Open Access

OBM Genetics

Review

Blinatumomab vs Chemotherapy for Pediatric and Adult Acute Lymphoblastic Leukemia

Arbnora Batalli-Kepuska [1], Lidvana Spahiu [1], Emir Behluli [1], Gazmend Temaj [2, *]

1. Pediatric Department, University Clinical Center of Kosovo, Prishtina, Kosovo; E-Mails: arbnore.batalli@uni-pr.edu; lidvanaspahiu@gmail.com; ebehluli_19@hotmail.com
2. Human Genetics, College UBT, Faculty of Pharmacy Prishtina, Kosovo; E-Mail: Gazmend.temaj@ubt-uni.net

* **Correspondence:** Gazmend Temaj; E-Mail: Gazmend.temaj@ubt-uni.net

Academic Editor: Masahiro Sato

OBM Genetics
2024, volume 8, issue 3
doi:10.21926/obm.genet.2403253

Received: February 08, 2024
Accepted: July 10, 2024
Published: July 19, 2024

Abstract

Several therapeutic methods are used to cure acute lymphoblastic leukemia (ALL). Relapsed/refractory B-cell *ALL* (R/R B-ALL) remains the primary cause of death worldwide due to the limitation of cure. Blinatumomab is a bispecific T-cell engaging antibody used to treat R/R B-ALL. The use of blinatumomab for treating R/R B-ALL has shown to be very efficient, especially as a bridge tool to hematopoietic stem cell transplantation (HSCT). The response to blinatumomab treatment ranged from 69% after two cycles in phase II clinical trials. Blinatumomab has shown great anti-leukemia activity as a single agent in children with R/R B-ALL. Here, we will review the data from several research groups that show pharmacological and clinical data on blinatumomab for pediatric and adult B-ALL, both as an immunotherapeutic and in combination.

Keywords

Acute lymphoblastic leukemia; blinatumomab; CD19; CD3

1. Introduction

Acute lymphoblastic leukemia (ALL) is a widespread disease, with an incidence of approximately 1.86 cases per 100,000 population. More than 95% of these cases occur in childhood [1]. ALL is a malignancy characterized by the abnormal proliferation of lymphoid progenitor cells known as blasts. These blasts accumulate in the bone marrow, peripheral blood, and extramedullary sites. The most common signs and symptoms associated with ALL include anemia, neutropenia, thrombocytopenia, fever, pain, and malaise [2]. Unlike older children affected by ALL, infants have not had good outcomes in recent decades [3]. For 6-year event-free survival (EFS) and overall survival (OS), the results from the international infant trials, including Interfant-99 and Interfant-06, were 46.4%, 53.8%, 46.1%, and 58.2%, respectively. Higher-risk infants in the Interfant-06 trial had EFS and OS rates of 20.9% and 29.9%, respectively, despite receiving hematopoietic stem cell transplantation (HSCT) in first complete remission (CR1) [4, 5]. The results after relapse showed a 3-year OS rate of 20.9% [6]. Immune therapy, including chimeric antigen receptor (CAR) T cells and blinatumomab, offers excellent potential for improving and curing rates. Blinatumomab is a bispecific T-cell engaging antibody that links the targeted regions of antibodies directed against CD19 and CD3. CD19 is expressed by precursor-B ALL cells, and CD3 is part of the T-cell receptor (TCR) complex. Therefore, blinatumomab is reported to be closely linked between malignant B cells and T cells [7]. This unstimulated cytotoxicity of T cells is known to specifically target and lyse CD19-positive B cells, including both malignant and normal B cells. The blinatumomab single-chain antibody has a molecular weight of 54 kilodaltons (kDa). The recommended administration of blinatumomab is through continuous intravenous (IV) infusion for four weeks, followed by a two-week interval [8-10].

The FDA approved blinatumomab for the treatment of adult and pediatric patients with B-cell ALL (B-ALL) in first or second complete remission with minimal residual disease (MRD) of 0.1% or greater. According to the European Medicines Agency (EMA), blinatumomab is approved for use in patients aged one year or older with Philadelphia chromosome (Ph) -negative, CD19-positive B-precursor ALL who are in relapse after receiving at least two therapies or are in relapse after allogeneic HSCT [7, 11]. Pediatric and adult ALL are biologically distinct, with different genetic alterations and distinguishing features [11, 12].

Figure 1 illustrates the interaction of blinatumomab with CD19 and CD3 in patients diagnosed with ALL before treatment. Here, we will present the data that incriminate blinatumomab's pharmacological and clinical results for adult B-ALL, both as an immunotherapeutic agent and in combination with other treatments.

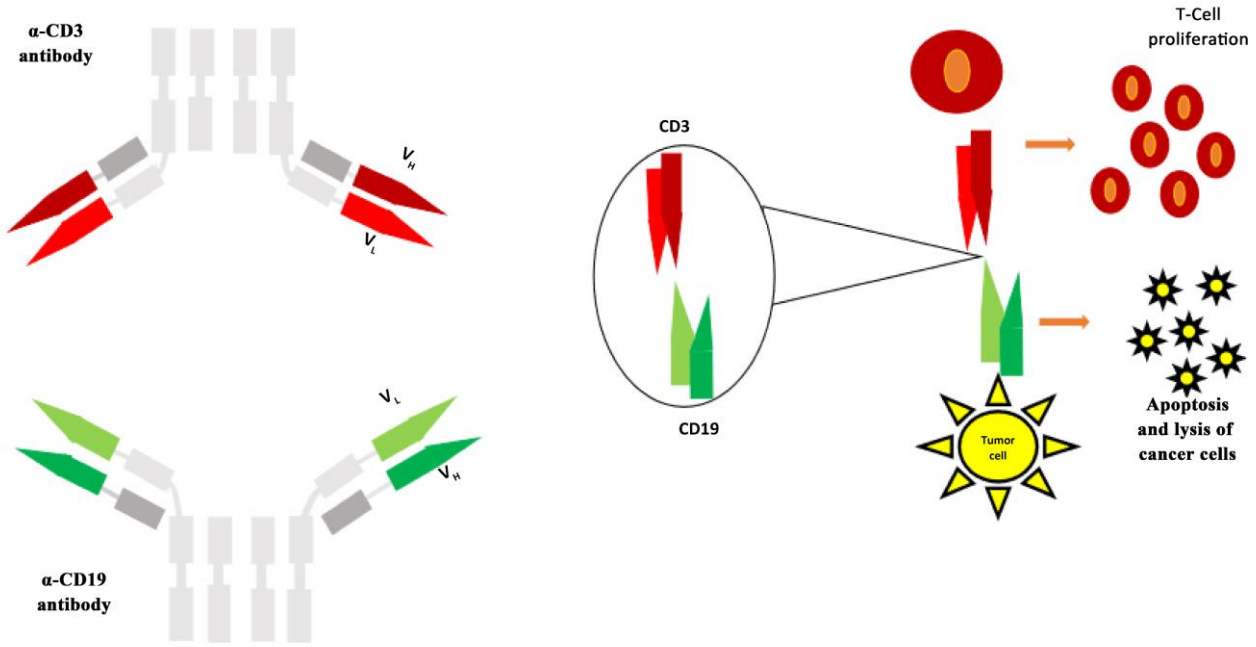

Figure 1 Blinatumomab structure and interaction with CD19 and CD3 in the context of the T-cell antibody class. The binding of CD3 triggers a cell signal that leads to the release of cytotoxins. These cytotoxins activate caspases and induce cell apoptosis.

1.1 The History of ALL Treatment

The historical way of treating ALL has evolved. Here are some key developments:

I. Early Treatment (1980s):

- The primary treatment for ALL in the 1980s was chemotherapy, which was often combined with cranial radiation therapy to prevent central nervous system (CNS) relapse.
- This approach was effective in achieving remission, but relapses were common, and treatment options were limited [13, 14].

II. Introduction of Targeted Therapies (1990s-2000s):

- Introducing targeted therapies like imatinib, nilotinib, and dasatinib, which target specific genetic mutations, significantly improved treatment outcomes [15, 16].
- These targeted therapies were particularly effective for patients with Ph-negative ALL, characterized by the *BCR-ABL1* fusion gene (breakpoint cluster region- Abelson murine leukemia viral oncogene homolog 1) [15].

III. Stem Cell Transplantation (1990s-present):

- Stem cell transplantation, either autologous or allogeneic, has become a crucial component of treatment for high-risk patients and those with relapsed or refractory disease [15].
- This approach allows for high-dose chemotherapy and other treatments, which can more effectively eradicate leukemic cells [15].

VI. Immunotherapy and Clinical Trials (2000s-present):

- Immunotherapy, such as blinatumomab and inotuzumab ozogamicin, has been introduced to target specific leukemic cell populations.
- Clinical trials have become increasingly important in developing new treatments and improving treatment outcomes. Patients may have the option to participate in clinical trials,

which can offer access to innovative therapies and contribute to the advancement of ALL treatments [17].

2. Early Clinical Development Program

The classification of ALL was made with the aim of better-treating patients globally. The classification of hematolymphoid tumors and diagnostic criteria and symptoms associated with this type of disorder are presented in a review by Alaggio et al. 2022 [18].

The early clinical development program for blinatumomab in the treatment of children with relapsed/refractory (R/R) B-ALL included the following critical studies:

- A phase I/II study (MT103-205) evaluated the safety, pharmacokinetics, dosage, and efficacy of blinatumomab in children and adolescents with R/R B- ALL to be R/R B-ALL (or R/R B-ALL) [2]. In the phase I part, 49 patients were treated, while in the phase II part, 44 patients received blinatumomab.
- In phase I/II study, 11% (8/70) of the patients treated with the step-up dose of 5/15 μg/m^2/day had cytokine release syndrome (CRS), with 6% (4 patients) experiencing grade ≥3 CRS [2]. Two patients had to interrupt treatment due to CRS.
- The recommended blinatumomab dosage for children with R/R B-ALL was determined to be 5 μg/m^2/day for the first 7 days, followed by 15 μg/m^2/day thereafter [19]. This dosage was used in the phase II part of the study.
- Among the 70 patients who received the recommended dosage, 39% (27 patients) achieved complete remission within the first two cycles, with 52% (14 patients) achieving complete minimal residual disease response [19].
- The most frequent grade ≥3 adverse events were anemia (36%), thrombocytopenia (21%), and hypokalemia (17%) [19]. No patients developed anti-blinatumomab antibodies [19].

Table 1 presents the treatment of children with blinatumomab who were previously diagnosed with ALL and the side effects of blinatumomab. The first evaluation of blinatumomab was made by continuous intravenous (cIV) infusion in patients affected by non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia [20, 21]. The first phase in R/R NHL patients was started with blinatumomab, which was administered as a cIV infusion at a dose of 0.5-9 μg/m²/day due to the short half-life (approximately 2 hours) of blinatumomab in the human body [13, 14].

Table 1 Treatment with Blinatumomab of pediatric patients diagnosed with ALL and side effects.

Trial	Number of patients	Toxicities	Grade/Adverse event	Reference
KMT2A- (lysine methyltransferase 2A) rearranged in infant	11	CRS Neurotoxicity	Grade 2	[3]
R/R BCP-ALL	38	CRS; Neurotoxicity	AEs (adverse events) of ≥ grade 3 were experienced by 65% of patients. TRAEs were reported in 74% of	[22]

			patients; 26% were ≥ grade 3	
R/R BCP-ALL	70	CRS; Neurotoxicity	4.3% patients experienced grade 3; no grade 4 or 5 neurologic events occurred; 2.9% patients interrupted blinatumomab treatment because of grade 2 neurotoxicity.	[23]
R/R B-ALL	652	CRS; Neurotoxicity	Grade 3	[24]
R/R B-ALL	208	Febrile, neutropenia, infection	grade ≥ 3	[25]
R/R BCP-ALL	39	Neurotoxicity	In 58.7% of patients were ≤2 grade	[26]
R/R BCP-ALL	208	Infection; Neutropenia; Sepsis	The MRD negatively for group treated with Blinatumomab was 75% (first cycles; 66% second cycles	[27]
R/R B-ALL	108	Death rate 17.8% vs 29.6%	Grade 3	[28]

In the Phase II clinical trial of blinatumomab in patients with R/R B-ALL, 36 patients were R/R B-ALL. The rate of complete remission (CR) plus CR with partial hematologic recovery (CRh) was 69% (25/36) after the first two cycles, with 88% (22/25) of these patients achieving remission. In the multicenter study, at Phase II, 189 adult participants with Ph-negative R/R B-ALL patients were registered to further assess the clinical activity of blinatumomab [10, 29]. In the same project, patients who relapsed within 12 months after allogenic HSCT (allo-HSCT) were included. The blinatumomab dosage was 9 μg/day for the first week, followed by 28 μg/day for three additional weeks. This treatment cycle was repeated every 6 weeks. The results showed that the rate of CR plus CR with CRh was 43% (33% CR + 10% CRh) of patients after the first two cycles [15]. Among the 81 patients who achieved CR/CR with CRh, approximately 40% proceeded to allo-HSCT. The common adverse events (AE) were febrile neutropenia and anemia. Severe CRS, including hypoxia, high fever, and hypotension, was reported in three patients, while other features included neurotoxicity. In 20% of patients in this study, survival was observed after two years [16].

In the phase III trial to confirm the efficacy of blinatumomab for R/R B-ALL, a comparison was made between blinatumomab and salvage chemotherapy. In this study, approximately 405 patients were registered; of these, 271 received blinatumomab and 124 received salvage chemotherapy. The results showed that blinatumomab monotherapy had better survival outcomes, with a median survival of 7.7 months compared to 4.0 months for patients receiving salvage chemotherapy [8].

3. CD19 -Targeted Therapy

The CD19 is well known as a B-cell marker with high potential for immunotherapy in B-cell disorders. Despite initial unsuccessful attempts to target CD19, new research has been conducted, and new agents have been developed. This has opened up possibilities for better therapeutic potential of CD19 [30].

Blinatumomab has played a pivotal role in Phase 2 trials and is the most advanced CD19 program. Blinatumomab is part of the bispecific antibody class, which has the ability to connect T-cells to cancer cells [18, 19]. The first evaluation of blinatumomab in Phase 2 was conducted in ALL patients with minimal residual disease (MRD) [31]. The MRD refers to the presence of a small amount of leukemia cells. According to the data, MRD is linked to aggressive diseases and poor prognosis [21, 29].

From this data, it is shown that 80% of patients experienced an MRD response. Another biomarker is SAR3419 (coltuximab ravtansine) is an anti-CD19 antibody-drug conjugate (ADC) that is currently in Phase 2 studies. SAR3419 is an ADC that targets CD19 and forms a conjugation with maytansine, a potent antimitotic agent, using a version of the anti-CD19 antibody, anti-B4, that was humanized as an IgG1 [22].

The MEDI-551 is a compound developed by Gallagher et al. MEDI-551 has been shown to have affinity for targeting human CD19 for B-cell depletion. This type of compound is under investigation in multiple clinical trials. Based on the pharmacological data presented in hCD19 (human CD19) Tg transgenic mice, further studies are needed for clinical trials involving B-cell malignancies and autoimmune diseases [32].

Combotox is a 1:1 mixture of RFB4-dgA and HD37-dgA. RFB4-dgA and HD37-dgA are antibody-based immunotoxins that target CD22 and CD19 respectively, with the goal of selectively killing B-cell cancer cells. Combotox is an immunotoxin with the ability to target the CD22 and CD19 antigens. The dose from 5-15 $\mu g/m^2$/day is recommended for R/R B-ALL [33].

The DT2219ARL is a bispecific immunotoxin that has been shown to have affinity for targeting CD19 and CD22. This compound is suggested as an alternative therapy for B cells that are resistant to chemotherapy, including B-ALL, B-cell chronic lymphocytic leukemia (B-CLL), and B-cell lymphoma [32].

Tafasitamab is a monoclonal antibody that has the ability to bind to CD19. Her et al. in preclinical studies have shown that combinations of tafasitamab with γδ T cells or allogeneic natural killer (NK) cells are a promising strategy and support the future therapeutic potential of tafasitamab as an agent against CD19-positive B-cell tumors [34].

The compound XmAb-5871 is another anti-CD19 antibody for the treatment of autoimmune diseases. In preclinical studies, it has been shown to inhibit antigen-specific B-cell activation in vitro and demonstrate strong activity in vivo in mice with lupus-like disease [35].

The compound denintuzumab mafodotin (SGN-CD19A) is a CD19-targeting agent. In a study by Marrapodi et al., denintuzumab mafodotin was shown to be active against pediatric ALL patient-derived xenografts (PDXs). However, the activity of this compound did not distinguish it from that of vincristine as a single agent [23].

AFM11 is involved in the production of bispecific antibodies and has been shown to bind to a specific site of CD19 present on the surface of cancer cells. In a study by Top et al., treatment with AFM11 was associated with frequent neurological adverse reactions. In patients, some signs of

activity were observed, but no activity was observed in patients with NHL. Further clinical studies are needed to draw definitive conclusions [24].

Another compound is GBR 401, which has been suggested to have therapeutic potential for human B-cell malignancies. The results from Breton et al. contribute to further clinical research to develop GBR 401 for the treatment of patients diagnosed with hematopoietic B-cell malignancies [25].

Recently, the supervision of anti-CD19 chimeric antigen receptor (CAR)-modified T cells for B-cell malignancies has been shown to be very effective in clinical trials. The anti-CD19 CAR-modified T cells have been shown to have therapeutic efficacy in patients diagnosed with B-lineage malignancies, and they were well-tolerated in most patients. Control of chemotherapy is necessary to improve clinical outcomes [30].

4. Efficacity of Blinatumomab

First description of blinatumomab used in cure of pediatric patients was been in a small group with relapse of ALL after allogeneic HSCT. Handgretinger and colleagues in here research show complete remission (CR) after blinatumomab -induced donor T-cell activation in pediatric patients (3 patients) with post-transplant relapsed ALL was possible [26].

Until two years ago, there had been only one published phase I/II clinical study evaluating the treatment of R/R B-ALL ALL in pediatric patients. These patients had R/R ALL with 25% bone marrow blasts show that blinatumomab has a great anti-leukemia activity as a single agent in children with R/R ALL; between 70 patients who took the blinatumomab, 27 achieved CR within the first two cycles, 14 pediatric patients arrived complete MRD [19]. The following study showing allogenic HSCT before and after blinatumomab was associated with a positive effect on survival [35]. In the post hoc analysis for minimal residual disease (MRD) predict complete response to blinatumomab after the first two treatment cycles so that patients at day > 15 being predict of survival, could pursue alternative therapy, such as dose escalation or combination therapies [26, 36]. Locatelli et al. have made comparation of study, when blinatumomab is used as a single agent for the treatment of R/R ALL in pediatric patients, it has shown longer survival and a trend towards higher CR rates compared to chemotherapy [26, 32]. Also, Locatelli and colleagues show that blinatumomab was associated with low of incidence Grade 3 or 4 CRS and neurological events. The same author show that best outcomes are after treatment of patients with blinatumomab and allo-HSCT, independent of genetic abnormalities [37].

5. Blinatumomab vs Chemotherapy

To investigate the importance of blinatumomab versus consolidation chemotherapy, the results from 47 centers in 13 countries were collected. The number of children who participated was 108, with ages ranging from 28 days to 18 years. All participants were treated with either one cycle of blinatumomab at a dose of 15 μg/m²/day for four weeks or chemotherapy. Based on this data, it is shown that among children diagnosed with B-cell B-ALL, treatment with one cycle of blinatumomab results in an improvement in EFS[38].

In the report by Brown et al., the administration of blinatumomab was conducted over six weeks (four weeks on, two weeks off). The number of patients who participated was 70, and in the recommended phase, the treatment consisted of two doses at 5 μg/m²/day in the first week,

followed by 15 μg/m²/day. Of all participants, 64 had a response, and six did not have a response assessment. Based on these analyses of MRD in bone marrow (BM), it is shown that complete response with blinatumomab was achieved for the first two cycles, and these results suggest the possibility of allowing personalized treatment in pediatric patients with R/R B-ALL [37, 39].

The KMT2A gene is rearranged in ALL in infants. This form is a very aggressive disease with a 3-year survival rate below 40%. For this rearrangement, studies were conducted by van der Sluis and colleagues in 30 patients (median age 26.3 months) who received the full course of blinatumomab. They showed that blinatumomab added to chemotherapy in infants is safe and has higher efficacy [39].

In the meta-analysis conducted by Chen and colleagues, it was found that blinatumomab provides significant benefits in children with R/R B-ALL. They concluded that treatment with blinatumomab is very safe and feasible and should be started as soon as possible [40].

In the comparison study conducted by Locatelli and colleagues, it was shown that blinatumomab is more efficacious than chemotherapy in children diagnosed before with B-cell B-ALL. This study included children greater than 28 days and less than 18 years. These patients received either one cycle of blinatumomab (15 μg/m²/day for four weeks) or chemotherapy [41].

The treatment of infants with KMT2A rearrangements with Blinatumomab has been studied in a Phase II trial. The trial aimed to evaluate the safety and efficacy of adding Blinatumomab to standard chemotherapy in infants with KMT2A-rearranged ALL compared to historical controls.

The trial included 30 infants aged less than one year who received one month of induction chemotherapy from the Interfant-06 trial, followed by a single postinduction course of Blinatumomab at 15 μg/m^2/day via 28-day continuous infusion. Patients then continued treatment according to the Interfant-06 protocol, which included consecutive courses of chemotherapy and maintenance therapy. The median follow-up was 26.3 months, and all 30 patients received the full course of Blinatumomab. No toxic effects meeting the primary endpoint definition (permanent discontinuation of Blinatumomab or death) occurred. Serious adverse events were reported in nine patients, including fever, infection, hypertension, and vomiting. No fatal adverse events or neurologic adverse events were reported. Common grade 3 or 4 adverse events included anemia, febrile neutropenia, neutropenia, and elevated γ-glutamyltransferase. After Blinatumomab infusion, 28 patients (93%) became MRD-negative or had low levels of MRD. All patients who continued chemotherapy became MRD-negative during treatment. Disease-free survival at 2 years was 81.6% compared to 49.4% in historical controls, and overall survival at 2 years was 93.3% compared to 65.8% in historical controls. The study concluded that the addition of Blinatumomab to standard chemotherapy appeared to be safe and had a high level of efficacy in infants with newly diagnosed KMT2A-rearranged ALL compared to historical controls from the Interfant-06 trial [42-44]. These results are promising for improving outcomes in this aggressive disease, which has a 3-year EFS of below 40% and a high rate of relapse. The treatment of infants with KMT2A rearrangements using the bispecific T-cell engager Blinatumomab in combination with standard chemotherapy has shown promising results in a Phase II trial [43, 45]. Infants with *KMT2A*-rearranged ALL have an aggressive disease with a 3-year event-free survival below 40% and high relapse rates. In the trial, 30 infants received 1 month of induction chemotherapy followed by a single course of Blinatumomab at 15 μg/m^2/day via 28-day continuous infusion [45]. After Blinatumomab, patients continued treatment according to the Interfant-06 protocol [45]. The addition of Blinatumomab appeared to be safe, with no toxic effects leading to treatment discontinuation or death [43, 45]. The most common adverse

events were anemia, febrile neutropenia, neutropenia, and elevated γ-glutamyltransferase [45]. Efficacy outcomes were promising, with 93% of patients becoming measurable residual disease (MRD)-negative or having low levels of MRD after Blinatumomab [43, 45]. Disease-free survival at 2 years was 81.6% compared to 49.4% in historical controls, and overall survival at 2 years was 93.3% compared to 65.8% [45].

While the results are encouraging, *KMT2A*-rearranged leukemias can display lineage plasticity and switch to myeloid phenotypes under the selective pressure of CD19-directed therapies [7, 43]. Combining Blinatumomab with other targeted agents may be a strategy to prevent this [7].

The BCR::ABL fusion gene resulting from the t(9;22) translocation is another important cytogenetic abnormality in ALL with prognostic significance [46]. Tyrosine kinase inhibitors like imatinib have significantly improved outcomes in BCR::ABL-positive ALL [46]. However, the treatment of infants with this abnormality is not discussed in the provided search results.

In summary, the addition of Blinatumomab to standard chemotherapy appears to be a promising approach for infants with *KMT2A*-rearranged ALL, but further research is needed to optimize treatment and prevent lineage switch [43, 45]. The impact of BCR::ABL in infant ALL is not addressed in these results.

6. Blinatumomab vs Hematopoietic Stem Cell Therapy

Mouttet et al. described the duration of remission in nine patients, most of whom were treated in the consolidation phase with blinatumomab as a bridge to allo-HSCT [47]. In a study by Keating et al., 15 pediatric patients received blinatumomab prior to undergoing HSCT. The use of blinatumomab in this setting reduced MRD levels and resulted in improved overall survival and better toxicity outcomes for the patients with leukemia [27].

Queudeville and colleagues conducted a retrospective analysis of 38 patients diagnosed ALL over a 10-year period. Of these patients, 71% had undergone HSCT prior to treatment with blinatumomab. The same authors showed that 13 out of 38 patients responded to blinatumomab. The reported side effects included febrile reactions, with half of the patients developing CRS. Additionally, eight events of neurotoxicity were reported after 78 cycles, and to date, nine patients are alive and in complete remission [48].

7. Blinatumomab as Drug for Treatment of Down Syndrome Patients Diagnosed with ALL

Children with Down syndrome (DS) are at a markedly increased risk for ALL [49].

Blinatumomab has been used for the treatment of patients with DS who are at a higher risk of being affected by ALL [50, 51] and severe as a bridge for further therapy with cytostatic [52]. The vulnerable group of infants diagnosed with ALL often harbor *KMT2A* gene rearrangements and have a higher risk of relapse [3].

A study from colleagues in Spain has described the effect of blinatumomab and/or inotuzumab in 27 patients diagnosed with ALL. This study demonstrated that both immunotherapeutic drugs can induce remission, and blinatumomab can serve as a bridge therapy during severe infections [53].

The data from Marrapodi et al. support the safety profile of blinatumomab in patients treated for ALL. From a systematic analysis in PubMed, four out of the 255 initial research articles reported data from two phase 1/2 clinical trials and two phase 3 clinical trials. These studies showed that blinatumomab was associated with a lower risk of adverse events, febrile neutropenia, infection,

and grade ≥3 adverse events compared to chemotherapy [25]. Lau et al. have identified 20 patients diagnosed with ALL. Of these, four developed extramedullary relapses following blinatumomab treatment, with a median time to relapse of 179 days. The sites of extramedullary relapse included the pancreas, adrenal gland, kidneys, liver, parotid gland, and brain. Further studies are needed to prevent extramedullary relapse following blinatumomab treatment [54].

Pillai et al. showed that preinfusion of CD19 expression and rare CD19-negative events in ALL do not affect relapse or response to CD19-directed chimeric antigen CAR-cells. Preliminary treatment with blinatumomab has the ability to increase the rate of failure to MRD remission and CD19-negative MRD and relapse [54].

Rambaldi et al. conducted a comparison study between patients treated with blinatumomab and standard of care (SOC). They showed that the ratio of complete remission or complete remission with partial hematological recovery was 36% for blinatumomab and 25% for SOC. These results further support blinatumomab as a treatment option for patients diagnosed with ALL [55].

In the study by Topp et al., it was shown that complete remission or complete remission with partial hematological recovery in the first two cycles was 7.7 months; the median follow-up time for relapse-free survival (RFS) was 35.0 months. The same authors, based on these outcomes, suggest that long-term survival is possible after treatment of patients with blinatumomab [29, 56-58].

In China, patients aged ≥18 years were treated with blinatumomab (five cycles), and the primary aim was to evaluate the hematological response rate (complete remission/complete remission with partial hematological recovery) with two cycles of blinatumomab. The number of patients who participated in this study was 90. The median overall survival was 9.2 months, and the median RFS was 4.3 months. The mean serum concentration of blinatumomab in these Chinese group patients was within the range reported in adults from global clinical trials, and no side effects were found in Chinese patients [57, 59].

8. Conclusion

Blinatumomab presents a significant treatment for patients diagnosed with ALL. In comparison with other therapies, it has been shown to be very effective in eliminating MRD. Patients in current studies have been heavily pretreated, and blinatumomab evaluation is the first step of salvage therapy in many clinics specialized for the treatment and cure of ALL. Many data from different research groups have shown that combinations of blinatumomab and other chemotherapeutic agents, such as inotuzumab ozogamicin (INO), are very effective in treating patients. All data for R/R B-ALL suggest HSCT after a bridge therapy with blinatumomab. The ongoing trials in the future will show if blinatumomab has the ability to induce remission without HSCT treatment or if it is capable of being a maintenance therapy post-HSCT. The data from adult patients suggest that not all MRD-positive patients necessarily require transplantation [59]. The main risks associated with blinatumomab are CRS, neurotoxicity affecting CNS, and errors that may occur during treatment of ALL patients. However, many questions remain unanswered and require further investigation in the near future, including:

1. What is the optimal time to initiate blinatumomab treatment?
2. How many cycles are necessary for a patient to achieve remission after treatment with blinatumomab?
3. Why do some patients respond positively to blinatumomab treatment, while others do not?

4. What is the optimal dosage required for the best possible cure?

These early studies demonstrated the potential of blinatumomab as a targeted immunotherapy for children with R/R B- ALL [28, 51], with promising efficacy and a manageable safety profile. Some authors concluded that the addition of Blinatumomab to standard chemotherapy appeared to be safe and had a high level of efficacy in infants with newly diagnosed KMT2A-rearranged ALL compared to historical controls from the Interfant-06 trial. These results are promising for improving outcomes in this aggressive disease, which has a 3-year EFS 40% and a high rate of relapse.

The study highlights the need for further research to improve outcomes in higher-risk patients and to evaluate the therapeutic potential of Blinatumomab consolidation and men in inhibitors. International cooperation is also necessary to accelerate data collection and clinical understanding in this rare and aggressive subtype of ALL.

The available data suggest that blinatumomab is a more effective treatment option than chemotherapy for patients with R/R B- ALL, offering improved overall survival, EFS, and remission rates. The drug's safety profile is also comparable to that of chemotherapy, with a lower incidence of myelosuppression and associated complications. Further research is ongoing to optimize the use of blinatumomab in this patient population.

Author Contributions

ABK, GT and EB conceived and wrote the manuscript; GT polished the manuscript; GT, ABK, LS and EB revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Competing Interests

The authors declare no conflict of interest.

References

1. Graiqevci-Uka V, Behluli E, Spahiu L, Liehr T, Temaj G. Targeted treatment and immunotherapy in high-risk and relapsed/refractory pediatric acute lymphoblastic leukemia. Curr Pediatr Rev. 2022; 19: 150-156.
2. Stein A, Franklin JL, Chia VM, Arrindell D, Kormany W, Wright J, et al. Benefit-risk assessment of blinatumomab in the treatment of relapsed/refractory B-cell precursor acute lymphoblastic leukemia. Drug Saf. 2019; 42: 587-601.
3. Clesham K, Rao V, Bartram J, Ancliff P, Ghorashian S, O'Connor D, et al. Blinatumomab for infant acute lymphoblastic leukemia. Blood. 2020; 135: 1501-1504.
4. Pieters R, Schrappe M, De Lorenzo P, Hann I, De Rossi G, Felice M, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (interfant-99): An observational study and a multicentre randomised trial. Lancet. 2007; 370: 240-250.
5. Pieters R, De Lorenzo P, Ancliffe P, Aversa LA, Brethon B, Biondi A, et al. Outcome of infants younger than 1 year with acute lymphoblastic leukemia treated with the interfant-06 protocol: Results from an international phase III randomized study. J Clin Oncol. 2019; 37: 2246-2256.

6. Driessen EM, De Lorenzo P, Campbell M, Felice M, Ferster A, Hann I, et al. Outcome of relapsed infant acute lymphoblastic leukemia treated on the interfant-99 protocol. Leukemia. 2016; 30: 1184-1187.
7. Queudeville M, Ebinger M. Blinatumomab in pediatric acute lymphoblastic leukemia-from salvage to first line therapy (a systematic review). J Clin Med. 2021; 10: 2544.
8. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017; 376: 836-847.
9. Nägele V, Kratzer A, Zugmaier G, Holland C, Hijazi Y, Topp MS, et al. Changes in clinical laboratory parameters and pharmacodynamic markers in response to blinatumomab treatment of patients with relapsed/refractory ALL. Exp Hematol Oncol. 2017; 6: 14.
10. Topp MS, Gökbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: A multicentre, single-arm, phase 2 study. Lancet Oncol. 2015; 16: 57-66.
11. Graiqevci-Uka V, Behluli E, Hadziselimovic R, Liehr T, Temaj G. Implementation of pharmacogenetics for treatment of patients with acute lymphoblastic leukemia. Res Results Pharmacol. 2024; 10: 27-39.
12. Greaves M. Molecular genetics, natural history and the demise of childhood leukaemia. Eur J Cancer. 1999; 35: 173-185.
13. Pui CH, Evans WE. Acute lymphoblastic leukemia. N Engl J Med. 1998; 339: 605-615.
14. Ribeiro RC, Conter V. Optimizing pediatric leukemia care in countries with limited resources. J Clin Oncol. 2023; 41: 3482-3485.
15. Graiqevci-Uka V, Behluli E, Spahiu L, Liehr T, Temaj G. A new case of childhood acute lymphoblastic B-cell leukemia from Pristina. Acta Med Bulg. 2023; 50: 59-62.
16. Hayashi H, Makimoto A, Yuza Y. Treatment of pediatric acute lymphoblastic leukemia: A historical perspective. Cancers. 2024; 16: 723.
17. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IB, Berti E, et al. The 5th edition of the world health organization classification of haematolymphoid tumours: Lymphoid neoplasms. Leukemia. 2022; 36: 1720-1748.
18. von Stackelberg A, Locatelli F, Zugmaier G, Handgretinger R, Trippett TM, Rizzari C, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol. 2016; 34: 4381-4389.
19. Goebeler ME, Knop S, Viardot A, Kufer P, Topp MS, Einsele H, et al. Bispecific T-cell engager (BiTE) antibody construct blinatumomab for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma: Final results from a phase I study. J Clin Oncol. 2016; 34: 1104-1111.
20. Zhu M, Wu B, Brandl C, Johnson J, Wolf A, Chow A, et al. Blinatumomab, a bispecific T-cell engager (BiTE®) for CD-19 targeted cancer immunotherapy: Clinical pharmacology and its implications. Clin Pharmacokinet. 2016; 55: 1271-1288.
21. Sigmund AM, Sahasrabudhe KD, Bhatnagar B. Evaluating blinatumomab for the treatment of relapsed/refractory ALL: Design, development, and place in therapy. Blood Lymphat Cancer. 2020; 10: 7-20.
22. Gallagher S, Turman S, Yusuf I, Akhgar A, Wu Y, Roskos LK, et al. Pharmacological profile of MEDI-551, a novel anti-CD19 antibody, in human CD19 transgenic mice. Int Immunopharmacol. 2016; 36: 205-212.

23. Chen B, Zou Z, Zhang Q, Chen K, Zhang X, Xiao D, et al. Efficacy and safety of blinatumomab in children with relapsed/refractory B cell acute lymphoblastic leukemia: A systematic review and meta-analysis. Front Pharmacol. 2023; 13: 1032664.
24. Marrapodi MM, Mascolo A, di Mauro G, Mondillo G, Pota E, Rossi F. The safety of blinatumomab in pediatric patients with acute lymphoblastic leukemia: A systematic review and meta-analysis. Front Pediatr. 2022; 10: 929122.
25. Hammer O. CD19 as an attractive target for antibody-based therapy. MAbs. 2012; 4: 571-577.
26. Locatelli F, Whitlock JA, Peters C, Chen-Santel C, Chia V, Dennis RM, et al. Blinatumomab versus historical standard therapy in pediatric patients with relapsed/refractory Ph-negative B-cell precursor acute lymphoblastic leukemia. Leukemia. 2020; 34: 2473-2478.
27. Queudeville M, Schlegel P, Heinz AT, Lenz T, Döring M, Holzer U, et al. Blinatumomab in pediatric patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia. Eur J Haematol. 2021; 106: 473-483.
28. Temaj G. Immunotherapy in childhood acute lymphoblastic leukemia. 2021 UBT International Conference; 2021 October; Kosovo Polje Kosovo. Doi: 10.33107/ubt-ic.2021.97.
29. Topp MS, Gökbuget N, Zugmaier G, Klappers P, Stelljes M, Neumann S, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. J Clin Oncol. 2014; 32: 4134-4140.
30. Baeuerle PA, Reinhardt C. Bispecific T-cell engaging antibodies for cancer therapy. Cancer Res. 2009; 69: 4941-4944.
31. Cazzaniga G, Valsecchi MG, Gaipa G, Conter V, Biondi A. Defining the correct role of minimal residual disease tests in the management of acute lymphoblastic leukaemia. Br J Haematol. 2011; 155: 45-52.
32. Herrera L, Bostrom B, Gore L, Sandler E, Lew G, Schlegel PG, et al. A phase 1 study of Combotox in pediatric patients with refractory B-lineage acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2009; 31: 936-941.
33. Locatelli F, Zugmaier G, Mergen N, Bader P, Jeha S, Schlegel PG, et al. Blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia: Results of the RIALTO trial, an expanded access study. Blood Cancer J. 2020; 10: 77.
34. Horton HM, Chu SY, Ortiz EC, Pong E, Cemerski S, Leung IW, et al. Antibody-mediated coengagement of FcγRIIb and B cell receptor complex suppresses humoral immunity in systemic lupus erythematosus. J Immunol. 2011; 186: 4223-4233.
35. Gore L, Locatelli F, Zugmaier G, Handgretinger R, O'Brien MM, Bader P, et al. Survival after blinatumomab treatment in pediatric patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia. Blood Cancer J. 2018; 8: 80.
36. Locatelli F, Zugmaier G, Mergen N, Bader P, Jeha S, Schlegel PG, et al. Blinatumomab in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia: RIALTO expanded access study final analysis. Blood Adv. 2022; 6: 1004-1014.
37. Brown P, Zugmaier G, Gore L, Tuglus CA, von Stackelberg A. Day 15 bone marrow minimal residual disease predicts response to blinatumomab in relapsed/refractory Paediatric B-ALL. Br J Haematol. 2020; 188: e36-e39.
38. Brown PA, Ji L, Xu X, Devidas M, Hogan LE, Borowitz MJ, et al. Effect of postreinduction therapy consolidation with blinatumomab vs chemotherapy on disease-free survival in children,

adolescents, and young adults with first relapse of B-cell acute lymphoblastic leukemia: A randomized clinical trial. JAMA. 2021; 325: 833-842.
39. van der Sluis IM, de Lorenzo P, Kotecha RS, Attarbaschi A, Escherich G, Nysom K, et al. Blinatumomab added to chemotherapy in infant lymphoblastic leukemia. N Engl J Med. 2023; 388: 1572-1581.
40. Jones L, McCalmont H, Evans K, Mayoh C, Kurmasheva RT, Billups CA, et al. Preclinical activity of the antibody-drug conjugate denintuzumab mafodotin (SGN-CD19A) against pediatric acute lymphoblastic leukemia xenografts. Pediatr Blood Cancer. 2019; 66: e27765.
41. Shimony S, Luskin MR. Unraveling KMT2A-rearranged ALL. Blood. 2023; 142: 1764-1766.
42. Newman H, Tasian SK. The brilliant success of blinatumomab for babies with acute lymphoblastic leukemia. Hematologist. 2023; 20: 1572-1581.
43. Burmeister T, Ströh AS, Kehden B, Trautmann H, Meyer C, Marschalek R, et al. Measurable residual disease quantification in adult patients with KMT2A-rearranged acute lymphoblastic leukemia. Leukemia. 2024; 38: 1600-1603.
44. Brown P, Pieters R, Biondi A. How I treat infant leukemia. Blood. 2019; 133: 205-214.
45. Locatelli F, Eckert C, Hrusak O, Buldini B, Sartor M, Zugmaier G, et al. Blinatumomab overcomes poor prognostic impact of measurable residual disease in pediatric high-risk first relapse B-cell precursor acute lymphoblastic leukemia. Pediatr Blood Cancer. 2022; 69: e29715.
46. Mouttet B, Vinti L, Ancliff P, Bodmer N, Brethon B, Cario G, et al. Durable remissions in TCF3-HLF positive acute lymphoblastic leukemia with blinatumomab and stem cell transplantation. Haematologica. 2019; 104: e244-e247.
47. Keating AK, Gossai N, Phillips CL, Maloney K, Campbell K, Doan A, et al. Reducing minimal residual disease with blinatumomab prior to HCT for pediatric patients with acute lymphoblastic leukemia. Blood Adv. 2019; 3: 1926-1929.
48. Behluli E, Nuhii N, Liehr T, Temaj G. Suspicions regarding the genetic inheritance of acute lymphoblastic leukemia in patients with down syndrome. J Mother Child. 2022; 26: 104-110.
49. Brown PA, Ji L, Xu X, Devidas M, Hogan L, Borowitz MJ, et al. A randomized phase 3 trial of blinatumomab vs. chemotherapy as post-reinduction therapy in high and intermediate risk (HR/IR) first relapse of B-acute lymphoblastic leukemia (B-ALL) in children and adolescents/young adults (AYAs) demonstrates superior efficacy and tolerability of blinatumomab: A report from children's oncology group study AALL1331. Blood. 2019; 134: LBA-1.
50. Elitzur S, Arad-Cohen N, Barzilai-Birenboim S, Ben-Harush M, Bielorai B, Elhasid R, et al. Blinatumomab as a bridge to further therapy in cases of overwhelming toxicity in pediatric B-cell precursor acute lymphoblastic leukemia: Report from the Israeli study group of childhood leukemia. Pediatr Blood Cancer. 2019; 66: e27898.
51. Zhou H, Yin Q, Jin J, Liu T, Cai Z, Jiang B, et al. Efficacy and safety of blinatumomab in Chinese adults with Ph-negative relapsed/refractory B-cell precursor acute lymphoblastic leukemia: A multicenter open-label single-arm China registrational study. Hematology. 2022; 27: 917-927.
52. Contreras CF, Higham CS, Behnert A, Kim K, Stieglitz E, Tasian SK. Clinical utilization of blinatumomab and inotuzumab immunotherapy in children with relapsed or refractory B-acute lymphoblastic leukemia. Pediatr Blood Cancer. 2021; 68: e28718.
53. Lau KM, Saunders IM, Goodman AM. Characterization of relapse patterns in patients with acute lymphoblastic leukemia treated with blinatumomab. J Oncol Pharm Pract. 2021; 27: 821-826.

54. Pillai V, Muralidharan K, Meng W, Bagashev A, Oldridge DA, Rosenthal J, et al. CAR T-cell therapy is effective for CD19-dim B-lymphoblastic leukemia but is impacted by prior blinatumomab therapy. Blood Adv. 2019; 3: 3539-3549.
55. Rambaldi A, Ribera JM, Kantarjian HM, Dombret H, Ottmann OG, Stein AS, et al. Blinatumomab compared with standard of care for the treatment of adult patients with relapsed/refractory philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia. Cancer. 2020; 126: 304-310.
56. Topp MS, Gökbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: A multicentre, single-arm, phase 2 study. Lancet Oncol. 2015; 16: 57-66.
57. Topp MS, Kufer P, Gökbuget N, Goebeler M, Klinger M, Neumann S, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol. 2011; 29: 2493-2498.
58. Topp M, Dlugosz-Danecka M, Skotnicki AB, Salogub G, Viardot A, Klein AK, et al. Safety of AFM11 in the treatment of patients with B-cell malignancies: Findings from two phase 1 studies. Trials. 2023; 24: 4.
59. Topp MS, Gökbuget N, Zugmaier G, Stein AS, Dombret H, Chen Y, et al. Long-term survival of patients with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab. Cancer. 2021; 127: 554-559.