BTK and BCL-2 Inhibitors in the First-Line Treatment of Chronic Lymphocytic Leukemia in High-Risk Patients: Systematic Review and Network Meta-Analysis

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Inibidores BTK e BCL-2 no Tratamento de Primeira Linha da Leucemia Linfocítica Crônica em Pacientes de Alto Risco: Revisão Sistemática e Meta-Análise em Rede

Inhibidores de BTK Y BCL-2 en el Tratamiento de Primera Línea de la Leucemia Linfocítica Crónica en Pacientes de Alto Riesgo: Revisión Sistemática y un Metaanálisis en Red

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ABSTRACT

Introduction: Patients with high-risk chronic lymphocytic leukemia (CLL) have lower response rates, a more aggressive clinical course, and resistance to standard chemotherapy, representing a treatment challenge. Bruton's tyrosine kinase inhibitors (BTK – ibrutinib and acalabrutinib) and the BCL-2 inhibitor (venetoclax) can be used in these cases. **Objective:** To identify and evaluate studies on the efficacy and safety of the use of ibrutinib, acalabrutinib and venetoclax in first-line treatment in patients with high-risk CLL. **Method:** Systematic review of randomized clinical trials that evaluated adult patients with CLL, carriers of 17p deletion or TP53 mutation and without prior treatment. The PubMed, EMBASE, LILACS and Cochrane Library databases were searched, and the risk of bias was assessed using the Cochrane RoB 2 tool and the quality of evidence was assessed with GRADE. **Results:** In the network meta-analysis for progression-free survival (PFS) venetoclax + obinutuzumab (RR: 0.62; 95%CI 0.41-0.95; *p* value 0.027) and acalabrutinib + obinutuzumab (RR: 0. 74; 95% CI 0.55-0.99; *p* value 0.043) presented a lower risk of progression or death, with significance considered borderline. Ibrutinib + obinutuzumab (RR: 0.93; 95% CI 0.86-1.00; *p* value 0.054) did not show a significant difference in PFS for patients with high-risk CLL. **Conclusion:** First-line treatment with BTK inhibitors (ibrutinib and acalabrutinib) and the BCL-2 inhibitor (venetoclax) associated with anti-CD20 monoclonal agents – especially obinutuzumab – have been proposed as the standard for most patients with CLL. However, based on the results of this review with network meta-analysis, it was not possible to confirm this recommendation.

Key words: Leukemia, Lymphocytic, Chronic, B-Cell; Tyrosine Protein Kinase Inhibitors; Antineoplastic Protocols; Systematic Review; Network Meta-Analysis.

RESUMO

Introdução: Pacientes com leucemia linfocítica crônica (LLC) com alto risco têm menores taxas de resposta, curso clínico mais agressivo e resistência à quimioterapia padrão, representando um desafio para o tratamento. Os inibidores da tirosina quinase de Bruton (BTK – ibrutinibe e acalabrutinibe) e o inibidor BCL-2 (venetoclax) podem ser utilizados nesses casos. **Objetivo:** Identificar e avaliar a eficácia e a segurança do uso de ibrutinibe, acalabrutinibe e venetoclax no tratamento de primeira linha em pacientes com LLC de alto risco. **Método:** Revisão sistemática de ensaios clínicos randomizados que avaliaram pacientes adultos com LLC, portadores de deleção 17p ou mutação TP53 e sem tratamento prévio. Foram pesquisadas as bases PubMed, EMBASE, LILACS e *Cochrane Library*, e realizadas avaliação do risco de viés pela ferramenta RoB 2 da Cochrane e avaliação da qualidade da evidência pelo GRADE. **Resultados:** Na meta-análise em rede para sobrevida livre de progressão (SLP), venetoclax + obinutuzumabe (RR: 0,62; IC 95% 0,41-0,95; *p* = 0,027) e acalabrutinibe + obinutuzumabe (RR: 0,74; IC 95% 0,55-0,99; p = 0,043) apresentaram menor risco de progressão ou óbito, com significância considerada limítrofe. Ibrutinibe + obinutuzumabe (RR: 0,93; IC 95% 0,86-1,00; *p* = 0,054) não apresentou diferença significativa na SLP para pacientes com LLC de alto risco. **Conclusão:** O tratamento de primeira linha com inibidores de BTK (ibrutinibe e acalabrutinibe) e o inibidor BCL-2 (venetoclax), associados a agentes monoclonais anti-CD20 – especialmente o obinutuzumabe –, tem sido proposto como padrão para a maioria dos pacientes com LLC. Entretanto, pelos resultados desta revisão com meta-análise em rede, não foi possível confirmar essa recomendação.

Palavras-chave: Leucemia Linfocítica Crônica de Células B; Inibidores de Proteína Tirosina Quinase; Protocolos Antineoplásicos; Revisão Sistemática; Metanálise em Rede.

RESUMEN

Introducción: Los pacientes con leucemia linfocítica crónica (LLC) de alto riesgo tienen tasas de respuesta más bajas, un curso clínico más agresivo y resistencia a la quimioterapia estándar, lo que representa un desafío para el tratamiento. En estos casos se pueden utilizar los inhibidores de la tirosina quinasa de Bruton (BTK - ibrutinib y acalabrutinib) y el inhibidor de BCL-2 (venetoclax). **Objetivo:** Identificar y evaluar estudios sobre la eficacia y seguridad del uso de ibrutinib, acalabrutinib y venetoclax en el tratamiento de primera línea en pacientes con LLC de alto riesgo. **Método:** Revisión sistemática de ensayos clínicos aleatorios que evaluaron pacientes adultos con LLC, portadores de deleción 17p o mutación TP53 y sin tratamiento previo. Se realizaron búsquedas en las bases de datos PubMed, EMBASE, LILACS y Cochrane Library y se evaluó el riesgo de sesgo mediante la herramienta Cochrane RoB 2 y la calidad de la evidencia se evaluó mediante GRADE. **Resultados:** En el metaanálisis en red para la supervivencia libre de progresión (SSP) venetoclax + obinutuzumab (RR: 0,62; IC 95% 0,41-0,95; valor de p 0,027) y acalabrutinib + obinutuzumab (RR: 0,74; IC 95%). 0,55-0,99; valor de p 0,043) presentaron un menor riesgo de progresión o muerte, con una significación considerada límite. Ibrutinib + obinutuzumab (RR: 0,93; IC del 95 %: 0,86-1,00; valor de p 0,054) no mostró una diferencia significativa en la SSP para pacientes con LLC de alto riesgo. **Conclusión:** El tratamiento de primera línea con inhibidores de BTK (ibrutinib y acalabrutinib) y el inhibidor de BCL-2 (venetoclax), asociados con agentes monoclonales anti-CD20, especialmente obinutuzumab, se ha propuesto como estándar para la mayoría de los pacientes con LLC. Sin embargo, según los resultados de esta revisión con metaanálisis en red, no fue posible confirmar esta recomendación.

Palabras clave: Leucemia Linfocítica Crónica de Células B; Inhibidores de la Tirosina Proteína Quinasa; Protocolos Antineoplásicos; Revisión Sistemática; Metaanálisis en Red.

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INTRODUCTION

Accumulation of monomorphic round B lymphocytes in chronic lymphocytic leukemia (CLL) occurs in the blood, bone marrow, and lymphoid organs[1]. Its clinical course is very heterogeneous. For most patients, it is an asymptomatic disease at diagnosis and does not demand treatment, while others experience disease evolution, and treatment should begin soon after the diagnosis. Most common clinical findings include anemia, thrombocytopenia, palpable lymphadenopathy, splenomegaly, fatigue, fever, night sweats, unintentional weight loss, abdominal plenitude with early satiety and potential susceptibility to infections[2,3].

CLL diagnosis is most frequent in 65-74 years old Caucasian men. Between 2016 and 2020, the age-adjusted incidence rate in the United States was 4.6 per 100 thousand individuals per year. In the same period, the age-adjusted mortality rate was 1.1 per 100 thousand individuals. The 5-year relative survival rate (2013-2019) was 88%. According to the Surveillance, Epidemiology, and End Results (SEER) 18,740 new cases and 4,490 (0.7%) deaths were estimated for 2023[4].

Considering all leukemias combined, as there are no specific estimates for CLL in Brazil, the mortality rate adjusted for the world population in 2020 was 3.18 deaths per 100,000 individuals, corresponding to 6,738 deaths by leukemia. For the triennium 2023-2025, 11,540 new cases are estimated for each year, an estimated risk of 5.33 per 100,000 individuals[5].

Cytogenetic markers are evaluated for the treatment since in up to 80% of the patients with CLL, chromosomal alterations such as 13q deletion, 11q deletion, 17p deletion, and trisomy 12 are found. The most common, 13q deletion, occurs in 55-60% of the cases and is associated with a long benign course if detected isolate.

The 11q deletion is present in approximately 10% of the cases in the initial stage and 25% in the advanced stages of the disease, and there is no previous chemotherapy treatment. Usually, the progression is fast, with a dismal prognosis for the carriers of this alteration. The 17p deletion is found in 5-8% of chemotherapy-naive patients and frequently occurs in association with the inactivation of the suppressor gene of tumor TP53. The trisomy 12 is noticed in 10-20% of the patients and is associated with intermediate prognosis[6].

The 17p deletion and TP53 mutation are predictive markers and important prognostic factors for decision-taking to treat CLL because these profiles tend to present low response and more aggressive clinical course with progression-free survival (PFS) and overall survival (OS) reduction. In addition, these patients are standard chemotherapy resistant and have impaired responses to chemoimmunotherapy. For this reason, the investigation of genetic mutations is recommended for patients with CLL before beginning the treatment[3,7].

Studies indicate that for patients with a dismal prognosis, called high-risk patients in the present study, the use of Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib and acalabrutinib and inhibitor BCL-2 (venetoclax) can be delivered.

This systematic review and network meta-analysis (NMA) attempts to identify and evaluate studies addressing the efficacy and safety of ibrutinib, acalabrutinib, and venetoclax in first-line treatment of high-risk CLL patients.

METHOD

The screening process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[8] to elaborate this systematic review. The protocol (CRD42023417320) was earlier registered at the repository International Prospective Register of Systematic Reviews (PROSPERO)[9].

The research question was: are BTK inhibitors (ibrutinib e acalabrutinib) and BCL-2 (venetoclax) inhibitors more effective and safer than chemoimmunotherapy (chlorambucil + obinutuzumab) for first-line treatment of CLL in patients with 17P deletion or TP53 mutation?

The population of interest were adult patients diagnosed with CLL with 17P deletion or TP53 mutation and no previous treatment; the interventions investigated were BTK inhibitors (ibrutinib and acalabrutinib) and BCL-2 (venetoclax) inhibitor; the outcomes evaluated were efficacy (survival) and safety (adverse events – AE grades 3-4, discontinuation of the treatment and death); the study design was randomized clinical trial (RCT).

On April 24, 2023, searches at the electronic databases PubMed, EMBASE, LILACS, and Cochrane Library were performed and updated on August 2, 2023. Search strategies are available in complementary material. Descriptors indexed on Health Science Descriptors (DeCS, Medical Subject Headings (MeSH), and Embase Subject Headings (Emtree). Articles published in any language or year were searched with a filter for RCT. The search strategies process followed the Peer Review of Electronic Search Strategies (PRESS) recommendations[10].

Two investigators (RCRA and CLV) selected the articles independently, first by reading titles and abstracts and then by a full evaluation of texts utilizing the Rayyan[11] software. Discrepancies were discussed and resolved by consensus. Studies excluded are listed in complementary material.

These two investigators adopting the same methodology extracted the following data and entered it in a Microsoft Office Excel spreadsheet: author and year of publication, study design, inclusion and exclusion criteria, number of participants, interventions, age, sex, follow-up, and efficacy and safety outcomes.

The Cochrane Risk of Bias (RoB 2) tool version 2.0[12] was used to evaluate the risk of bias. This was also performed independently by the same two investigators, and discrepancies were solved by consensus. The quality of the evidence was assessed with the tool Grading of Recommendations Assessment, Development and Evaluation (GRADE)[13].

For the NMA, direct and indirect effects of treatments were combined in a single analysis utilizing a frequentist approach to estimate the relative effects comparing all treatments among themselves and generate probabilities given the subjacent assumptions that a specific treatment is better than the others[14,15].

NMA has advantages over pairwise meta-analysis, such as clarification of inconsistent outcomes from studies, including numerous standard comparators, and indirect effect calculation of missing direct comparisons between important treatments. Also, it can provide increased statistical power and cross-validation of the observed treatment effect of weak connections with reasonable network connectivity and sufficient sample sizes. However, its inappropriate use can cause misleading results and may emerge with low network connectivity and statistical power. Furthermore, indirect evidence is still observational and should be interpreted cautiously[14] whereas it is possible to compare multiple treatments at once with network meta-analysis (NMA). The analysis was performed with the Shiny web app[16].

The data were extracted and summarized using the random effect model and forest plots were generated visually to present the indirect comparisons among the studies. PFS was measured from the beginning of the treatment until disease progression or death by any cause at 48 months. The authors defined this cutoff to standardize the follow-up time of the studies. A particular treatment was deemed effective when the upper limit of the confidence interval of 95% (CI 95%) for relative risk (RR) did not exceed 1.0. Additionally, *p* scores were calculated to evaluate the classification of the treatments through a certainty that one treatment is better than the other by calculating the mean of all competing treatments[17,18].

RESULTS

From 2,360 identified articles, 506 duplicates were removed, and the remaining 1,854 publications were selected for abstracts and titles reading. Of these, 1,799 articles did not meet the eligibility criteria, and only 55 were fully read. Eventually, six studies related to three RCTs were selected. (Figure 1). The list of excluded articles, after the full reading is presented in complementary material.

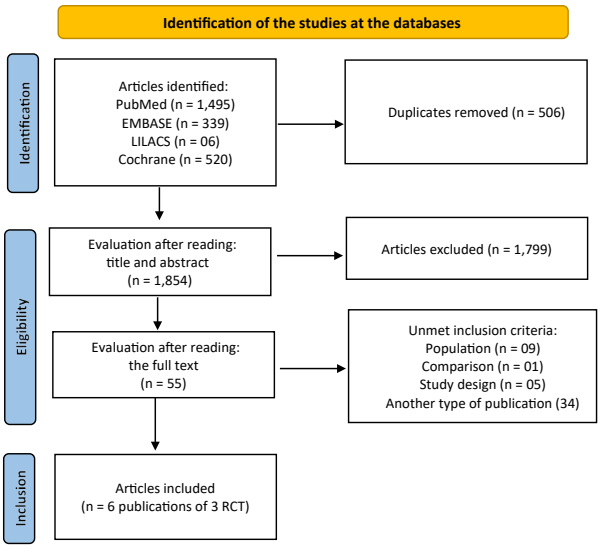

Figure 1. Flowchart of selection and eligibility

Source: Adapted from PRISMA 2020[8].

The characteristics of selected studies are portrayed in Chart 1, and in Chart 2, the PFS results for the three phase-III multicenter RCTs for high-risk patients with CLL.

The population of the CLL14[19] study consisted of 432 patients diagnosed with CLL and among these, 49 carried one or both of the mutations (17p and TP53). Participants' median age was 72 years with a range of 41-89 years. This RCT compared the use of venetoclax + obinutuzumab *vs* chlorambucil + obinutuzumab. The patients who received venetoclax + obinutuzumab presented a 52% decline in the risk of death or disease progression compared to patients who received chlorambucil + obinutuzumab (hazard ratio – HR: 0.48; CI 95% 0.24-0.94).

The total population of the ELEVATE-TN study[20] consisted of 535 patients diagnosed with CLL; among these, 50 had (17p) (p13.1) deletion or TP53 mutation, or both. The median age of this population was 70 years, ranging from 41 and 91 years. The RCT evaluated the utilization of acalabrutinib + obinutuzumab *vs* acalabrutinib in monotherapy *vs* chlorambucil + obinutuzumab. The risk of death or disease progression (HR: 0.17; CI 95% 0.07-0.42; $p < 0.0001$) declined by 83% for the patients who received acalabrutinib + obinutuzumab when compared with those who received chlorambucil + obinutuzumab.

Chart 1. Characterization of clinical trials selected to be included in the systematic review

Study	Country	Participants	Population	Interventions	Males (n; %)	Age (median in years)*	Follow-up*
CLL14 Study (NCT02242942)	Multicenter (21 countries)	432 patients	Patients of both sexes ≥18 years with active CLL not earlier treated requiring treatment according to iwCLL	Venetoclax + obinutuzumab Chlorambucil + obinutuzumab	Venetoclax + obinutuzumab: (146; 67.6%) Chlorambucil + obinutuzumab: (143; 66.2%)	Venetoclax + obinutuzumab: 72 (43–89) Chlorambucil + obinutuzumab: 71 (41–89)	72 months
ELEVATE-TN (NCT02475681)	Multicenter (18 countries)	535 patients	Patients of both sexes, ≥65 years or 18–65 years with comorbidities (cumulative scale of classification of geriatric-disease > 6, creatinine clearance 30–69 mL/min by Cockcroft-Gault), performance status ECOG 0, 1 or 2 and others	Acalabrutinibe + obinutuzumabe Acalabrutinibe Clorambucil + obinutuzumabe	Acalabrutinib + obinutuzumab: (111; 62%) Acalabrutinib: (111; 62%) Chlorambucil + obinutuzumab: (106; 59.9%)	Acalabrutinib + obinutuzumab: 70 (41–88) Acalabrutinib: 70 (44–87) Chlorambucil + obinutuzumab: 71 (46–91)	59 months
iLLUMINATE (NCT02264574)	Multicenter (16 countries)	229 patients	Patients of both sexes with CLL earlier untreated, requiring treatment per iwCLL criteria; age ≥ 65 years or < 65 years (score of cumulative disease > 6, creatinine clearance < 70 mL/min, ECOG performance status 0-2)	Ibrutinibe + obinutuzumabe Clorambucil + obinutuzumabe	Ibrutinib + obinutuzumab: (67; 59%) Chlorambucil + obinutuzumab: (79; 68%)	Ibrutinib + obinutuzumab: 70 (66–75) Chlorambucil + obinutuzumab: 72 (66–77)	48 months

Captions: CLL = chronic lymphocytic leukemia; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; and ECOG = Eastern Cooperative Oncology Group.

*Data of the most recent publications (longer follow-up) and for the whole population with CLL (regardless of deletion and mutation).

At last, the iLLUMINATE[21] study enrolled 229 patients; of these, 148 had high-risk genetic characteristics as del[17p], del[17p]/TP53 mutation, del[11q], or IGHV-unmutated or all. The mean age of the participants was 71 years, with interquartile range from 66 to 76 years. This RCT compared the use of ibrutinib + obinutuzumab *vs* chlorambucil + obinutuzumab. The risk of death or disease progression declined by 83% for the group of patients who received ibrutinib + obinutuzumab compared to the group who received chlorambucil + obinutuzumab (HR: 0.17; CI 95% 0.10-0.28).

The follow-up for the three studies ranged from 48 to 72 months. For the subpopulation of interest, high-risk patients, the three studies presented only data on PFS (Chart 2).

The NMA used PFS to analyze the clinical efficacy of the therapies considering chlorambucil + obinutuzumab as the comparator.

Treatments with venetoclax + obinutuzumab (RR: 0.62; CI 95% 0.41-0.95; p = 0.027) and acalabrutinib + obinutuzumab (RR: 0.74; CI 95% 0.55-0.99; p = 0.043) presented a low risk of progression or death with borderline significance. Ibrutinib + obinutuzumab (RR: 0.93; CI 95% 0.86-1;00; p = 0.054) did not present a significant difference in PFS for high-risk patients with CLL since the upper limit of the CI 95% reached the null value.

Venetoclax presented the highest p-score, with 90% odds of being better than all the other treatments, followed by acalabrutinib at 72%, and ibrutinib at 36%. Chlorambucil (reference treatment) presented a 2% odds of being better than all the other treatments.

The ranking likelihood for every possible treatment classification (rank chart) is presented in complementary material. The charts suggest that venetoclax has the highest odds of being the best treatment followed by acalabrutinib in second place, ibrutinib in third, and chlorambucil as the last treatment option (Figures 2 and 3).

The safety profile in the three studies comprehended grades 3 and 4 AE for all population, but no results were presented for the subpopulation of interests (complementary material). Deaths due to AE occurred in the three studies, and the highest frequency occurred in the group who received chlorambucil + obinutuzumab in trials CLL14[19] and ELEVATE-TN[20].

Chart 2. Progression-free survival for patients with high-risk CLL

Study	Medications utilized and the number of individuals	Estimate	Observations*
CLL14 Study (NCT02242942)	Venetoclax + obinutuzumab (n= 25)	HR: 0.48 (0.24-0.94) (Did not present p)	Patients with mutation del(17p) or TP53 or both presented higher PFS when treated with venetoclax + obinutuzumab in comparison with chlorambucil + obinutuzumab (PFS in 5 years: 40.6% vs 15.6%)
	Chlorambucil + obinutuzumab (n= 24)		
ELEVATE-TN (NCT02475681)	Acalabrutinib + obinutuzumab (n= 25)	HR: 0.17 (0.07-0.42) p < 0.0001	Patients in high-risk genetic subgroups including del(17) (p13.1) or TP53 mutated or both, the PFS median was not reached in the arms containing acalabrutinib vs 17.5 months for obinutuzumab+ chlorambucil (both p < 0.0001) In the arms of acalabrutinib + obinutuzumab and acalabrutinib in monotherapy, PFS rates in 48 months were 74.8% and 76.2% respectively for patients with del(17)(p13.1) and/or TP53 mutated
	Chlorambucil + obinutuzumab (n= 25)		
iLLUMINATE (NCT02264574)	Ibrutinib + obinutuzumab (n= 73)	HR: 0.17 (0.10-0.28) p < 0.0001	Patients with high-risk characteristics (del[17p], del[17p]/TP53 mutation, del[11q] or IGHV unmutated or all) presented higher PFS when treated with ibrutinib + obinutuzumab vs chlorambucil + obinutuzumab (PFS in 42 months: 70% vs 12%)
	Chlorambucil + obinutuzumab (n= 75)		

Captions: CLL = chronic lymphocytic leukemia; HR = hazard ratio; PFS = progression-free survival.

*Individuals with high-risk genetic subgroups found at each RCT: the CLL14 Study (17p deletion, TP53 mutation); the ELEVATE-TN study (17p deletion, TP53 mutation, 13q deletion); the iLLUMINATE study (17p deletion, TP53 mutation, 11q deletion, IGHV unmutated).

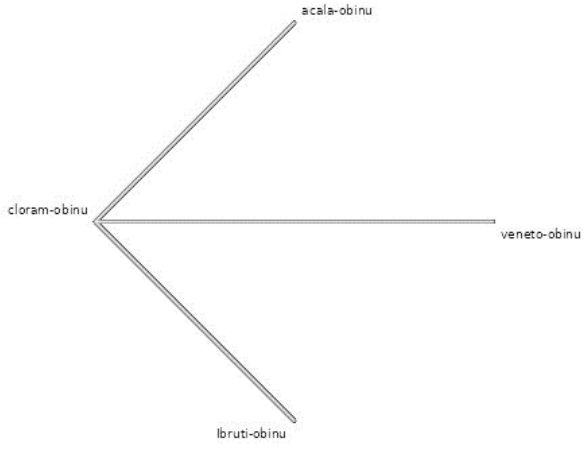

Figure 2. Graph of the treatments considered in network meta-analysis

Caption: cloram-obinu = chlorambucil + obinutuzumab; acala-obinu = Acalabrutinib + obinutuzumab; veneto-obinu = venetoclax + obinutuzumab; ibruti-obinu = ibrutinib + obinutuzumab.

The frequency of deaths in the iLLUMINATE[21] study was higher in the group receiving ibrutinib + obinutuzumab. Neutropenia was the most present grade 3 and 4 AE in the three RCTs and it was most frequent in the control group for the iLLUMINATE[21] (chlorambucil + obinutuzumab) and ELEVATE-TN[20] (chlorambucil + obinutuzumab) studies, and the most frequent in the intervention group (venetoclax + obinutuzumab) for CLL14[19] study. Thrombocytopenia, second primary malignancy, anemia, pneumonia, and infusion-related reactions were also reported in CLL14[19] and iLLUMINATE[21]. Thrombocytopenia and second primary malignancy were more frequent in the intervention group for both studies. Anemia and pneumonia were more frequent in the intervention group for CLL14[19] and in the control group for iLLUMINATE[21]. The infusion-related reactions had similar frequency in the control and intervention groups in CLL14[19]; for the iLLUMINATE[21] trial it was more frequent in the control group. Finally, infections and cardiac events occurred only in ELEVATE-TN[20], being more common in the group receiving acalabrutinib + obinutuzumab.

According to the global evaluation, the three RCTs were classified as low risk of bias. The analysis was performed for PFS and neutropenia outcomes. According to GRADE, the confidence in the evidence was high for both outcomes (complementary material).

It was impossible to evaluate the inconsistency and statistical heterogeneity in this current meta-analysis because only three studies were assessed. However, the

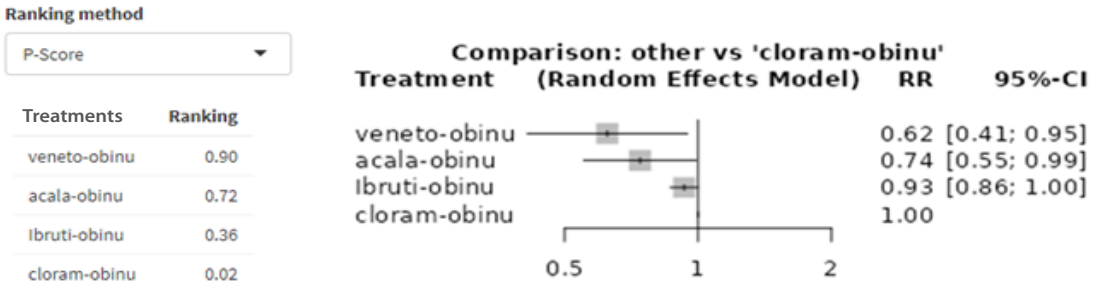

Figure 3. Forest plot of the relative risk and progression of the disease or death for each treatment compared with chlorambucil for participants with high-risk of CLL (individuals with 11q, 13q, 17p deletions TP53 mutation or IGHV unmutated or all)

Caption: RR = relative risk.

magnitude and directness of the effect estimates, through visual inspection with forest plot, were similar, and the CI of the three studies overlapped. The studies present clinical homogeneity among them because the age of the participants, time of follow-up, plan of treatment, form of administration, and doses of the comparator are similar.

DISCUSSION

The results of the three RCTs, individually, indicated higher PFS in patients with high-risk CLL treated with first-line BTK inhibitors (ibrutinib and acalabrutinib) and BCL-2 inhibitor (venetoclax) in association with obinutuzumab, compared with chemoimmunotherapy (chlorambucil + obinutuzumab).

However, the NMA favored the indication of venetoclax and acalabrutinib, both associated with obinutuzumab. Nevertheless, this benefit presented borderline CI and should be interpreted cautiously. No significant difference was found for the outcome efficacy of ibrutinib + obinutuzumab measured by PFS compared with chlorambucil + obinutuzumab.

Molica et al.[22] evaluated the data of these three RCTs utilizing fixed-effects NMA. The results for PFS comparing ibrutinib + obinutuzumab *vs* venetoclax + obinutuzumab revealed no significant difference given that the upper limit of CI 95% for RR exceeded 1.0 (RR: 1.52; CI 95% 0.82-2.81).

In counterpart, the authors noticed that the associations of acalabrutinib + obinutuzumab increased PFS in 57% compared with ibrutinib + obinutuzumab (RR: 0.43; CI 95%: 0.22-0.87) and in 71% compared to venetoclax + obinutuzumab (RR: 0.29; CI 95%: 0.15-0.56). In addition, it was observed that for PFS the results were similar for all participants with CLL, regardless of the presence or absence of high-risk characteristics (aberrations of TP53 and 11q deletion), except for individuals with IGHV unmutated. These presented higher PFS with acalabrutinib + obinutuzumab compared to venetoclax + obinutuzumab. No differences in the frequencies were noticed among the treatments evaluated for AE.

In the NMA performed by Sheng et al.[23] data of the patients with CLL who presented 17p deletion or TP53 mutation or both were evaluated and were treated with first-line acalabrutinib + obinutuzumab, ibrutinib + obinutuzumab, venetoclax + obinutuzumab or chlorambucil + obinutuzumab. Similar to the present study, no significant difference was found among the treatments of this subgroup of patients (acalabrutinib + obinutuzumab *vs* ibrutinib + obinutuzumab: HR:0.91; CI 95% 0.16-5.25 and acalabrutinib + obinutuzumab *vs* venetoclax + obinutuzumab: HR:0.32; CI 95% 0.07-1.45).

The three RCTs included in the NMA enrolled patients with CLL carriers of 17p deletion and TP53 mutation, but two of the studies (ELEVATE-TN and iLLUMINATE)[20,21] enrolled other high-risk genetic subgroups as 11q deletion, 13q deletion and IGVH unmutated, which is a limitation of the study. In addition, AE associated with using BTK and BCL-2 inhibitors for all the participants with CLL were presented, but specific results for high-risk genetic subgroups were not. Finally, identifying significant differences among treatments would require a larger sample of patients with high-risk CLL, which was not the case in the present study.

The authors decided not to reduce the level of evidence for inconsistency (heterogeneity) for both outcomes evaluated, given the evidence quality assessment with GRADE. For the outcome efficacy, the three studies were similar regarding the directness of evidence, indicating the benefit of PFS for high-risk patients who received acalabrutinib, ibrutinib, and venetoclax associated with obinutuzumab[24].

The positive aspect of this study is that it uses mature survival data with longer follow-up (48 months). In both NMA[22,23] which evaluated the use of BTK and BCL-2 inhibitors associated with an anti-CD[20]

monoclonal antibody, survival data utilized were with smaller follow-ups, 28.1 months for CLL14[19], 28.3 months for ELEVATE- TN[20] and 31.3 months for iLLUMINATE[21].

CONCLUSION

First-line treatment with BTK inhibitors (ibrutinib and acalabrutinib) and BCL-2 inhibitor (venetoclax), associated with anti-CD20 monoclonal antibodies – specially obinutuzumab – has been proposed currently as standard for most of the patients with CLL. However, it was not possible to confirm this recommendation based on the results of this systematic review with NMA.

Few comparative RCTs utilizing BTK inhibitors (ibrutinib and acalabrutinib) and BCL-2 inhibitor (venetoclax) for initial therapy of high-risk patients with CLL are available yet. This population may need more specific recommendations. Additional studies and the completion of those on going could improve and support the decision about which first-line treatment should be utilized for high-risk patients with CLL.

CONTRIBUTIONS

Rita de Cássia Ribeiro de Albuquerque and Cláudia Lima Vieira contributed to the study design, acquisition, analysis, and interpretation of the data and wording. Raphael Duarte Chança contributed to the acquisition, analysis, and interpretation of the data. Isabel Cristina de Almeida Santiago, Aline do Nascimento and Laura Augusta Barufaldi contributed to the study design and critical review. Bernardo Rangel Tura and Marcelo Goulart Correia contributed to the critical review. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

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