A Review on Bispecific Antibody (Blinatumomab) for the Treatment of Acute Lymphoblastic Leukemia

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A thesis submitted to the School of Pharmacy in partial fulfilment of the requirements for the degree of Bachelor of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis/project titled "A Review on Bispecific Antibody (Blinatumomab) for the Treatment of Acute Lymphoblastic Leukaemia" submitted by Kinley Choki (20346072) of Summer, 2020 has been accepted as satisfactory in partial fulfilment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on March, 2024.

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Ethics Statement

This study does not involve any animal or human trial.

Abstract

Acute lymphoblastic Leukemia has currently about 6,550 new cases from which about 3,590 are male and about 2,960 are females. ALL occurs in fewer than half of 1% of all cancer in the US. There are multiple subtypes of ALL out of which there are two main types and only in some cases it can be cured. Treatment of different types are available for the acute lymphoblastic Leukemia (ALL). Some treatments are in the ongoing trials and some are standard treatments that are currently used. Blinatumomab is a bispecific monoclonal antibody approved by the US, FDA for the treatment in patients with relapsed or refractory B-cell precursor of ALL on the basis of phase 3 clinical trials that shows the efficacy and some manageable toxic effects. It shows superior overall survival as compared to standard chemotherapy. The refractory or relapsed acute lymphoblastic Leukemia (ALL) patients, when treated with the allogeneic stem cell transplantation and cytotoxic chemotherapy have poor prognosis or the pitiful rate of survival approximately 5%. In this review, the clinical trial data of blinatumomab is analysed, an evaluation of its effectiveness and safety in comparison to the chemotherapy is provided, which can be used to unfold the full potential of this drug in the future.

Keywords: Acute lymphoblastic Leukemia (ALL); blinatumomab; blinatumomab clinical trials; R/R B-cell precursor ALL: Acute B-Lymphoblastic Leukemia; Acute precursor B-cell Leukemia.

Dedication

Dedicated to those who have been suffering from Acute Lymphoblastic Leukemia and to my parents who have always been supportive and encouraging.

Acknowledgement

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List of Acronyms

ALL	Acute Lymphoblastic Leukaemia
CNS	Central Nervous System
MRD	Minimal Residual Disease
DNA	Deoxyribonucleic acid
CRS	Cytokine release syndrome
TKI	Tyrosine Kinase Inhibitor
AHSS	Aryl-hydrocarbon receptor repressor
DFS	Disease free survival
SOC	Standard of care
FDA	Food and Drug Administration
BCP-ALL	B-cell Precursor Acute Lymphoblastic Leukaemia
B-ALL	B-cell acute lymphoblastic leukaemia
T-ALL	T -cell acute lymphoblastic leukaemia
BsAb	Bispecific Antibody
INN	International non-proprietary name
MTD	Maximum tolerated dose

Chapter 1: Introduction

1.1 Introduction to Acute Lymphoblastic Leukaemia (ALL)

A haematological cancer which is characterized by the proliferation of lymphoid progenitor cells that are immature is called acute lymphoblastic leukaemia also known as acute lymphocytic leukaemia. The chromosomal abnormalities and genetic alteration that are associated with proliferation and differentiation of the malignant cells are the hallmarks involved in ALL. Many stem cells become lymphoblast, T lymphoblast and B lymphoblast in ALL. Those cells are also called as leukaemia cells that are not able to fight back infections and increases in the blood and bone marrow. It left with very few healthy white blood cells, red blood cells and platelets, causing anaemia or easy bleeding. It can spread to the lymph nodes, spleen liver, testicles, central nervous system (CNS) and other organs. If it's not treated on time, it quickly gets worse and difficult to treat (Adult Acute Lymphoblastic Leukaemia Treatment, 2023). According to the Queudeville et al. (2017) the survival rate in the past 50 years had improved drastically with about 85% exceeding the cure rate for the predicate ALL in children. Nonetheless for some adolescents or children it develops resistance and clearly many therapy doesn't work which result in using several rounds of different chemotherapy. In addition to the present therapies that lead to certain long term side effects such as cardiovascular effect, growth defects of bone and the impairment of central nervous system. Hence, particularly for the resistant and refractory children, for ALL more effective and safer treatment need to be developed. Regardless of the advance management of the multi-agent cytotoxic chemotherapy and allogeneic stem cell transplantation remains the frontline therapy for the adults. In adult the long term remission is attained in about 30-40% ALL patients. Bray et al. (2018) mentioned that acute leukaemia is the most common cancer affecting all age groups. In 2018 globally it ranked as the fifteen being the most common cancer diagnosed with cases of 437,033 and moralities of 309,006 accounting due to the malignant disorder leading to eleventh cause of death.

Table 1: American Cancer society statistics on ALL (Key Statistics for Acute Lymphocytic Leukaemia (ALL), 2024)

1. New cases per year	About 3000 to 5000
Female	About 2,960
Male	About 3590
2. Death from ALL	About 1,330
Female	About 690
Male	About 640

The risk of ALL is higher in men than in women's and greater in white people than the people of African Americans.

1.2 Etiologies of ALL

The knowledge regarding the etiology of ALL is unknown. Nonetheless, there are certain genetic and environmental factors that have been indicated in the Acute Lymphoblastic Leukaemia etiology such as:

Genetic factors involved are the following:

1. Inherited genetic susceptibility: Significant risk factors in developing childhood ALL is germline mutation, detected susceptibility loci in CEBPE, ARID5B, CDKN2A/2B, BMI1 and others childhood ALL related with high risks. In certain racial groups some genes are regarded as for the racial predilection. The higher incidence rates spotted in this group are held to be due to the presence of ARID 58 which is found to be in Hispanics (Greaves, 2018). The uncommon germ line mutations shown in certain growing hematopoietic genes such as PAX5, ETV6 and IKZF1 which are predispose children to ALL. Greaves (2018) mentions some of the uncommon syndromes linked with childhood ALL such as Rubinstein-Taybi syndrome and Cornelia de Lange syndrome. Some other syndromes related to growing childhood ALL include Down syndrome, constitutional mismatch repair deficiency, Noonan syndrome and Franconia

anaemia. The pathogenic germline mutation is 44% prevalence and known as one of the genes in adolescents and with ALL that cause cancer. The emergence of the new germline risk variants with the improvement of the technology and growth in the novel techniques for detecting the predisposition of cancer.

2. Epigenetics: A hallmark of cancer is the childhood ALL characteristics with environmental, metabolic and genetic factors that put up to the epigenetic changes (Schmidt et al., 2021). Some environmental factors linked to this condition may result in DNA methylation in the children. Association of the large-scale epigenome-wide studies have shown factors linked between maternal exposures during pregnancy which includes body mass index, air pollution, smoking, with DNA methylation in the blood of offspring. For example, during pregnancy, exposure of the maternal smoking is linked to the methylation decreasing at AHRR which is aryl-hydrocarbon receptor repressor, CpG cg05575921.The phenotypic of leukemic cells and pathogenesis are the outcomes of a targeted specific and wide alteration of the genome of DNA methylation (Nordlund & Syvanen, 2018).

Environmental factors involve:

1. Ionizing radiations: For decades, moderate and high doses of chronic leukaemia are linked to the strong risk factors, specifically exposure throughout childhood linked with high risk of cancer development in contrast to the exposure to adulthood. After IR exposure the leukaemia dose response is characterized as linear-quadratic which changes slowly at low dose and at high dose changes quickly. Ekpa et al. (2023) mention the evidence of developing when exposure to the radiation of low dose defined as less than 100 mGy radiation is infrequent but high doses can be linked with notable risk.

2. Infections: About 100 years which is a century has passed since the idea of infection which plays a normal role in ALL. Greave's "delayed infection "and Kinlen's "population mixing" are the two hypothesis that have been put forward to explain how infections predispose to ALL. According to both theories, acute lymphoblastic leukaemia is as a result of an uncommon response to the familiar infection. Observing cases of leukaemia in close spatial and temporal proximity than would be expected if

they occur from one another independently indicating for the infectious etiology. A study was conducted by Ekpa et al. (2023) where between the age of zero and five years old children including for the leukaemia's peak incidence between the age two and four years old children, the clustering of chronic leukaemia (CL) of strong evidence was shown at the time of the children's diagnosis with a result comparable to ALL. The regular observation of the clustering from time to time could be described by "mini-epidemics" of a single infection resulting in local clusters of cases of leukaemia. Maternal infections can also be a potential risk factor for developing All as discovered by some of the research studies which indicate that the All development and the infection risk is not only bounded to the postnatal period (Hwee et al., 2017). Viral infections are most often studied linked to ALL followed by the fungal and bacterial infections. In general the chronic leukaemia are linked with rubella, during pregnancy the varicella infections and influenza whereas the influenza infection, infection associated with specific ALL.

3. Immensely low-frequency magnetic field: The research relationship between the ALL risk and the extremely low frequency magnetic field is still in progress. The high risk of chronic leukaemia development and particularly ALL with the exposure of above 0.3 or 0.4μT magnetic field are generally consistent with the result shown by the present studies. Other risk factors identified involve sex and high and low birth weight with males more frequently affected than females, air pollution, smoking, paints, exposure to pesticides, delivery of prelabour caesarean and cured meats intake by the maternal in which when the cured meat which contain the precursor n-nitro, in stomach, that converts to carcinogenic components by HCL which then transported to the developing fetus through placenta (Cao et al., 2019).

1.3 Signs, Symptoms and Prodromes

The sign and the symptoms of the acute lymphoblastic leukaemia include: dizziness, cough, bleeding, anaemia, fatigue, high fever, joint pain, loss of appetite, night sweats, shortness of breath, swollen lumps nodes, weight loss, viral and bacterial infections frequently and etc. Many of the times it is not possible to accurately identify all the signs and symptoms as there is a large range of clinical manifestations. Nonetheless several signs and symptoms of ALL

might mimic the other conditions which are less serious. The possibility of having one or more symptoms does not indicate the person having acute lymphoblastic leukaemia (Professional, n.d.).

Most of the signs and symptoms of the ALL are the result of the shortage of the blood cells. Which appear cells crowd out the normal blood making cells in the usual blood making cells in the bone marrow. Some of the symptoms are not just cause by the ALL but also often cause as a result of some other conditions.one of the general symptoms which is the swelling of the abdomen due to the fluid build-up in the body particular at the side of neck, in the underarm areas and also in the gorin. Swelling might occur in lymph node inside the chest. Moreover Leukemia less often might spread to the other organs as well and cause headache, vomiting, weakness as it gets spread to the spinal cord and the brain as well as it might spread to eye, skins, and kidney (signs and symptoms of acute lymphoblastic leukemia (ALL), 2024).

Prodromes are early symptoms that indicate the forthcoming of a disease or illness. According to Lee et al. (1994) in a report, with a typical manifestation a boy who was 7 years old had erythema infectiosum. No signs of regression were shown by the lesions and by each passing time it progressively became more severe, the chronic anaemia for over 40 years. After the onset showed abnormal such as sezary-like lymphocytes after 20 days of electron microscopic examination. Later it was discovered to be acute lymphoblastic leukaemia with a B19 infection linked with immunosuppression. In addition an ALL patient had an unfamiliar prodromes which includes pulmonary infiltrates, spontaneous pneumothorax bilateral and hypereosinophilic syndromes within the four months of the onset of leukaemia (Geltner, D. (1978).

1.4 Classification of ALL

ALL can be classified into two main subtypes which are T -cell acute lymphoblastic leukemia (T-ALL) and B-cell acute lymphoblastic leukemia (B-ALL).

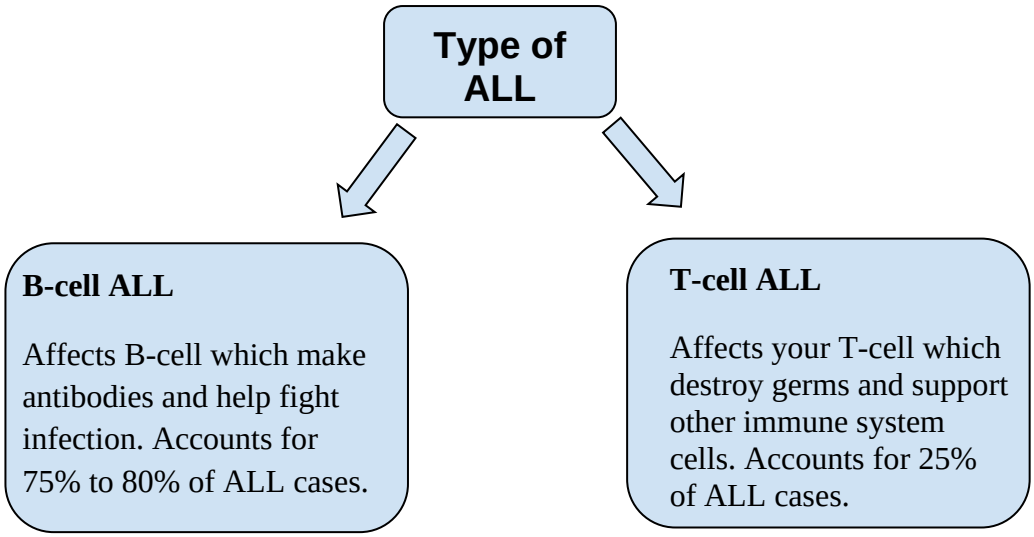

Figure 1 Type of ALL (Queudeville et al., 2017)

Queudeville et al. (2017) mentions that acute lymphoblastic leukemia is the B-ALL which occurs in the immature cell that is developed normally in children about 88% of cases and approximately 75% cases in adults. Furthermore T-ALL is more common in adults than in children. The new case of ALL in 2019 was estimated to be approximately 6000 which happen in the US and 4% and less of all blood cancer. About 50% of the cases of ALL occur in children whereas more than 30% of the cases were in paediatric cancer. It follows a distribution that is bimodal with the first peak happening in childhood and second peak happening around at the age of 50 years old.

1.5 Pathophysiology

After the damage to the DNA it causes the lymphoid cells to undergo uncontrollable cell growth and spread, resulting in the acute lymphocytic leukemia. Consequently with the removal of platelets and lymphocytes the enlargement of the liver, hepatomegaly and the enlargement of spleen, Splenomegaly occurs in order to filter out the abnormal white blood cell (Puckett & Chan., 2023).It is a very complicated disease that involves several factors such as genes, biological as well as environmental factors. With the utilizations of the advanced genomic studies it's been proven that there is interconnection between the inherited and somatic genetic alterations. Over the last three decades, many cytogenetic studies have been carried out and thanks to that, all the required and necessary information on Pathogenesis of the ALL is widely

available. The understanding of the particular lesions of molecules and analytical pathways of the leukemogenesis have dramatically elevated with the assistance of the more yield of genes and NGS technologies. Hematopoietic cell from which ALL is originated. It can either be the T-ALL or B-ALL. The two types of leukemia-ALL and the B-ALL and each subtype based on the particular changes in chromosomes are said to trigger the leukemia-initiating. In children the common translocation are seen with B-ALL, including t(12;21) [ETV6-RUNX1] (25%), t(1;19) [TCF3-PBX1] (5%), t(9;11) [BCR-ABL1] (3%),translocations involving the MLL gene with various partner fusion genes (5%),Childhood ALL that gains in whole chromosomes or high-hyperdiploidy (>50 chromosomes) which add up for 25%,whereas about 1% of the cases is result of hypodiploidy (<44 chromosomes).A newly diagnosed 20% of BCP-ALL cases, however, is not included in any of the subtypes of genetics which are familiar. As a result those subtypes are known as B-other (Ekpa et al., 2023).

1.6 Management and Treatment

ALL is long treated with chemotherapy, immunotherapy or the stem cells transplantation and target therapy. About 90% of the adults with ALL may experience remission which indicates that the patients had fully recovered or cured from ALL. In some of the patients unfortunately may relapse as a result of remaining leukemia cells or frequently due to developing resistance to the drugs used to treat ALL. Repeating the remission induction programme would be the first step in relapse ALL treatment, expecting to be more intense than the previous one. After trying out for the second time, about 40% of the participants or the patients in a clinical trial were able to carry off remission induction using chemotherapy (Blood Cancer UK; Treatment for the Relapse Acute Lymphoblastic Leukemia (ALL),n.d).

I. Chemotherapy

It is used to treat the front line or the initial ALL treatment. Patients receive four phases of chemotherapy. To put ALL into complete remission which is to eliminate the signs and symptoms of the cancer with the treatment is the goal of chemotherapy. Chemotherapy takes several months or year generally involving a high dose of drug that kills cancer cells in ALL (Adult ALL treatment, 2023). Some of the ALL chemotherapy includes:

- CNS directed therapy to kill any cancerous cell or the leukemia cell in CNS and prevent the spreading of ALL to the spinal fluid.

- Consolidation therapy, it starts in remission of ALL. It works to kill or destroy as much as possible of the left out cancer cell. It involves receiving high dose drugs during the weekly administered chemotherapy for many days being in hospital.
- Maintenance therapy is that it may last for two to three years and it's a long term treatment where it's not necessary for the patient to be at hospital.
- Remission induction therapy, ALL goes into complete remission as it kills leukemia cells or the cancerous cell to the furthest extent. During the remission induction therapy, patients are kept in the hospital. The treatment course lasts between four to six weeks.
- Studies indicate that after the remission induction therapy, about 95% or more children and in adults about 75% to 80% with ALL experiences complete remission.

II. Targeted therapy

Use of drugs or other substances to detect and attack particular cells of the cancer is the kind of uses involved in target therapy while the specific genetic changes being focused here. Some children and adults approximately 25% have chromosomal mutations. Tyrosine kinase (TKI) therapy is presently used to treat children and adults ALL with Philadelphia chromosome (9; 22) a specific mutation by the healthcare providers. The enzyme important for the growth of ALL is blocked by TKI therapy. It kills cells of ALL as a result for the body to return the production of normal blood cells.

III. Monoclonal antibodies

To treat several diseases including cancer a protein in the immune system is made in the laboratory known as monoclonal antibodies. It can attach to a particular or specific target on the other cells that help grow cancer cells or target on cancer cells. After binding to the specific target cancer cell it then capable of eliminating the cancerous cells, stop the browsing of the cancer, or prevent it from expanding. By infusion, it is administered and might be used on its own or to deliver toxins or radioactive materials, drugs right up to the cancer cells. To treat ALL in adults, inotuzumab ozogamicin and blinatumomab which are monoclonal antibodies are used with stem cell transplant.

IV. Tyrosine kinase inhibitor therapy

It blocks the enzyme and results in preventing the stem cells from expanding into more white blood cells than the body requires by the tyrosine kinase inhibitor such as dasatinib, imatinib and nilotinib used for the treatment of ALL in adults.

V. Immunotherapy

It promotes the body's own immune system to recognize and attack or fight back cancerous cells. CAR-T cell therapy or the monoclonal antibodies therapy are the immunotherapy for ALL with help of the substance synthesized in the lab or produced in the body are used to strengthen or, direct or bring back the body's natural defence in opposition to cancer.

VI. Stem cell (bone marrow) transplantation

To replace the blood-forming cells, stem cell transplant is introduced. It is an immature blood cell, the stem cells, that are taken out for the patient's or the donor's bone marrow or the blood and are kept in reserve. The stored stem cells are used after the chemotherapy and radiation therapy of the total body and are given back through the infusion into the patient's body which will grow and restore the blood cell in the patient's body.

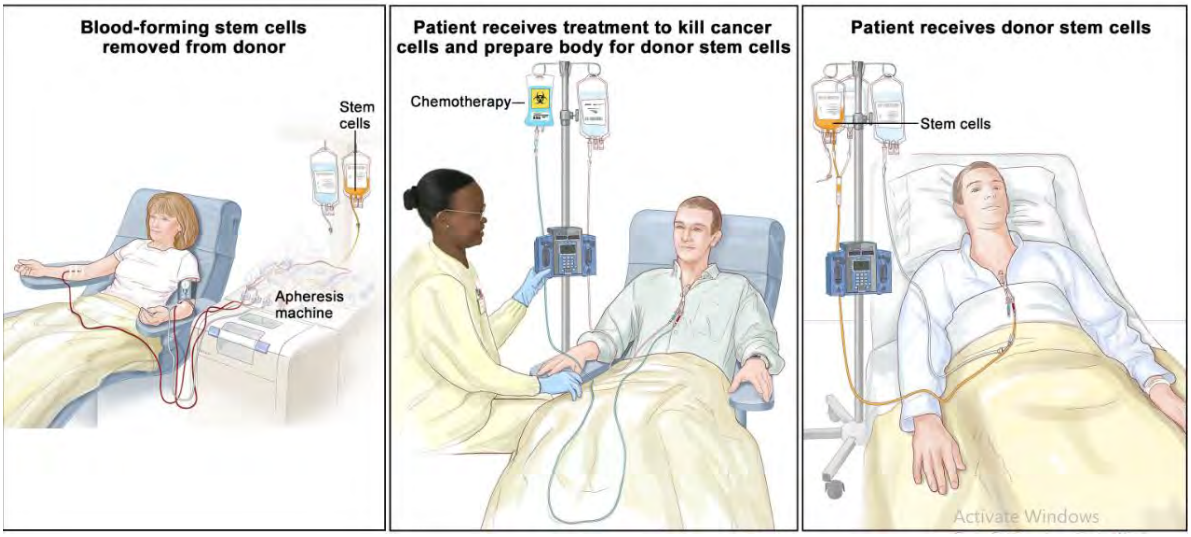

Figure 2 Donor stem cell transplants (Cancer.gov, 2023)

VII. Radiation therapy

High energy x-rays or other types of radiation are used to either kill or prevent the growth of cancer cells. To direct the radiation toward the area of the body where it is spreads, a machine outside the body is used by the external radiation therapy. To treat the ALL in adults that has lay out or might metastasize to the spinal cord and the brain called as the CNS prophylaxis or

the CNS sanctuary therapy. When getting ready for transplant of the stem cell, to send radiation directed toward the whole body might use the total body irradiation. To enhance the standard of life and to lower the symptoms external radiation therapy might be used as palliative therapy.

1.7 Aim and Objectives

1.7.1 Aim of the Study:

To evaluate the efficacy, safety and effectiveness of blinatumomab for the treatment of acute lymphoblastic leukemia by comparing its clinical outcomes with chemotherapy.

1.7.2 Objective of the Study:

- To assess the pharmacological characteristic of the drug.
- To determine treatment options for ALL.
- To determine the efficacy of blinatumomab on the overall survival when compared with the SOC chemotherapy.
- To analyse the clinical outcome of blinatumomab
- To discuss the future aspects and challenges

Chapter 2: Novel ALL Treatment

2.1 Bispecific Antibody

The two distinct binding domains on the bispecific antibodies concurrently allow binding at same time on the two epitopes of the antigen. The development of the BsAb over the past two decades has been altered dramatically due to the approach of genetic engineering that allows variation of structures of the molecules giving different pros and cons. The clinical applications are the result of the effort of the research and development. In clinical advancement more than 100 BsAbs are there in the initial stage. FDA since 2014 has approved nine BsAb applications for marketing in treating cancer. Furthermore in the treatment of the ocular and hematologic disease (FDA; bispecific antibodies. 2024).

Table 2. FDA approved bispecific antibody (FDA; bispecific antibodies. 2024).

Trade name	Active Ingredients	Year of Approval	Indications
Blincyto	Blinatumomab	2024	To treat Philadelphia chromosome-negative relapsed or refractory B cell precursor acute lymphoblastic leukemia
Hemlibra	Emicizumab-kxwh	2017	To prevent or reduce the frequency of bleeding episodes in haemophilia A with factor VIII inhibitors
Rybrevant	amivantamab-vmjw	2021	To treat locally advanced or metastatic non-small cell lung cancer with certain mutations
Kimmark*	Tebentafusp-tebn	2022	To treat a form of unrespectable or metastatic uveal melanoma
Vabysmo	Faricimab-svoa	2022	To treat neovascular (wet) age-related macular degenerated and diabetic macular edema
Tecvayli	Teclistamab-cqyv	2022	To treat relapsed or refractory multiple myeloma
Lunsumio	mosunetuzumab-axgb	2022	To treat relapsed or refractory follicular lymphoma

Epkinly	Epcoritamab-sysp	2023	To treat relapsed or refractory diffuse large B-cell lymphoma
Columvi	Glofitamab-Gxbm	2023	To treat relapsed or refractory diffuse large B cell lymphoma or large B-cell lymphoma

2.2 New Drug for ALL

Blinatumomab and inotuzumab, known as the monoclonal antibodies, are the currently available two new drugs for the treatment of relapse ALL. These drugs bind to the leukemia cells whereby the immune system will be able to recognize and search to kill the cancerous cells. Moreover showing favourable outcomes in the clinical trials with minimal side effects.

2.3 Reasons for Developing the Drug

Chemotherapy has been the beginning of the treatment of the patient with B cell malignancies. The monoclonal antibodies, irradiation, and hematopoietic stem cell transplantations are added depending on individual specific disease. Nonetheless, specifically for the relapsed disease patients the present standard of care is not enough to accomplish the durable remissions. Blinatumomab (AMG103 or MT103) is a highly promising candidate of new drugs in the late stage clinical development for the treatment of the B cell malignancies such as ALL. It belong to the class of bispecific T cell engager(BiTE) antibodies, it has a dual specificity for the CD3 and CD19 with an ability to potentially take part in all cytotoxic T cells of a patients for redirecting tumor cells lysis. The world organization has designed the CD19/CD3 bispecific BiTE antibody with an international non-proprietary name (INN) blinatumomab. It originated from the term B lineage-specific antitumor mouse monoclonal antibody. Two of the researchers published the first description of blinatumomab and turned up with the basic characteristics of the construct bispecific antibody (Loffler et al., 2000).

Afterward a confirmatory in-vitro performance was conducted. Blinatumomab showed impressive activities that were rather novel for a bispecific T cell- engaging antibody with T cells, co-culture experiment and target cell CD19+. When the T cells from several healthy donors were tested, the half maximal concentration of the blinatumomab for redirecting lysis of the target cell CD19+ by the T cells ranges between 10 to 100 pg/ml(Pico-to femtomolar)

BiTE antibody. Animal testing with blinatumomab in chimpanzees as the molecule is cross reactive only in this animal. To study the pharmacodynamics effects in the species, some preliminary studies have been done. Studies quickly change into the mouse model using a surrogate or homologous model due to the given concerns for the general species used in the research (Schlereth et,. 2006).

In 2001, blinatumomab was taken up in the first in man trials where based on the safety data and pharmacodynamics parameters such as peripheral B cell reduce in number and release of cytokine, collectively describes the chimpanzees studies that were studied previously were used to determine the level of dos and schedules. In the three Phase I dose escalation studies was first experienced in humans using the short term intravenous infusion where later it switched to the continuous intravenous infusion of blinatumomab. A new study was begin 2004 as a result of considering the short serum half-life of blinatumomab in human of two hours and its mechanism of action depending on a continued search and destroy mode of BiTE antibody engaged T cells based with the short term intravenous infusion experiences. The safety and the benefit or the risk profile of the continuous intravenous blinatumomab administration in the phase I trial which designated MT103 to 104 investigated over the period of 4 or 8 weeks in the NHL (Bargou et al., 2008). MT103 to 104 starting dose in the patients was lower than 0.5 μg/m2 per day and reached to the highest at the dose of 90 0.5 μg/m2 per day with MTD to the extreme. Only patients from the start with the mantle cell lymphoma and indolent were given the permission to conduct trials, as the trial after revision with certain changes that involves the additional DLBCL patients. The current updated study had been published (Goebeler et al., 2016).

Indolent patients in NHL encourage further investigation of the safety profile and the clinical activity of blinatumomab in DLBCL. Several patients were treated and with an effective results. B-ALL patients with MRD positive have poor results and as in one of the NHL clinical trials which is MT103 to 104,seen that giving per day 15 μg/m2 of blinatumomab relieve from the infiltration of B-NHL in the bone marrow. In 2008 a phase II clinical trials begin to determine the blinatumomab efficacy in the MRD positive B-lineage ALL patients (Topp, Goekbuget., 2008). Frequently the disease affecting children than in adults is ALL. Meanwhile ALL can be cured in the pediatric patients though it's not effective in the relapsed or the refectory of ALL in the children. A complete molecular response for the ALL was accomplished in a trial

conducted on 3 patients (Handgretinger et al., 2011). A phase II trial was conducted based on the adult patients experiencing MRD positive and r/r ALL in the pediatric patient. The trial was conducted on adults with ALL which began in 2010 which is the study M103 to 206. The multicentre, open label details phase II trial, with the two cycles of treatment the primary endpoint of this trial was the partial haematological recovery.

The development of the clinical studies of the blinatumomab was one of the significant decisions where the reversal of the short term intermittent intravenous infusion into the constant intravenous infusion improved the therapeutic benefit of the drug. .It not only improves safety with less adverse effects linked with the activation of the starting polyclonal of T cells, mostly the one beginning of infusion is very little. Nevertheless the blinatumomab active serum level for the whole cycle of treatment, allowing to endure the T cell activity through constant maintenance. Hence the development of the blinatumomab was operates by the promising preclinical and clinical trials, being potential for pointing out the limitations of the existing treatments, its ideal mechanism of actions and its safety and effectiveness in the patients with ALL.

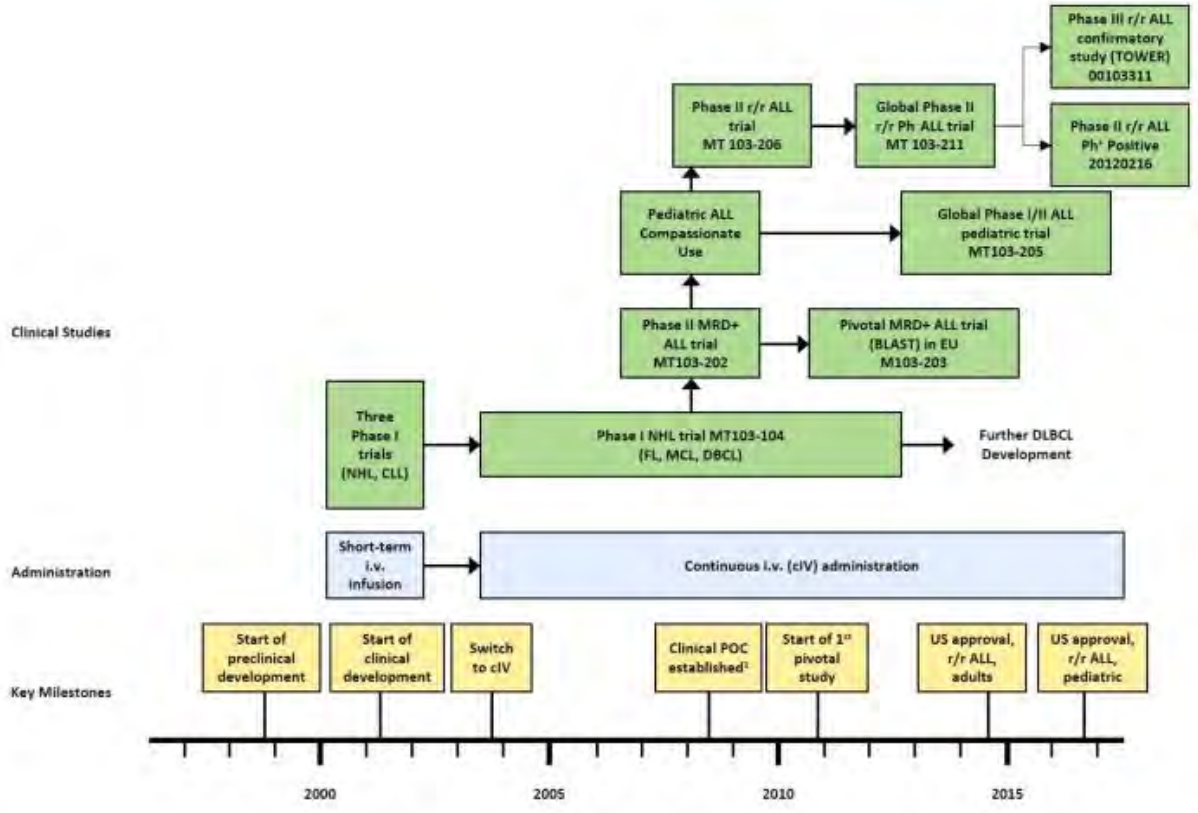

Figure 3. The overview of the clinical trials conducted for the approval of the blinatumomab (Yuraszeck et al., 2017)

2.4 Blinatumomab

2.4.1 Background

A cytotoxic immune response is induced by the blinatumomab, a bispecific T cell engaging antibody construct that was labelled BiTE, a novel immunotherapy for the relapse/refractory acute lymphoblastic leukemia (R/R ALL).Blinatumomab is small in size; it leads to apoptosis of the target cells and the polyclonal T cell proliferations as it allows it to form a strong cytolytic synapse (Nagorsen et al., 2009).The US Food and Drug Administration approved blinatumomab for the treatment of adults and children with relapsed / refractory B-ALL. Furthermore it received accelerated approval on which is a conditional on confirmatory trials, the MRD -positive B-ALL. The children ,adolescents, and young adults were tested in this trial which is one of the confirmatory trials to determine whether the chemotherapy consolidation substituted by the blinatumomab improved disease free survival after 1 cycle of standard of reinduction chemotherapy in the first relapse of B-All (Brown et al., 2021).

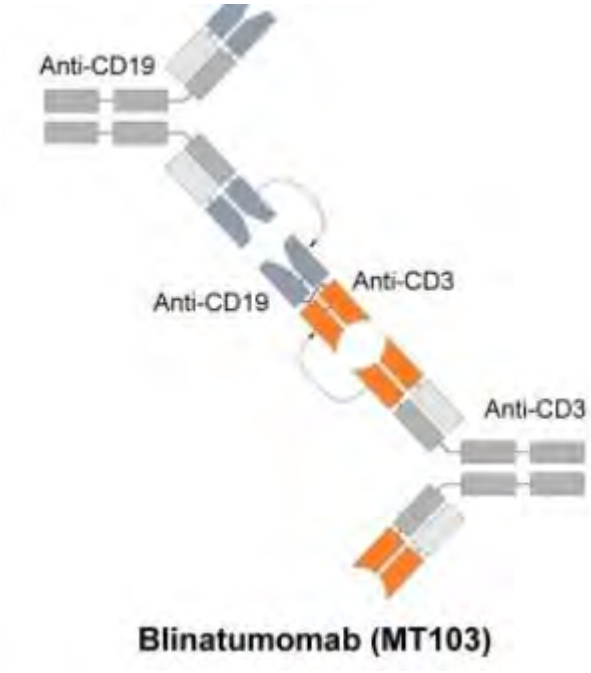

Figure 4 structure of blinatumomab (Queudeville et al., 2017)

2.4.2 Mechanism of Action

The first drug of a new class of antibody construct known as the BiTE is blinatumomab. It contains two single chain fragment variable, the fusion of variable region protein of

immunoglobulin, heavy and light chain connecting by the peptide linker made of 10-25 amino acid. The 55kDa BiTE molecule is a small molecule as compared to a complete IgG antibody of 150kDa. It is more advantageous over the monoclonal antibodies as it is constructed out of bispecific antibodies of the fast growing field, enhancing the killing of cancerous cell with the addition of CD3 where by redirecting the T-cells to the target cell (Queudeville et al,. 2017). The ability of the bispecific antibody to simultaneously bind two antigens by either enhancing the interaction specificity or blocking the two pathways. BiTE has a better penetration of tissue and is less immunogenic. The different fraction of T-cells which include regulatory T-cell and both CD8+ and CD4+ T-cells are activated by the blinatumomab, as it is constructed in such a way that one was armed with a antibody recognize CD3 on T-cell and the other is the part of the TCR complex that mediates the signalling which is constant. The T-cell is brought into close proximity with the target cell which as a result of cytolytic synapse ,the granzymes are released, T cell activation is triggered and lead to pore formation in the membrane, resulting in target cell(CD19) apoptosis. A stimulus which is strong of the T-cell engage that is independent of major histocompatibility complex (MHC) class I antigen presentation and the specificity of TCR as a result of the bivalent or multivalent binding. The serial and the direct lysis due the strong activation of the engaged T-cell. Nonetheless increased blinatumomab activity 1-2 days after onset of application led by the proliferation of the polyclonal induced by the blinatumomab (Hoffmann et al., 2005).

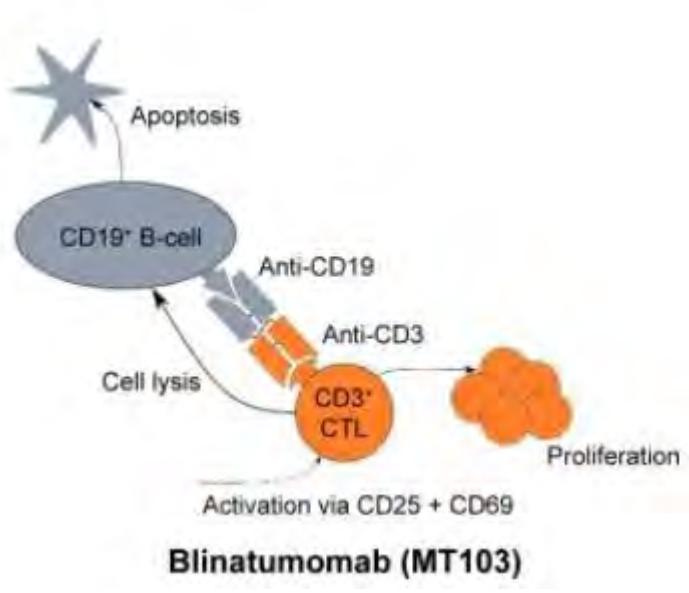

Figure 5 Mechanism action of blinatumomab (Queudeville et al., 2017)

Regardless of these optimistic outcomes, to optimize the bispecific antibodies and handle align toxicity mainly the cytokine release syndrome (CRS) remains a significant challenge. It is due to the immune system being rapidly activated and raised in the inflammatory cytokines leading to potentially severe side effects. During the treatment, careful monitoring and to ensure patients safety, supportive care are required to manage the toxicities. In addition, to adapt to the treatment more efficiently, it is required to have an understanding in depth of the disease biology due to the heterogeneity of the genetic mutation in ALL. For assisting the way for more personalized treatment approaches, new opportunities in the specific genetic alterations related to ALL are being provided by the advancement in molecular diagnostics and genomic profiling.

Chapter 3: Methodology

3.1 Study Selection

Multiple online databases were used such as PubMed, Google scholar and science direct to collect relevant clinical data and the information required for the projects. The search of the information took place around month February in 2024. The secondary data had been collected from the study that was already conducted consisting of six phase III randomized controlled trials designed with two treatment arms which are chemotherapy and blinatumomab. It involved the interventional model, the parallel assignments enabling the statistical comparisons between the two groups. As most recent trials show most data of the current state of acute lymphoblastic leukemia. The phase III clinical trial data was collected from 2017 to 2024 though some research was published in 2015 but later it was updated and published recently in 2024. Articles which were written in English were only accepted and analysed. The search strategy was based on the searching of relevant information using the databases and subheadings that had already been mentioned. Some of the terms which are searched include ‘leukemia’, ‘acute lymphoblastic leukemia’, ‘type of ALL’, ‘treatment for acute lymphoblastic leukemia’, ‘pathophysiology of ALL’ and ‘risk factor of ALL’. Only articles with the comprehensive and updated information most relevant, which include phase III clinical trials were selected from the multiple collection of articles.

3.2 Study Selection for Blinatumomab Clinical Trials

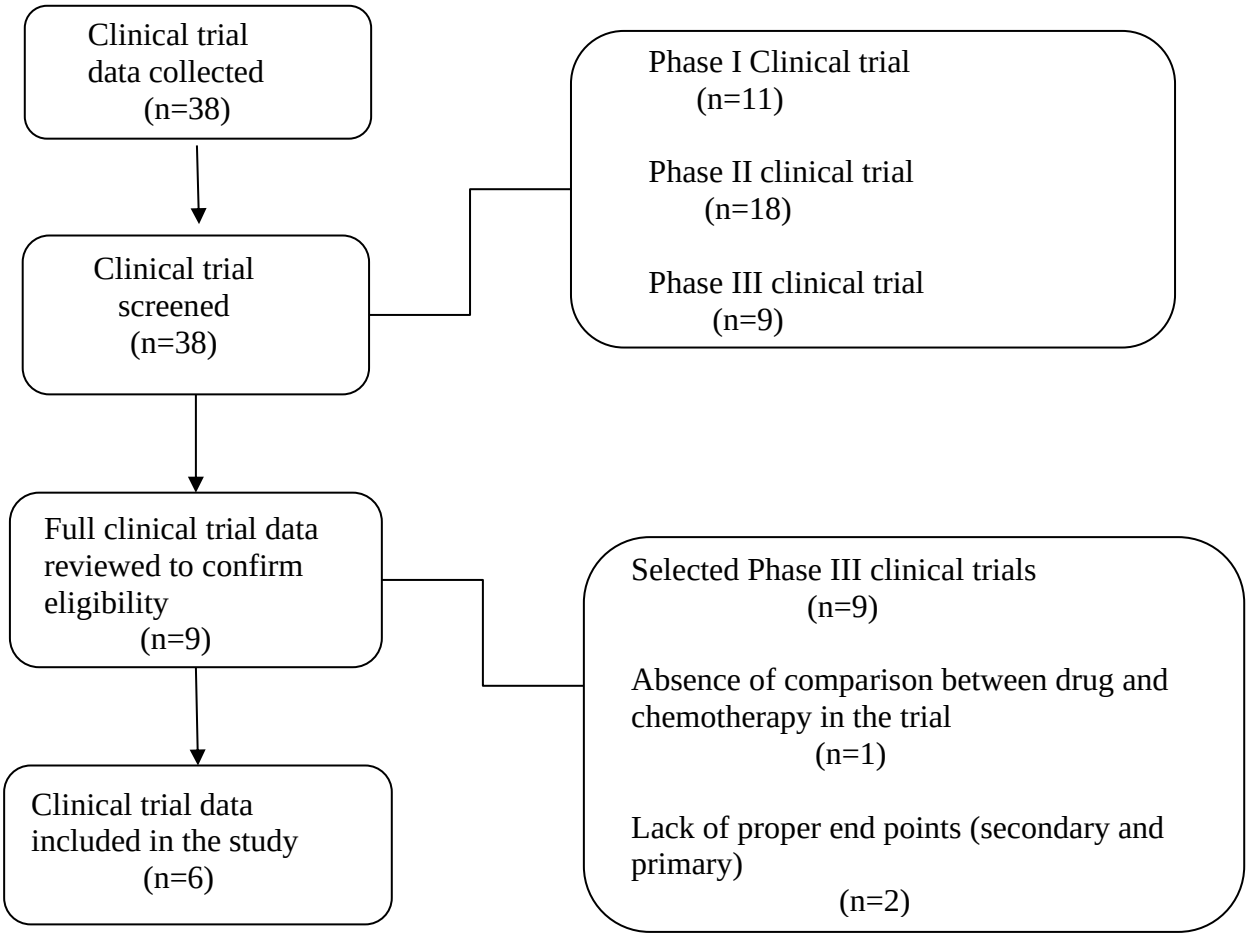

Figure 6 Search criteria for blinatumomab clinical trial data

The aim of selecting the clinical trial was to collect a minimum of six clinical trial data for the drug of interest which is blinatumomab. PubMed was used to search the term 'Blinatumomab' and screen out available clinical trial data. The search strategy has been explained in Fig 1. Six clinical trial data was chosen as it was fulfilling the eligibility criteria. Further search for the clinical trial was not needed as the number of trial data that required were met and provided necessary information needed.

3.3 Study Selection Criteria

3.3.1 Inclusion Criteria

Following are the inclusion criteria through which the clinical trial had been selected for this study:

1. Phase III clinical trial conducted for the study
2. Bispecific antibody, blinatumomab used as the intervention
3. Patients from any age group who are being treated for acute lymphoblastic leukemia.
4. Clinical data available for the evaluation of the efficacy of blinatumomab
5. Effectiveness of the drug for the acute lymphoblastic leukemia
6. Comparison of efficacy and safety of the bispecific antibody against chemotherapy.
7. Proper primary and secondary endpoints

3.3.2 Exclusion Criteria

Following are the exclusion criteria through which the clinical trials had been discarded for and were not used or had not selected for the study:

1. Use of drugs other than blinatumomab for ALL treatment. .
2. No proper primary and secondary outcomes
3. Clinical trial are of phase 1 and phase 3
4. Clinical data comparing the blinatumomab and the chemotherapy for the treatment of ALL.
5. Irrelevant information of the drugs

Chapter 4: Result and Discussion

4.1 Clinical Trial Results

Table 3. Clinical trial data of Blinatumomab

Sl. no	Disease	Patients no	Intervention	Overall survival	PFS	Other outcomes
1	Acute Lymphoblastic Leukemia	Total: 111 54	blinatumomab	Total 74 participants 91.6%	2 years: 59%	EFS of 51.9 months. Estimated 6-month for EFS 31% The median duration of remission: 4.6 months MRD negativity:80% of patients treated P-value: < 0.001
		57	Chemotherapy	25.6 months 83.3%	2 years 41%	Estimated 6-month for EFS 12% The median duration of remission: 7.3 month MRD negativity: 58% of patients
Reference: National Library of Medicine. (2024). *ClinicalTrials.gov*. https://classic.clinicaltrials.gov/ct2/show/study/NCT02393859						

Sl. no	Disease	Patients no	Intervention	Overall survival	PFS	Other outcomes
2	Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL)	Total patients: 405 134 Received treatment: 109	blinatumomab	The median OS:7.7 months	2.2 months.	Hazard Ratio: 0.71 (95% CI: 0.55 to 0.93), Complete Remission Rate: 34% 6-month EFS rate was 31.1% (95% CI: 24.4% to 38.0%) AE of all is greater than grade II (87%) CRS greater than grade II (13/267) 5% Greater than the grade II, neurotoxicity (25/267) 9%
		271 Received treatment: 267	Chemotherapy	The median OS:4.0 months	1.8 months	Complete remission rate of 16%. AE All is greater than grade II (92%) CRS greater than II(0/109) Neurotoxicity greater than II(9/109) 8% 6-month EFS rate was 12.5% (95% CI: 8.2% to 17.8%)

Reference:

National Library of Medicine. (2021). *Blinatumomab Versus Standard of Care Chemotherapy in Patients With Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL).* https://clinicaltrials.gov/ct2/show/NCT02013167

Sl.no	Disease	Patients no	Intervention	Overall survival	PFS	Other outcomes
3	relapse of B-cell acute lymphoblastic leukemia	total:208 patients 105	blinatumomab	Total: 78 The 2-year OS was approximately 71.3%	24-months	2 year DFS 54% I. Number (95%Confidence Interval) = 54.44 (44.30 to 63.51) for (HR and IR Blinatumomab) II. Number (95% Confidence Interval) = 71.33(61.34 to 79.17) for (HR and IR Blinatumomab) III. Rates of notable serious adverse events: Infection (15%), febrile neutropenia (5%), sepsis (2%), and mucositis (1%)
		103	Chemotherapy	The 2-year OS was approximately 58.4%	24 months	2 year DFS 39% With febrile neutropenia (58%), 65% Infection, 27 %sepsis, and 28% mucositis

Reference:

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. (2021). National Library of Medicine. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7926290/

Sl. no	Disease	Patients no	Intervention	Overall survival	PFS	Other outcomes
4	Ph-negative relapsed or refractory ALL	total:405 271	blinatumomab	Total 74 participants 91.6%	6-month estimate of 31%	I.7.3 month the Remission median durations. II. 34 % with full hematologic with complete remission. Significance level (P-value): <0.001 III. Complete remission with full, partial, or incomplete hematologic recovery:44% Significance level (P-value): <0.001 IV. AE of grade 3 or more : 87% of patients had been reported.
		134	Chemotherapy	4 month	6-month estimate of 12%	I. Complete remission with full hematologic recovery: 16% II. Complete remission with full, partial, or incomplete hematologic recovery: 25% III. Significance level (P-value): <0.001 IV. Adverse events of grade 3 or higher: Reported in 92% of patients

Reference:

Kantarjian, H. M., Stein, A. S.Gokbuget,N.,Fielding,A.K.,Schuh,A.C., Ribera, J., Wei, A. H., Dombret, H.,Foa,R., Bassan, R., Arslan, O., Sanz, M. A., Bergeron, J., Demırkan, F., Lech-Maranda, E., Rambaldi, A., Thomas, X., Horst, H., Bruggemann, M.,Topp, M. S. (2017).Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *New England Journal of Medicine/the New England Journal of Medicine*, *376*(9), 836–847. https://doi.org/10.1056/nejmoa1609783

Sl. no	Disease	Patients no	Intervention	Overall survival	PFS	Other outcomes
5	relapsed or refractory (R/R) ALL	206 65 patients treated with blinatumomab +HSCT	blinatumomab	10.1 months	11.7 months	I. Median overall survival(OS): 7.7 months II. Proportion of patients achieving complete remission (CR), CRh, or CRi:44% III. Effect of CR, CRh, or CRi: Reduced the risk of death by 77% (HR: 0.23; 95% CI: 0.16-0.34; P < 0.0001) V. Effect of On-Study HSCT: Risk of death lowered by 55% (HR: 0.45; 95% CI: 0.24-0.84; P = 0.012)
		102 32 treated with SOC +HSCT	Chemotherapy	5.9 months	11.8 months, SOC groups.	I. Median overall survival(OS):4.0 months (95% CI, 2.8-5.3 months) II. Proportion of patients achieving complete remission (CR), CRh, or CRi:25% III. Effect of CR, CRh, or CRi: Risk of death lowered by 66% (HR: 0.34; 95% CI: 0.19-0.60; P equals 0.0002). Reduced the risk of death by 46%, (HR: 0.54; 95% CI: 0.26-1.09; P = 0.086) SOC chemotherapy

Reference:

Jabber, E. J., Gokbuget, N., Kantarjian, H. M., Thomas, X., Larson, R. A., Yoon, S., Ghobadi, A., Topp, M. S., Tran, Q., Franklin, J. L., Forman, S. J., & Stein, A. S. (2019b). Transplantation in adults with relapsed/refractory acute lymphoblastic leukemia who are treated with blinatumomab from a phase 3 study. https://doi.org/10.1002/cncr.32335

Sl.no	Disease	Patients no	Intervention	Overall survival	PFS	Other outcomes
6	Relapsed or refractory (R/R) ALL	Total:108 patients 54	blinatumomab	Total: 84 8 death (14.8%)	16.8 month	I.Events (relapses or disease progression):17/54 patients (31.5%) II.The median follow-up time for OS: 19.5 months, ranging (0.1 to 44.1 months). III.MRD remission observed: (90% [44/49] IV.Percentage of patients experiencing relapse:24.1% (13/54) V.Percentage of patients with adverse events of grade 3 or higher:57.4% (31/54)
		54	Chemotherapy	16 death (29.6%)	5.6 months	I.Events (relapses or disease progression): 31/54 patients (57.4%) II.24-Month Kaplan-Meier Estimate: 7.1% (95% CI, 13.2%-43.0%) III.MRD remission observed: 54% [26/48 IV.Percentage of patients experiencing relapse:53.7% (29/54) V.Percentage of patients with AE grade 3 or greater :82.4% (42/51)

Reference:

Locatelli, F., Zugmaier, G., Rizzari, C., Morris, J., Gruhn, B., Klingebiel, T., Parasole, R., Linderkamp, C., Flotho, C., Petit, A., Micalizzi, C., Mergen, N., Mohammad, A., Kormany, W., Eckert, C., Moricke, A., Sartor, M., Hrusak, O., Peters, C., Von Stackelberg, A. (2021). Effect of Blinatumomab vs. Chemotherapy on Event-Free Survival Among Children With High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia. *JAMA*, *325*(9), 843. https://doi.org/10.1001/jama.2021.0987

4.2 Overview

The compilation of research, which consists of six research articles clearly focused on the Phase 3 clinical trial, consistently emphasizes and compares the effectiveness and the safeness of blinatumomab, a bispecific antibody (T-cell engager) to SOC chemotherapy in the patients with ALL. To provide a bigger picture of the related clinical trials and peer reviewed articles, providing a comprehensive information about the blinatumomab being the better option in term of the treating the Acute Lymphoblastic Leukemia(R/R B-Cell) comparing each of the findings and data collections of each clinical trials. The findings conclude that the Blinatumomab induces a high rate of complete remission (CR) in the patient population both young children and adults with manageable safety profile and less side effects.

4.3 Discussion of Clinical Trial Results

A phase III clinical trial was conducted (clinical trials.gov ID.NCT02393859) conducted on 111 participants with includes 58 females and 53 male participants were analysing. Here assessed an aggressive malignant disease B-precursor ALL with a notable 91.6% overall response rate with blinatumomab as compared with the chemotherapy which is 83.3% of the participants. Moreover a progression-free survival of2 years 2 years (59%) and 4-year (74.0%) in contrast PFS of 2 years (41%) and 4 years (51.8%) PFS in patients treated with chemotherapy (ClinicalTrials.gov, n.d.). These findings clearly highlight the potential of blinatumomab as a promising therapeutic approach or treatment for patients with ALL. Furthermore, Response: Blinatumomab demonstrated a remarkable effect on minimal Residual Disease (MRD) with a MRD negativity was achieved in 80% of patients treated with blinatumomab, whereas only 58% of patients in the standard chemotherapy group achieved MRD negativity.

According to the TOWER Study, blinatumomab exhibits an overall survival of 7.7 months with some serious adverse events on the way which includes cytokine release syndrome, headache, pyrexia cytokine release syndrome and infections. In Contrast, standard of care (SOC) chemotherapy with an overall survival of 4 months, experiencing higher rate of hematologic toxicities such as anaemia (42.20%),thrombocytopenia (29.36%) and neutropenia(28.44%).Including 33.25% of adverse events which included infections and infestations were observed and recorded (clinicalTrial.gov,2024).

A phase III clinical trial (NCT02101853) highlights that blinatumomab did not remarkably enhance the disease-free survival in contrast to chemotherapy followed by hematopoietic stem cell transplant in high- and intermediate-risk B-ALL relapse among children, adolescents, and young adults but its use was supported by favourable outcomes in MRD negativity and adverse event profiles. 208 patients were included in the primary analysis set whereas initially planned instead of the 220, so for the primary endpoint, the trial was underpowered for disease-free survival. Based on the overall survival and other secondary endpoints favouring blinatumomab that result in the early termination of randomization, indicating a potential survival benefit. Future trials may refine treatment strategies based on MRD status and consider age-specific toxicity profiles in young adults (Brown et al., 2021).

Early treatment failure patients after the reinduction chemotherapy with at least 25% marrow blasts were not eligible for randomization neither the less blinatumomab was eligible to receive up to 2 cycles of treatment of blinatumomab. The success rate in the salvage setting was low, based on the experiences of the 22 patients who had early treatment failure and were not randomly assigned to receive blinatumomab therapy. This result corroborates the results of other research that showed a high percentage of bone marrow blasts as a risk factor for blinatumomab resistance. One essential component of blinatumomab, leukemia-fighting potential is that it activates T-cells to specifically target and destroy CD19-positive B-cells. Research on immunotherapy and clinical trials have provided ample documentation of this mechanism.

Contrary to the previously discussed trials, this is a phase 3 trial which was conducted (ClinicalTrials.gov number,NCT02013167)on 405 patients randomly assigned with 272 patients treated with blinatumomab and 134 patients treated with chemotherapy. The study published in the New England Journal of Medicine, which reported that the bispecific antibody (blinatumomab) significantly results in improved overall survival, that of chemotherapy with an 3.7months of median duration of survival and the death risk of 29%. Also within the 12 weeks of treatment, blinatumomab (33.6%) have a higher rate of complete remission as compared to chemotherapy which is 15.7%. Furthermore the single agent immunotherapy with blinatumomab of the randomized trial manifests a consequential benefit of survival in adults with Ph-negative relapsed or refractory ALL as compared with chemotherapy.

Significantly the quality of life and the global health scores improved in that analysis of the blinatumomab as compared to the chemotherapy, it gets worse. The hazard ratio for deterioration in a time-to-event analysis of 0.67 (95% CI, 0.52 to 0.87) in chemotherapy whereas in favour of the blinatumomab, hazard ratios ranged from 0.59 to 0.80 for other quality-of-life outcomes , 95% confidence intervals with upper boundaries that were less than 1.0 across all subscales and single items except for insomnia (95% CI, 0.62 to 1.02) (Kantarjian et al,.2017).Complete remission with full, partial or incomplete hematologic recovery and with the full recovery, the rate of complete remission being comparatively better than that of the chemotherapy. Some adverse events of interest such as cytokine release syndrome and neurologic events were identified. The activity of an immune-based therapy like blinatumomab, which depends on functional T cells for its activity, gives hope that responses may be further enhanced and made durable with additional immune activation strategies given the patients' prior exposure to myelosuppressive and immunosuppressive treatments (Kantarjian et al., 2017).

The similarities between the two groups in terms of the grade 3 rate of the neurologic events. Furthermore from the interim analysis data and the results its proven blinatumomab benefits the overall survival as compared with the chemotherapy and trial being ended or stopped by the monitoring committee of independent data and safety, earlier than expected as noted by Kantarjian et al.(2017).

Another phase III trial was conducted on the 405 patients with R/R Philadelphia chromosome (Ph)–negative B-cell precursor ALL. During the study 97 patients underwent HSCT and the baseline characteristics that is normally compared with the same type of donor between the 65 patients treated with blinatumomab and the 32 patients treated with the chemotherapy. Superior overall survival and morphology with superior rate of molecular response are associated with blinatumomab as compared with the SOC in patients R/R ALL. The current study data from the phase 3 TOWER study to better understand the survival benefit of blinatumomab followed by HSCT because, historically, HSCT has been the goal for cure in patients with the R/R ALL. In comparison to the no HSCT which is found to be associated with longer survival in the blinatumomab and SOC groups using a simon-Makuch day 70 landmark analysis. All the

patients who underwent on-study HSCT were included in this analysis, the responders and the responders to treatment (Jabbour et al., 2019).

The last clinical trial of blinatumomab in the study of phase III trial with an enrolment of 108 patients from which 54 patients were treated with blinatumomab and 54 patients were treated with chemotherapy. Children with high risk first relapse B-cell ALL in the randomized clinical trial, before allogeneic hematopoietic stem cell transplantation the consolidation block, when patients are treated with 1 cycle of blinatumomab as compared to the consolidation chemotherapy have significantly improved and better EFS with low possibility of recurrence of leukemia. Before allogeneic hematopoietic stem cell transplant, it display that less residual disease remission enhancing the post-transplant outcomes in childhood ALL. This finding provides a rationale for evaluating the role of blinatumomab in children with chemotherapy-sensitive leukemia, including newly diagnosed or low-risk first-relapse B-ALL (Locatelli et al., 2021). The induction chemotherapy is commonly associated with the experience and appearance of toxicities that might be fatal or reduce the likelihood of proceeding to allogeneic hematopoietic stem cell transplant for multidrug chemotherapy. With that for the multiple relapse or refractory childhood B-cell shows promising results by the CD19 CAR T-Cell therapy though there are some serious adverse effects but blinatumomab overshadow with its effective and safety profiles, being readily available.

This finding reported by Locatelli et al. (2021) gives a reasonable explanation for the role of blinatumomab in children with chemotherapy-sensitive leukemia, including recently recognized or low-chance first-relapse B-ALL. As the third consolidation is blocked earlier to the allogeneic hematopoietic stem cell transplant, blinatumomab come across being a better or more effective which seems to be better than the chemotherapy for the patients experiencing early relapse within 18 months from the diagnosis with a challenging subset of patients with a poor prognosis. Furthermore, blinatumomab does not appear to be affected by the high risk of genetic abnormalities and its toxicity profile was consistent with limited leukemia burbren patients. As in this study, treatment with blinatumomab led to more favourable and improve overall survival, fewer severe toxicities, and a higher chance of undergoing an allogeneic hematopoietic stem cell transplant and after the first cycle of blinatumomab, minimal residual disease clearance was seen.

In summary, the collective evidence from these studies positions blinatumomab as a more effective and safer option than SOC chemotherapy for treating patients with ALL. Furthermore, it is a useful treatment option for both adults and children as it not only shows a better safety profile but also improves overall survival and progression-free survival. Blinatumomab is preferred over the conventional chemotherapy mainly due to its manageable safety profile and ability to achieve higher rates of complete remission, especially MRD negativity.

4.4 Limitations

- Limited clinical trial data were available for the drug. Among those that are available there are mostly phase 3 and 2 clinical trial data but the participant count is very low for any phase 2 clinical trial data that is available.
- In some of the clinical trials available, It was difficult to find the proper primary and secondary endpoint of the clinical trials.
- Proper statistical analysis could not be conducted. A proper analysis with adequate data would ensure the reliability of results.
- ALL is a complex disease with various subtypes where each having different characteristics. Finding trials for the same type of cancer with the same baseline characteristic is not always possible.
- Multiple trials with the identical endpoints cannot be found. This makes it difficult to directly compare different clinical trial data and make an analysis on their effectiveness.
- Some trials lack the randomization of the trial and comparator arms.

Chapter 5: Future Aspects

Regardless of the understanding of the cancer biology in depth and with the development in the technologies to improve cancer immunotherapy bispecific antibodies hold the possibility to improve the cancer immunotherapy. Though the future for the treatment of ALL by the bispecific is optimistic, it needs constant research and development to get control of the present challenges such as the risk factors and certain adverse event experiences and limited clinical trials data available. Bispecific could develop and enhance the strategies of treatment in a broad range of patients (Wei et al., 2022).

Cooperating the blinatumomab with other modalities of treatments, such as chemotherapy, tyrosine kinase inhibitors (TKIs), and addition with immunotherapies resulting in a major area of research of the combination therapies. Moreover the therapy, improving the overall efficacy and overcoming the resistance related to the treatment. To lower the incidence and the severity of the adverse effects such as neurotoxicity and CRS, the investigators would look forward to exploring the ways to optimize the dosage regimens and the measures to be taken care of. The use of the blinatumomab in the pediatric might be further studied where it might give fewer alternatives of toxicities contrasts to the traditional chemotherapy particularly in the cases of relapse and refractory (Von Stackelberg et al., 2016). For using the blinatumomab as the first line of therapy the researchers are doing clinical trials on the early patients who are diagnosed where by enhancing the results when used first in the treatment regimen. Focusing on understanding and overcoming resistance of the blinatumomab mechanism which include the CD19 expression loss and tumor escape strategies (Klinger et al., 2012).

To lower the toxicities and relapse in progress research will develop new treatments for a promising future. Personalized treatment regimens, collaborative decision-making, and care objectives are prioritized in order to achieve better results. The diagnoses which are done early have a greater chance of overall survival and the patients who survive have a greater probability of the DFY. to conclude the advancement to increase and improve the number of overall survival and the disease free years further on than the recent or the current five year standard with not many complications (Ekpa Q L.,2023).

Chapter 6: Conclusion

The systematic analysis for the ALL treatment using blinatumomab involves six clinical trials of phase III showing optimistic results. A bispecific antibody, blinatumomab exhibits greater benefits over the standard chemotherapy. Despite some limitations in the available data and the designs of the trial, blinatumomab shows promising options for the therapeutic effect in ALL. It provides potential advancement in the result and enhances the standard of life of the patients, specifically with it lowers the hematologic toxicities linked with the chemotherapy. In terms of accomplishing the negative MRD and complete remission, blinatumomab favours these activities over a variety of the pollution of patients. More over its focus on improving the progression free survival and over survival, particularly in the case of the relapsed or refractory ALL patients in comparison to the chemotherapy.

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