horizon of experimental modalities, including BTK degraders, bispecific antibodies, and CAR-T cell therapies, which aim to rewire the tumor microenvironment and overcome resistance.

Keywords: Chronic Lymphocytic Leukemia (CLL), Targeted Therapy, BTK Inhibitors, BCL2 Inhibitors, Double-Refractory CLL