# Efficacy and Safety of Blinatumomab in the Treatment of Acute Lymphoblastic Leukemia: Systematic Literature Review

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*Eficácia e Segurança do Blinatumomabe no Tratamento da Leucemia Linfoblástica Aguda: Revisão Sistemática da Literatura*

Eficacia y Seguridad de Blinatumumab en el Tratamiento de la Leucemia Linfoblástica Aguda: Revisión Sistemática de la Literatura

**Renan do Nascimento Gonçalves[1]; Aline do Nascimento[2]; Raphael Duarte Chança[3]; Laura Augusta Barufaldi[4]**

***ABSTRACT***

**Introduction:** The conventional treatment options for acute lymphoblastic leukemia (ALL) are chemotherapy, blood transfusion, and bone marrow transplant. Blinatumomab is a novel form of treatment that uses bispecific antibody technology to fight ALL. **Objective:** Systematic literature review to evaluate the efficacy and safety of blinatumomab for the treatment of patients with ALL. **Method:** Studies on the topic were searched in the Cochrane, Embase, LILACS and PubMed databases. The Rayyan and EndNote tools were used for reference management. The selection, extraction and quality assessment stages were conducted in pairs and disagreements were resolved by consensus. The quality of the evidence obtained and the risk of bias were assessed using Cochrane's GRADE and RoB 2 tools. **Results:** Five scientific articles referred to three multicenter and international randomized clinical trials were included for analysis. The results related to overall survival, progression-free survival and adverse events were better in the blinatumomab group compared with conventional chemotherapy. The analysis of risk of bias raised some concerns for the progression-free survival and adverse events outcomes, mainly due to the blinding of participants, which also determined that the degree of certainty of the evidence was classified as moderate. **Conclusion:** Increased survival and lower rate of adverse events were observed for the blinatumomab group, suggesting that it is more effective and safer when compared to conventional chemotherapy for the treatment of ALL.

**Key words**: Leukemia, Biphenotypic, Acute; Antibodies, Bispecific; Technology Assessment, Biomedical; Review.

RESUMO

**Introdução:** As opções de tratamento convencionais para leucemia linfoblástica aguda (LLA) são a quimioterapia, a transfusão de sangue e o transplante de medula óssea. O blinatumomabe é uma forma mais recente de tratamento que utiliza a tecnologia de um anticorpo biespecífico para o combate da LLA. **Objetivo:** Avaliar a eficácia e a segurança do blinatumomabe para tratamento de pacientes com LLA por meio de uma revisão sistemática. **Método:** Estudos sobre a temática foram pesquisados nas bases de dados Cochrane, Embase, LILACS e PubMed. Foram utilizadas as ferramentas *Rayyan* e *EndNote* para o gerenciamento de referências. Etapas de seleção, extração e avaliação da qualidade foram conduzidas em dupla e as divergências foram resolvidas por consenso. A qualidade das evidências obtidas e o risco de viés foram avaliados com as ferramentas GRADE e RoB 2 da Cochrane. **Resultados:** Foram incluídos para análise cinco artigos científicos referentes a três ensaios clínicos randomizados multicêntricos e internacionais. Os resultados relacionados à sobrevida global, à sobrevida livre de progressão e a eventos adversos foram superiores no grupo blinatumomabe comparado com a quimioterapia convencional. A análise de risco de viés mostrou algumas preocupações para os desfechos sobrevida livre de progressão e eventos adversos, principalmente em razão do cegamento dos participantes, o que também determinou que o grau de certeza das evidências fosse classificado como moderado. **Conclusão:** Aumento da sobrevida e menor taxa de eventos adversos foram observados para o grupo blinatumomabe, sugerindo que o medicamento é mais eficaz e seguro quando comparado à quimioterapia convencional para o tratamento da LLA.

**Palavras-chave:** Leucemia Aguda Bifenotípica; Anticorpos Biespecíficos; Avaliação da Tecnologia Biomédica; Revisão.

RESUMEN

**Introducción:** Las opciones de tratamiento convencionales para la leucemia linfoblástica aguda (LLA) son la quimioterapia, la transfusión de sangre y el trasplante de médula ósea. Blinatumomab es una nueva forma de tratamiento que utiliza tecnología de anticuerpos biespecíficos para combatir la LLA. **Objetivo:** Evaluar la eficacia y seguridad de blinatumomab para el tratamiento de pacientes con LLA mediante una revisión sistemática. **Método:** Se buscaron estudios sobre el tema en las bases de datos Cochrane, Embase, LILACS y PubMed. Para la gestión de referencias se utilizaron las herramientas Rayyan y EndNote. Las etapas de selección, extracción y evaluación de la calidad se realizaron por parejas y los desacuerdos se resolvieron por consenso. La calidad de la evidencia obtenida y el riesgo de sesgo se evaluaron mediante las herramientas GRADE y RoB 2 de Cochrane. **Resultados:** Se incluyeron para el análisis cinco artículos científicos referentes a tres ensayos clínicos aleatorizados, multicéntricos e internacionales. Los resultados relacionados con la supervivencia general, la supervivencia libre de progresión y los eventos adversos fueron superiores en el grupo de blinatumomab en comparación con la quimioterapia convencional. El análisis de riesgo de sesgo mostró algunas preocupaciones sobre los resultados de supervivencia libre de progresión y eventos adversos, principalmente debido al cegamiento de los participantes, lo que también determinó que el grado de certeza de la evidencia se clasificara como moderado. **Conclusión:** Se observó una mayor supervivencia y una menor tasa de eventos adversos para el grupo de blinatumomab, lo que sugiere que blinatumomab es más eficaz y seguro en comparación con la quimioterapia convencional para el tratamiento de la LLA.

**Palabras clave:** Leucemia Bifenotípica Aguda, Anticuerpos Biespecíficos, Evaluación de Tecnologías Sanitarias; Revisión.

[1]Hospital Municipal de Juína. Juína (MT), Brasil. E-mail: renan.nascimento@farmacia.ufjf.br. Orcid iD: https://orcid.org/0000-0002-4184-0220
[2-4]Instituto Nacional de Câncer (INCA), Coordenação de Prevenção e Vigilância (Conprev), Divisão de Avaliação de Tecnologias em Saúde (DATS). Rio de Janeiro (RJ), Brasil. E-mails: aline.nascimento@inca.gov.br; raphael.chanca@inca.gov.br; laura.barufaldi@inca.gov.br. Orcid iD: https://orcid.org/0000-0001-8801-6012; Orcid iD: https://orcid.org/0000-0002-1023-245X; Orcid iD: https://orcid.org/0000-0001-9040-4399
**Corresponding author:** Laura Augusta Barufaldi. Rua Marquês de Pombal 125, 7º andar – Centro. Rio de Janeiro (RJ), Brasil. CEP 20230-240. E-mail: laura.barufaldi@inca.gov.br

## INTRODUCTION

Dysplasia, hyperplasia, and metaplasia are types of cellular growth resulting from controlled responses to the stimulation to which the tissues are being submitted. If the response is uncontrolled and does not reverse when stimulation stops, neoplasia occurs, encompassing hundreds of diseases that compromise the physiology of the human body. Among those affecting blood tissues, leukemias are one of the most known due to its high world incidence. Early detection and treatment are crucial for a positive prognosis of the patient affected by this disease[2].

Leukemias are clonal diseases of lymphocytes whose physiopathological mechanism is the appearance of hematopoietic or progenitor stem cells genetic alterations[3]. According to the National Cancer Institute (INCA)[4], there are more than 12 types of leukemia. The main types are acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic lymphoblastic leukemia (CLL) and acute lymphoblastic leukemia (ALL).

In acute leukemias, the maturation of hematopoietic cells occurs, and primitive cells do not develop, remaining as blasts. Immature cells follow a clonal proliferation process and accumulate in the blood tissue[5].

According to the International Agency for Research on Cancer (IARC)[6], leukemias are the 13$^{th}$ most incident cancer worldwide, with 437,033 new cases and 309,600 deaths, accounting for 3.5% for all places.

In Brazil, INCA[4] estimated for each year of the triennium 2023-2025, 6,250 new cases of all leukemias in men and 5,290 in women, totaling 11,540 cases, representing an estimated risk of 5.90 new cases for each 100 thousand men and 4.78 new cases for 100 thousand women.

ALL results from the clonal proliferation of abnormal precursor lymphoid cells in the bone marrow. A malignant transformation and proliferation of precursor progenitor cells occurs in the bone marrow, blood and extramedullary sites[7]. The hallmark of ALL is chromosomal abnormalities and genetic alterations involved in the differentiation and proliferation of precursor lymphoid cells[8], affecting persons of all ages, but its incidence is higher in 2 to 5 years old children, declining in adolescents and young adults, and increasing in 60 years-old and older adults[7].

Conventional treatments are chemotherapy, blood transfusion, bone marrow transplantation and target-therapies through inhibitors of tyrosine kinase (mesylate of imatinib, nilotinib and dasatinib), if the patient has the Philadelphia chromosome[5,9].

The cancer treatment scenario has been changing considerably in the last decades with fewer cytotoxic cellular therapies compared to classic chemotherapies[10]. In this context, blinatumomab, a bispecific antibody[11], was developed to treat patients with ALL. Currently, the Brazilian Health Regulatory Agency (Anvisa) registry indicates the treatment for relapsed B-cell lineage ALL and for adults with ALL with positive minimal residual disease (MRD) who reached full remission[12].

Blinatumomab mediates the formation of a cytolytic synapse between the T-cell and the tumor cell, releasing proteolytic enzymes to kill both proliferating and resting target cells. After the destruction of target T-cells, the same drug is available to identify other malignant B-cells, reinitiating the process of induction of cellular death[11]. Blinatumomab binding to T-cell activates signaling pathways inducing cellular proliferation and increases the circulating T-cells ability to bind to malignant B-cells[13].

Due to the potential benefits of this technology to treat patients with ALL, the objective of this systematic review is to evaluate the efficacy and safety of blinatumomab to treat children and adults with ALL.

## METHOD

Systematic literature review registered at the International Prospective Register of Systematic Reviews (PROSPERO)[16] number CRD42022327491, based on the updated version of the Methodological Guidelines for Systematic Review and Meta-Analysis of Randomized Clinical Trials of the Ministry of Health[14] following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15].

The study adhered to PICOS (Chart 1). The research question is: "Is blinatumomab more effective and safer in patients with acute lymphoblastic leukemia compared to standard chemotherapy treatment?"

Randomized clinical trials evaluating patients with ALL with blinatumomab as intervention and conventional chemotherapy as a comparison, which met the acronym PICOS, were included, conducted in any year and language, or addressing any population age. Other study designs, such as opinion articles and editorials, were excluded, in addition to publications which failed to present the required data, such as conference abstracts.

The following databases were searched: MEDLINE (via PubMed), Embase, LILACS and Cochrane using keywords and controlled descriptors in Portuguese and English, specific of each platform and considering the singularities of each database.

The results obtained were stored in personal files and exported to reference management tool EndNote[17] and web based Rayyan[18] to expedite the selection of the studies. Two independent investigators utilized an Excel spreadsheet to select the studies and extract the data.

Chart 1. PICOS

| Acronym | Definition |
|---|---|
| **P:** Population | Adult and pediatric patients with acute lymphoblastic leukemia |
| **I:** Intervention | Blinatumomab |
| **C:** Comparison | Standard chemotherapy |
| **O:** Outcome | Progression-free survival, overall survival, response rate and adverse events |
| **S:** Study design | Randomized clinical trial |

Discrepancies were discussed and resolved to reach a consensus.

The data extracted were: author, year of publication, acronym of the study, inclusion and exclusion criteria, number of participants, intervention, mean age, sex, time of follow-up, outcomes, measurement tools and results obtained.

The Cochrane Risk-of-Bias tool, version 2.0 (RoB 2)[19] was utilized to assess the risk of bias performed independently by two investigators and discrepancies resolved by consensus. The tool Grading of Recommendations Assessment, Development and Evaluation (GRADE)[20] was applied to assess the certainty of the evidence.

## RESULTS

After searching the databases, 274 studies were identified and evaluated for eligibility. Of these, only five met the inclusion criteria and were included[21-25]. Figure 1 describes the selection process of the present review.

Five scientific articles related to three multicenter, international randomized clinical trials, one published in 2017, two in 2018 and two in 2021 have been selected.

Chart 2 portrays the summary of the studies.

In the study of Brown et al.[21], 208 patients aged 1-30 years with the first ALL relapse were randomized to receive 4-week re-induction chemotherapy followed by two cycles of blinatumomab (n = 105) or 4-week re-induction chemotherapy followed by two cycles of multiagent chemotherapy (n = 103). Kantarjian et al.[22] randomized 405 adolescents and adults with ALL to receive blinatumomab or conventional chemotherapy. The outcomes analyzed in both studies were overall survival (OS), progression-free survival (PFS) and adverse events (AE).

Children and adolescents from 1 to 17 years of age from 47 oncology sites in 13 countries participated in the clinical trial of Locatelli et al.[23]. A total of 105 individuals were randomized to receive blinatumomab or standard chemotherapy. The primary outcome was progression-free survival (relapse, death, second malignancy or failure to reach complete remission). Another important outcome was OS. Minimal residual disease remission and incidence of AE were assessed as well.

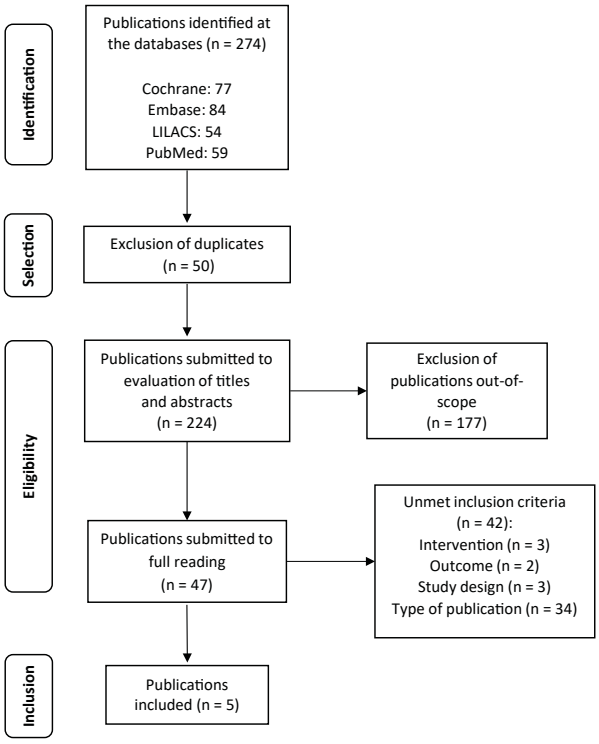


**Figure 1.** Flowchart PRISMA: identification, selection and eligibility of the studies.

Adapted from PRISMA 2020[16].

In addition to the clinical trials referenced earlier, the systematic review included the studies of Stein et al.[24] and Topp et al.[25]; both referenced the study TOWER of Kantarijian et al.[22] with patients randomized to receive standard chemotherapy or blinatumomab. As described in Chart 2, the results of these studies indicated advantages of blinatumomab *vs* chemotherapy.

The risk of bias for the outcome OS was classified as low in the studies of Locatelli et al.[23] and Kantarijian et al.[22], and some concerns in the study of Brown et al.[21]. For the outcome PFS, the study of Kantarijian et al.[22] was classified as low risk of bias while the studies of Brown et

Chart 2. Main findings of the studies selected

| Author/year | Country | Population | Participants | Outcomes and Main Findings |
|---|---|---|---|---|
| **Brown et al., 2021**[21] | USA, Canada, Australia and New Zealand | Children, young adults and adults with first relapse of B-cells ALL | 208 | **PFS:** 54.4% of blinatumomab *vs.* 39% of CT (HR 0.70 [CI 95%, 0.47-1.03]) had no progression of the disease, with no statistically significant difference; **OS:** 71.3% for blinatumomab *vs.* 58.4% for CT (HR 0.62 [CI 95%, 0.39-0.98]), in two years, OS was higher in blinatumomab; **AE:** Cycle 1: 76% in blinatumomab and 91% in CT; Cycle 2: 56% in blinatumomab and 84% in CT. AE were more frequent in patients receiving conventional CT |
| **Kantarijian et al., 2017**[22] **Study TOWER** | 101 sites in 21 countries | Adolescents and adults previously treated for B-cells ALL | 405 | **PFS:** 31% of blinatumomab *vs.* 12% of conventional CT (HR 0.55 [CI95%, 0.43-0.71]) had no disease progression in six months. **OS:** Median of 7.7 months for blinatumomab; for CT, four months with no progression of the disease (HR 0.71; CI 95%, 0.55 to 0.93; $p = 0.01$); **AE:** grade 3 AE or higher were reported in 87% of the patients of blinatumomab and in 92% of CT |
| **Locatelli et al., 2021**[23] | 47 sites in 13 countries | Children and adolescents with high-risk of relapse of B-cells ALL | 105 | **PFS:** Events-free survival risk rate was 0.33 (CI 95%, 0.18-0.61) in favor of blinatumomab (Cox proportional hazards model). By Kaplan-Meier, PFS was 66.2% (CI 95%) for blinatumomab and 27.1% (CI 95%) for QT in 24 months. **OS:** HR was 0.43 (CI 95%, ranging from 0.18-1.01); **AE:** 24.1% for blinatumomab *vs.* 43.1% for CT and the incidence of AE higher or equal to grade 3 was 57.4% for blinatumomab and 82.4% for conventional CT |
| **Stein et al., 2018**[24] **Study TOWER** | 101 sites in 21 countries | Adults and older adults from 18 to 80 years | 376 | **AE:** higher in the arm blinatumomab vs CT for CRL (16% *vs.* 0%), neurologic events (61% *vs.* 50%) and tumor lysis syndrome (4% *vs.* 1 %), but lower for cytopenia (60% *vs.* 72%). Gastrointestinal disorders: 56% for blinatumomab *vs.* 80% for CT. Grade-3: 87% for blinatumomab *vs.* 92% for CT; Infections: 34% for blinatumomab *vs.* 52% for CT; CRL: 5% in blinatumomab, no occurrence (0%) for CT |
| **Topp et al., 2018**[25] **Study TOWER** | 101 sites in 21 countries | Adults | 247 | **QoL:** Patients who received blinatumomab (n = 152) reported better post-treatment HRQoL for all subscales of EORTC QLQ-C30, based on descriptive mean change from baseline than did those receiving chemotherapy (n = 95). The hazard ratios to TTD of 10 points from a baseline of HRQoL or death ranged from 0.42 to 0.81 in favor of blinatumomab, with upper bounds of 95%CI < 1.0 across all measures, except insomnia, functioning and financial difficulties |

**Captions:** ALL = acute lymphoblastic leukemia; PFS = progression-free survival; OS = overall survival; AE = adverse events; CT = chemotherapy; CI = confidence interval; HR = hazard ratio; CRL = cytokines release syndrome; TTD = time to deterioration; QoL = quality of life; HRQoL = health-related quality of life; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

al.[21] and Locatelli et al.[23] presented some concerns. In the study of Kantarijian[22], the outcome AE was considered to have a low risk of bias and for the other studies, there were just some concerns. The outcome quality-of-life (QoL) was evaluated only by Topp et al.[25], with some concerns about randomization and blinding.

Figure 2 shows the result obtained after the risk of bias assessment utilizing Cochrane RoB 2 tool.

## DISCUSSION

The main outcomes of the five articles associated with three phase-III randomized clinical trials were presented in this review. As anticipated, few publications about blinatumomab were found because it is a relatively new technology, only in 2014 the drug was approved within the scope of ALL management options[26].

The efficacy and safety of blinatumomab to treat ALL is based on the main outcomes usually highlighted for hematologic tumors such as OS, PFS and AE, upon reviewing the references of the systematic review. Drug safety is relative and many factors are involved in this concept, therefore, the post-analysis conclusions consider the therapeutic margin of a drug, the usual effective dose and the dose producing severe side effects or life-threatening[27]. The studies have been well classified in the scale of risk of bias by the authors, but the heterogeneity, mainly in relation to the population investigated and some particularities related to the conclusion of the studies should not be neglected. Due to the heterogeneity, a meta-analysis was not performed since the population differs among the studies, mainly in age range.

The results obtained by Brown et al.[21] favor blinatumomab for the population from 1 to 30 years with initial relapsed-refractory ALL. The primary outcome was progression-free disease and the secondary, OS, both since randomization. AE were also evaluated and the findings were advantageous to blinatumomab.

The randomized clinical trial by Kantarijian et al.[22], TOWER, supported Anvisa's approval of blinatumomab to treat B-cells relapsed ALL, which corroborated the findings of Brown et al.[21] strengthening the hypothesis

| Studies | Outcomes | D1 | D2 | D3 | D4 | D5 | General |
|---|---|---|---|---|---|---|---|
| Brown et al.[21] | Overall Survival | - | + | + | + | + | ! |
| | Progression-free survival | - | + | + | + | + | ! |
| | Adverse Events | - | + | + | + | + | ! |
| Kantarijian et al.[22] | Overall Survival | + | + | + | + | + | + |
| | Progression-free survival | + | + | + | + | + | + |
| | Adverse Events | + | + | + | + | + | + |
| Locatelli et al.[23] | Overall Survival | + | + | + | + | + | + |
| | Progression-free survival | + | ! | + | ! | ! | ! |
| | Adverse Events | + | ! | ! | ! | ! | ! |
| Topp et al.[24] | Quality-of-life | ! | ! | + | + | + | ! |
| Stein et al.[25] | Adverse events | + | ! | + | ! | + | ! |

**Figure 2.** General risk of bias classification of the studies by Cochrane Risk of Bias, version 2.0

**Captions:**

| | | | |
|---|---|---|---|
| + | Low risk | D2 | Bias due to deviations from intended interventions |
| ! | Some concerns | D3 | Bias due to missing outcome data |
| - | High risk | D4 | Bias in measurement of the outcome |
| D1 | Bias arising from randomization process | D5 | Bias in selection of the reported result |

**Chart 3.** Evaluation of the certainty of the evidence for outcomes of overall survival, progression-free survival, adverse events, and quality-of-life

| Quality Assessment | | | | | | | Impact | Quality of the evidence | Importance |
|---|---|---|---|---|---|---|---|---|---|
| **Studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirect evidence** | **Inaccuracy** | **Other considerations** | | | |
| Overall survival (follow-up: variation of 11.7-34.8 months – evaluated with HR) | | | | | | | | | |
| 3[21-23] | Randomized clinical trials | Non seriousa | Non serious[b] | Non serious | Non serious[c] | None | Brown et al.[21]: Outcome evaluated for n = 135, resulting in OS of 71.3% for blinatumomab and 58.4% for standard CT. Time defined: 24 months. HR = 0.62. CI 95% = 0.39 – 0.98 | ⊕⊕⊕◯ Moderate | Critical |
| | | | | | | | Kantarijian et al.[22]: Outcome evaluated for 100 patients, resulting in OS of 31% for blinatumomab and 12% for standard CT. Time defined: 6 months. HR = 0.71. CI 95% = 0.18-1.01 | ⊕⊕⊕◯ Moderate | |
| | | | | | | | Locatelli et al.[23]: Outcome evaluated for 24 patients, resulting in OS of 85.2% for blinatumomab and 70.4% for standard CT. Time defined: 19.5 months. HR = 0.43. CI 95% = 0.18-1.01 | ⊕⊕⊕◯ Moderate | Critical |
| Progression-free survival (follow-up: from 7.8 to 24 months; evaluated since randomization through treatment failure) | | | | | | | | | |
| 3[21-23] | Randomized clinical trial | Non serious[e] | Non serious[f] | Non serious[c] | Non serious[g] | None | Brown et al.[21]: Progression-free survival in two years was 54.4% for blinatumomab vs. 39.0% for CT (risk of progression of the disease or mortality = 0.70 [CI 95%, 0.47-1.03]) | ⊕⊕⊕◯ Moderate | Critical |
| | | | | | | | Kantarijian et all.[22]: 6-month estimates were 31% for blinatumomab and 12% for CT, HR of 55% for relapse after reaching complete remission with complete, partial or incomplete treatment, hematological recovery or death (95% CI, 0.43 to 0.71; p < 0.001) | ⊕⊕⊕◯ Moderate | Critical |
| | | | | | | | Locatelli et al.[23]: Mean follow-up time for progression-free survival was 22.4 months. Events-free survival was significantly prolonged for the group of blinatumomab vs CT | ⊕⊕⊕◯ Moderate | Critical |

to be continued

**Chart 3.** continuation

| Quality Assessment | | | | | | | Impact | Quality of the evidence | Importance |
|---|---|---|---|---|---|---|---|---|---|
| **Studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirect evidence** | **Inaccuracy** | **Other considerations** | | | |
| Adverse events (follow-up: from 11.7 to 34.8 months; evaluated with grade 3 or higher adverse reactions) | | | | | | | | | |
| 4[21-25] | Randomized clinical trials | Non serious[e] | Non serious[h] | Non serious[c] | Non serious[i] | None | In unblinded patients (open-label treatment) in the studies of Locatelli et al.[23], Stein et al[24] and Kantarijan et al.[22], the groups knew what they would receive. For Brown[21], only the investigators knew the allocation of the groups | ⊕⊕⊕◯ Moderate | Critical |
| Quality of life (follow-up: from one to 12 months; evaluation with self-applicable questionnaire (EORTC QLQ-C30)) | | | | | | | | | |
| 1[25] | Randomized clinical trials | Non serious[j] | Non serious[i] | Non serious[c] | Non serious | None | In unblinded patients (open-label treatment) in the studies of Locatelli et al.[23], Stein et al[24] e Kantarijan et al.[22], the groups were aware of what they will receive. For Brown[21], only the investigators knew the allocation of the groups | ⊕⊕⊕◯ Moderate | Critical |

[a]There is no information about the process of randomization and blinding; however, blinding is of little importance for the outcome evaluated.
[b]The quality assessment of quality-of-life in an open study can be influenced by the knowledge of the treatment group.
[c]There is no inconsistency in the selection, since "P" of PICOS includes adult and pediatric patients with acute lymphoblastic leukemia.
[d]Large confidence intervals. Study by Locatelli et al. 2021 with non-significant result ($p = 1$).
[e] Non-randomness in the allocation of participants may have favored the participants receiving blinatumomab. In this case, unblinding can impact the result.
[f]The effect of outcome overall survival was evaluated in the same direction for both studies, all favoring blinatumomab.
[g]Large confidence intervals.
[h]Although the results for adverse events have been presented differently, no conflict among the studies' results were found, all of them with better results of AE for the groups receiving blinatumomab.
[i]Distinct forms to describe adverse events.
[j]There is no information about the process of randomization and blinding of the participants.
[k]No inconsistency in the description of adverse events.

**Captions:** OS = overall survival; CT = chemotherapy; CI = confidence interval; HR = hazard ratio; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

that blinatumomab has improved benefits over traditional chemotherapy adopted for ALL.

As already noticed in the literature, blinatumomab was better than the conventional treatment also in the clinical trial of Locatelli et al.[23], since the patients of the intervention group had better responses for the outcomes investigated.

The studies of Steint al.[24] and Topp et al.[25] evaluated the efficacy and safety of blinatumomab whose main focus were the outcomes QoL and AE. Although the findings of Stein et al. [24] have indicated high numbers of AE for the arm blinatumomab, the long-term results support even more the role of blinatumomab as an effective treatment option and well-tolerated for patients with ALL, considering that AE declined as the treatment progressed and their types were consistent with reports by other authors for blinatumomab.

While comparing the two technologies, it is anticipated that the randomization occurs at random and that this whole process is clearly described in the methodology and publication of the results, which occurred in the study of Kantarjian et al.[22], but not in the others. Therefore, for all the outcomes analyzed, a high risk of bias was considered for the study of Brown et al.[21]. Notwithstanding, baseline characteristics of the study patients indicate a balance of physiopathological characteristics of the sample investigated and the two reviewers reached a consensus that the final classification of risk of bias for this study was only "some concerns".

Reviewing the study of Topp[25], especially the first domain which assesses biases of the randomization process, some concerns were presented, since these authors evaluated the QoL of patients treated with standard chemotherapy or blinatumomab and unblinding can impact this outcome.

The study of Locatelli et al.[23] failed to mention the blinding of the study sample, therefore, it was considered that blinding did not occur and the overall risk of bias was classified as some concerns due to the outcomes of PFS and AE. For the outcome OS, the risk of bias was classified as low because the blinding or not of the study participants or caretakers is unable to impact the outcome of death.

The absence of blinding information in Locatelli et al.[23] significantly impacts bias, particularly in the third domain, which assesses biases in missing data. This omission raises concerns about the reliability of the study's findings.

The study conducted by Stein et al.[24], which focused on comparing adverse events (AE) of blinatumomab with conventional chemotherapy, was classified as having concerns for risk of bias. The primary reason for this classification was the blinding of the participants in relation to the evaluated outcome. The open study design introduced the potential for bias, as adverse reactions associated with the gastrointestinal tract and neurologic events, such as insomnia, could be influenced by the unblinding of both study groups.

According to the results obtained with the tool Rob 2 upon the independent review of the two investigators and consensus, the first domain evaluated revealed a low risk of bias for most of the results; this did not happen in the study of Brown et al.[21], which, in the explanation of the sequence of allocation of the study participants, defined the intervention and control groups based in the characteristics of risk of each patient, as the investigators were aware of which group would receive each treatment and may have biased the randomization for the individuals with low likelihood of presenting the outcomes analyzed to receive the intervention with blinatumomab.

Evaluating the certainty of the evidence through the GRADE tool is considered a critical process in the conduction of a clinical trial and, overall, all the studies accepted the use of blinatumomab when compared to conventional chemotherapy with moderate certainty of the evidence due to factors related mainly to the process of randomization and blinding of the study participants.

Similar to what was mentioned for the risk of bias assessment with RoB 2, the process of randomization or blinding would barely have, if any, influence on the outcomes evaluated by the authors. In addition, the baseline characteristics of the participants presented in the studies are not discrepant.

On March 2022, the plenary of the National Committee of Incorporation of Technologies into the National Health System (Conitec) in its 106th ordinary meeting published a report[28] with preliminary favorable recommendation to adopting blinatumomab to treat B-cells ALL from the first high-risk medullary relapse in children.

The main considerations of the plenary's attendees indicated that the bispecific antibody treatment is associated with improved OS and PFS benefits and a lower number of AEs when compared to conventional chemotherapy[28].

In a public hearing, nearly 99% of agreement with the preliminary recommendation of Conitec was reached and the user's justifications corroborate the explanations presented in the plenary. Therefore, Directive SCTIE/MS 51[29], June 1st 2022 disclosed the decision to incorporate blinatumomab in SUS for B-cell-derived ALL for the first high-risk medullary relapse in children according to the protocol of the Ministry of Health.

## CONCLUSION

The findings of this review showed a rising progress in innovative technologies to treat ALL, with less AE, higher QoL and a significant decline in the outcome death, which are still strongly present in the statistics presented by the reference institutions with cancer information.

The studies reviewed indicated several benefits, such as increased survival, low odds of therapeutic failure, less frequent AE and improved QoL utilizing different scales for patients treated with blinatumomab, which, beyond the decline of death by ALL, improves the QoL of the patients affected. The results revealed better efficacy and safety of blinatumomab when compared to standard chemotherapy.

Few studies were found about this theme. The risk of bias assessment and evaluation of the certainty of the evidence show some errors, which reduces the reliability of the findings.

The current efforts to update the treatment of ALL internationally and in SUS are quite relevant. The results reinforce the hypothesis that it would be advisable that clinical protocols and therapeutic guidelines for ALL allow adults to utilize blinatumomab, since Conitec has approved its utilization for the pediatric population.

### CONTRIBUTIONS

Laura Augusta Barufaldi and Renan do Nascimento Gonçalves contributed to the study design, acquisition, analysis and interpretation of the data, wording and

critical review. Raphael Duarte Chança contributed to the acquisition, analysis and interpretation of the data, wording and critical review. Aline do Nascimento contributed to the acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

### DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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Associate-editor: Fernando Lopes Tavares de Lima. Orcid iD: https://orcid.org/0000-0002-8618-7608
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