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EFFECTIVENESS AND SAFETY OF INITIAL TARGETED TREATMENTS IN PATIENTS WITH UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Introduction: Chronic Lymphocytic Leukemia (CLL) is the most common adult leukemia in Western countries. Treatment choice depends on patient fitness, comorbidities, and molecular risk. First-line management has shifted from chemoimmunotherapy to targeted agents—Bruton's tyrosine kinase inhibitors (BTKis), BCL-2 inhibitors, and anti-CD20 monoclonal antibodies—which have improved progression-free survival (PFS) and, in some cases, overall survival (OS). Despite these advances, efficacy and safety differences require balancing disease control and toxicity. This systematic review and network meta-analysis synthesizes evidence to guide first-line therapy in treatment-naïve CLL. **Objectives:** Compare efficacy and safety of first-line targeted therapies for treatment-naïve CLL through systematic review and network meta-analysis, assessing PFS, OS, and adverse events across subgroups. **Material and methods:** A PubMed search identified systematic reviews, meta-analyses, and network meta-analyses from 2012–2025, combining terms for CLL (including the MeSH term "Leukemia, Lymphocytic, Chronic, B-Cell" and synonyms), first-line targeted therapies (e.g., ibrutinib, idelalisib, obinutuzumab), and outcomes (efficacy, safety, adverse events). Filters restricted results to these study types. Two reviewers independently screened all records, including studies on treatment-naïve CLL reporting quantitative efficacy and/or safety data. Forty-one articles met inclusion criteria for qualitative and quantitative synthesis. **Discussion and conclusion:** Robust evidence supports the comparative efficacy and safety of first-line targeted therapies for CLL across diverse subgroups. In elderly/unfit patients, ibrutinib significantly reduced all-cause mortality versus rituximab + chemotherapy (HR 0.39, 95% CI 0.21–0.72) and obinutuzumab + chlorambucil (HR 0.46, 95% CI 0.26–0.82), and lowered progression/death risk versus obinutuzumab + chlorambucil (HR 0.23, 95% CI 0.16–0.33). Acalabrutinib (± obinutuzumab) and ibrutinib showed comparable PFS (HR 1.02, 95% CI 0.72–1.45). Venetoclax + obinutuzumab demonstrated superior PFS over ibrutinib (HR 0.69, 95% CI 0.55– 0.85). Regarding safety, ibrutinib increased serious adverse events (HR 1.45, 95% CI 1.02–2.07), hypertension, atrial fibrillation (6.0%, 95% CI 3.5–9.4%), and hemorrhagic diathesis (6.5%, 95% CI 4.2–9.7%). Venetoclax was associated with higher odds of severe infections (OR 1.32, 95% CI 1.07–1.63), without significant differences in grade ≥ 3 infections or febrile neutropenia. Additional safety data addressed tumor lysis syndrome and infection incidence. Minimal residual disease (MRD) negativity correlated with improved PFS (HR 0.26, 95% CI 0.19–0.35) and OS (HR 0.33, 95% CI 0.21–0.53). Overall, targeted agents—especially BTK inhibitors and venetoclax-based regimens—offer substantial efficacy over chemoimmunotherapy, though toxicity profiles differ. BTKis and venetoclax-based regimens outperform chemoimmunotherapy in treatment-naïve CLL. Venetoclax + obinutuzumab and ibrutinib provide strong PFS benefits in select subgroups. Safety differs: ibrutinib raises atrial fibrillation, hypertension, and bleeding risk, while venetoclax increases severe infection risk. MRD negativity is linked to better long-term outcomes. Targeted agents should be preferred, with selection guided by comorbidities and toxicity profile.

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FIRST-LINE VENETOCLAX-BASED REGIMENS VERSUS CHEMOIMMUNOTHERAPY IN CHRONIC LYMPHOCYTIC LEUKEMIA: A REAL-WORLD ANALYSIS FROM THE BRAZILIAN CLL REGISTRY

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Introduction: Venetoclax, a selective BCL-2 inhibitor, has transformed the treatment of chronic lymphocytic leukemia (CLL). Randomized trials such as CLL14 and CLL13 have demonstrated the superiority of venetoclax-obinutuzumab (VenO) over chemoimmunotherapy in both elderly and younger, fit patients. To contextualize these findings in real-world settings, we conducted a retrospective analysis of first-line treatment data from the Brazilian CLL Registry. We used the treatment arms and comparator groups from the CLL14 and CLL13 trials as a framework for our analysis across different healthcare sectors in Brazil. **Objectives:** Assess the effectiveness and safety of venetoclax-based regimens as a first-line therapy for CLL compared to standard CIT using real-world data from the Brazilian CLL Registry. **Material and methods:** This retrospective multicenter study included patients with