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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

CLL treated in the frontline setting with either venetoclax-based regimens (with or without anti-CD20 antibodies) or standard CIT (e.g., FCR, BR, or chlorambucil-based combinations) between 2020 and 2024. Patients with <3 months of follow-up or incomplete data were excluded. **Results:** A total of 186 patients were analyzed. Median age was 64 years (range 37–92). Elevated β2-microglobulin was seen in 70% of the 97 tested. IGHV status was available for 111 patients (60%), with 71 (62%) unmutated. del(17p) and/or TP53 mutation was available in 126 patients (54%), with 5 (4%) positive. Venetoclax-based regimens were used in 47 patients (25%): 28 received VenO and 19 VenR. CIT was used in 75%: FCR in 81 (44%), R-chlorambucil in 34 (18%), G-chlorambucil in 8 (5%), and R-bendamustine in 15 (8%). After a median follow-up of 16 months (range 3-61), median time to next treatment (TTNT) was not reached in all groups except R-chlorambucil (16 months). TTNT at 2 years was 35% for anti-CD20 plus chlorambucil, 78% for R-bendamustine or FCR, 74% for VenR, and 73% for VenG. TTNT was slightly higher with venetoclax-based regimens (73%) versus CIT (64%), although not statistically significant (p = 0.08). **Discussion and conclusion:** In this real-world Brazilian cohort, venetoclax-based regimens showed favorable outcomes and manageable toxicity compared to CIT in the frontline setting, including among high-risk patients. These results support the expanding role of time-limited targeted regimens in clinical practice and stress the importance of access to novel fixed-duration therapies in resource-limited environments.

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FRONTLINE THERAPY PATTERNS AND OUTCOMES IN CHRONIC LYMPHOCYTIC LEUKEMIA: A REAL-WORLD, MULTICENTER ANALYSIS FROM LATIN AMERICA

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Introduction: Access to novel therapies for chronic lymphocytic leukemia (CLL) varies throughout Latin America. Many centers still rely on chemoimmunotherapy (CIT) or suboptimal regimens due to cost and availability issues. Real-world data comparing CIT and targeted therapies in this region are limited and urgently needed to inform clinical decisions and policy. **Objectives:** Compare efficacy CIT and targeted therapies in CLL patients in Latin America. **Material and methos:** We conducted a retrospective analysis of CLL patients who received first-line therapy in 11 Latin American countries (Argentina, Brazil, Chile, Colombia, Cuba, Guatemala, Mexico, Paraguay, Peru, Uruguay, and Venezuela) between 2010 and 2024. We grouped treatment regimens into six categories: a) venetoclax- based combinations with or without anti-CD20 antibodies; b) Bruton tyrosine kinase (BTK) inhibitors; c) standard CIT, including fludarabine, cyclophosphamide, and rituximab (FCR), or bendamustine and rituximab (BR); d) fludarabine and cyclophosphamide without rituximab (FC); e) rituximab or obinutuzumab combined with chlorambucil (R/G-chlorambucil); and f) suboptimal regimens, including chlorambucil monotherapy, R-CHOP, R-CVP, or any other nonstandard or unsupported combinations. Patients with less than 3 months of follow-up were excluded. We analyzed progression-free survival (PFS) to explore the impact of treatment backbone on outcomes. **Results:** Of the 2,175 patients who received treatment after 2010, the most common guideline-recommended regimens were FCR or BR (n = 528; 24.3%), BTK inhibitors (n = 198; 9.1%), chlorambucil plus anti-CD20 (n = 179; 8.2%), and venetoclax-based regimens (n = 97; 4.5%). However, 912 patients (41.9%) received suboptimal therapies, most commonly chlorambucil monotherapy (n = 561; 25.8%), FC (n = 261; 12.0%), and lymphoma-like regimens, such as CHOP or CVP ± anti-CD20 (n = 304; 14.0%). The median follow-up was 37 months (range, 3–167). Progression-free survival (PFS) at 3 years was 56%, with median PFS not reached. When stratified by treatment group, the 3-year PFS was 75% for venetoclax-based regimens, 71% for FCR/BR, 65% for BTK inhibitors, 59% for FC, 46% for R/G-chlorambucil, and 41% for suboptimal regimens. FISH testing for del(17p) and/or TP53 mutation was performed in 773 patients (35.5%), with abnormalities identified in 107 patients (13.8%). Of those, 68 patients (54%) received targeted therapies (venetoclax- or BTK-based), while 49 (46%) received CIT or other treatments. **Discussion and conclusion:** This real-world analysis reinforces the urgent need to abandon the use of non-CLL-directed regimens such as CHOP or CVP as well as chlorambucil monotherapy in the treatment of patients with CLL. Adding anti-CD20 antibodies significantly improved outcomes for FC-based regimens. Notably, FCR and targeted agents (venetoclax or BTK inhibitors) demonstrated similar efficacy in this diverse Latin American patient population. However, this observation should be interpreted with caution, given the retrospective nature of the data and potential differences in patient selection and baseline risk profiles. The continued use of suboptimal, non-guideline-concordant regimens demonstrates an urgent need to increase access to modern therapies and improve medical education to promote evidence-based CLL care in Latin America.

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