Chapman University

Chapman University Digital Commons

Pharmaceutical Sciences (MS) Theses

Dissertations and Theses

Summer 8-2021

Cost-Effectiveness Analysis of Tisagenlecleucel, Blinatumomab, and Clofarabine for Treatment of B-cell Precursor Acute Lymphoblastic Leukemia

Kamron Lotfi

Chapman University, klotfi@chapman.edu

Follow this and additional works at: https://digitalcommons.chapman.edu/pharmaceutical_sciences_theses

Part of the [Health Services Research Commons](#), [Other Pharmacy and Pharmaceutical Sciences Commons](#), [Patient Safety Commons](#), [Pharmacoeconomics and Pharmaceutical Economics Commons](#), and the [Pharmacy Administration, Policy and Regulation Commons](#)

Recommended Citation

Lotfi, K. *Cost-Effectiveness Analysis of Tisagenlecleucel, Blinatumomab, and Clofarabine for Treatment of B-cell Precursor Acute Lymphoblastic Leukemia*. [master's thesis]. Irvine, CA: Chapman University; 2021. <https://doi.org/10.36837/chapman.000294>

This Thesis is brought to you for free and open access by the Dissertations and Theses at Chapman University Digital Commons. It has been accepted for inclusion in Pharmaceutical Sciences (MS) Theses by an authorized administrator of Chapman University Digital Commons. For more information, please contact laughtin@chapman.edu.

Cost-Effectiveness Analysis of Tisagenlecleucel, Blinatumomab, and
Clofarabine for Treatment of B-cell Precursor Acute Lymphoblastic
Leukemia

A Thesis by

Kamron Lotfi

Chapman University

Irvine, CA

School of Pharmacy

Harry and Diane Rinker Health Science

Submitted in partial fulfillment of the requirements for the degree of

Master of Science in Pharmaceutical Science

August 2021

Committee in charge:

Enrique Seoane-Vazquez, Ph.D.; Chair

Rosa Rodriguez-Monguio, M.S, Ph.D.

Lawrence M. Brown, Pharm.D., Ph.D.; FAPhA

The thesis of Kamron Lotfi is approved.

Enrique Seoane-Vazquez, Ph.D.; Chair

Rosa Rodriguez-Monguio, M.S, Ph.D.

Lawrence M. Brown, Pharm.D., Ph.D.; FAPhA

June 2021

Cost-Effectiveness Analysis of Tisagenlecleucel, Blinatumomab, and Clofarabine for Treatment
of B-cell Precursor Acute Lymphoblastic

Copyright © 2021

by Kamron Lotfi

ABSTRACT

Cost-Effectiveness Analysis of Tisagenlecleucel, Blinatumomab, and Clofarabine for Treatment of B-cell Precursor Acute Lymphoblastic Leukemia

by Kamron Lotfi

Introduction

Acute lymphoblastic leukemia (ALL) is a common type of adolescent and young adult leukemia in the United States (U.S.). Patients who are refractory or relapsed after receiving two or more lines of systemic therapy have the option of taking tisagenlecleucel. Due to the high cost of this treatment, a cost-effectiveness analysis was performed to assess the treatments for tisagenlecleucel, clofarabine combination, and blinatumomab.

Objectives

The objective of this study is to evaluate the cost-effectiveness of tisagenlecleucel; clofarabine, etoposide, cyclophosphamide; and blinatumomab for the treatment of relapse-refractory ALL for adolescents and young adults from the U.S. health care payer perspective.

Material and Methods

Clinical data were collected from the FDA databases, RedBook online, National Institutes of Health (NIH) research database, PubMed database, and clinicaltrials.gov. The cost information was extracted from the Redbook and published studies. The cost-effective analysis was performed using TreeAge Pro (Healthcare Version) version 2021.

Results

The incremental cost of tisagenlecleucel was \$520,050 compared to blinatumomab. The base case showed tisagenlecleucel effectiveness was the highest at 19.284, and blinatumomab effectiveness was 12.580. Tisagenlecleucel had an ICER of \$77,573. The probability sensitivity

analysis showed that tisagenlecleucel was 63.1% of the time, and clofarabine combination was dominated by tisagenlecleucel and blinatumomab.

Conclusions

Tisagenlecleucel and blinatumomab dominated the clofarabine combination. According to the results of the sensitivity analysis, tisagenlecleucel was more cost-effective 63.1% of the time. Blinatumomab was more cost-effective at a lower WTP and 35.8% of the time.

TABLE OF CONTENTS

ABSTRACT	IV
LIST OF ABBREVIATIONS	IX
1. INTRODUCTION	1
2. OBJECTIVES	4
3. HYPOTHESIS	5
4. MATERIAL AND METHODS	6
4.1. Data Sources	6
4.2. Methods.....	6
4.3. Partitioned Survival Model	6
4.4. Treatment Strategies	8
4.5. Outcomes	12
4.6. Adverse Events	13
4.7. Costs.....	14
5. RESULTS	17
5.1. Patient Characteristics.....	17
5.2. Outcomes	20
5.3. Cost-Effectiveness and Incremental Cost-Effectiveness	23
5.4. Probabilistic Sensitivity Analysis	25
6. DISCUSSION	29
7. LIMITATIONS	30
8. CONCLUSIONS	31
REFERENCES	32

LIST OF TABLES

Table 1. Tisagenlecleucel, blinatumomab, and clofarabine FDA-Approved Indications.....	9
Table 2. Treatment dosages for tisagenlecleucel, blinatumomab, and clofarabine	10
Table 3. Treatment timeline of tisagenlecleucel	10
Table 4. Treatment timeline for blinatumomab	11
Table 5. Treatment timeline for clofarabine combination	11
Table 6. Cost and probabilities per patient for all treatment strategies	13
Table 7. Tisagenlecleucel healthcare costs	14
Table 8. Clofarabine combination healthcare costs	14
Table 9. Blinatumomab healthcare costs	15
Table 10. Cost of palliative chemotherapy for relapsed/refractory patients	15
Table 11. Cost of individual grade 3-4 adverse events for each treatment strategy	15
Table 12. Patient population of tisagenlecleucel clinical trial data (ELIANA).....	17
Table 13. Patient population of blinatumomab clinical trials	18
Table 14. Patient population of clofarabine with etoposide and cyclophosphamide clinical trials.....	19
Table 15. Incremental cost, incremental effectiveness, ICER for tisagenlecleucel, blinatumomab and clofarabine combination.....	24

LIST OF FIGURES

Figure 1. States of the partitioned survival model	7
Figure 2. Tisagenlecleucel overall patient survival	20
Figure 3. Blinatumomab overall patient survival	21
Figure 4. Clofarabine overall patient survival.....	21
Figure 5. Partitioned survival model curve of tisagenlecleucel.	22
Figure 6. Partitioned survival model curve of blinatumomab.	22
Figure 7. Partitioned survival model curve of clofarabine combination.	23
Figure 8. Cost-effectiveness analysis results for all treatments.	24
Figure 9. One-way cost-effectiveness sensitivity analysis of tisagenlecleucel.....	26
Figure 10. One-way cost-effectiveness sensitivity analysis of blinatumomab	26
Figure 11. Monte Carlo acceptability at WTP of 100,000 for all treatment alternatives.....	27
Figure 12. Cost-effectiveness acceptability curve of tisagenlecleucel, blinatumomab, and clofarabine.....	27
Figure 13. Monte Carlo probability distribution INMB of tisagenlecleucel vs. blinatumomab	28

LIST OF ABBREVIATIONS

ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AWP	Average wholesale price
CAR	Chimeric antigen receptor
CER	Comparative effectiveness research
CMS	Centers for Medicare & Medicaid Services
CPI	Consumer price index
DLBCL	Diffuse large B cell lymphoma
HSCT	Hematopoietic stem cell transplant
IC	Incremental cost
ICER	Incremental cost-effectiveness ratio
INMB	Incremental net monetary benefit
IVIG	Intravenous immunoglobulin
LYS	Life years saved
NHL	Non-Hodgkin lymphoma
NIH	National Institutes of Health
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life years
RR ALL	Relapsed-refractory acute lymphoblastic leukemia
RR DLBCL	Relapsed-refractory diffuse large B cell lymphoma
WAC	Weighted average cost
WTP	Willingness to pay

1. INTRODUCTION

In the past decade, breakthroughs in cancer drug research of the human immune system resulted in the development of a new category of cancer drugs called immunotherapy. There are different types of immunotherapy cancer treatments, including immune checkpoint inhibitors, T-cell transfer therapy, monoclonal antibodies, treatment vaccines, and immune system modulators.^{1,2} Immunotherapy drugs are enhanced to target specific checkpoints in the immune system and the body's defense systems to tackle the most challenging oncology diseases.^{3,4} However, the advancement of immunotherapy still has significant obstacles, including the need for biomarkers, deficiencies of clinical design to assess safety and efficacy, the incapability to predict the response of treatment for individual patients, and high cost.^{5,6} The cost of cancer immunotherapy is \$100,000 or more per patient, roughly two times the United States median household annual income.^{7,8} Even though immunotherapy is often covered by health insurance, it can still be unaffordable to patients due to high out-of-pocket costs.

Non-Hodgkin lymphoma (NHL) starts inside white blood cells called lymphocytes that can grow in areas of the immune system, such as the lymph nodes.⁹ NHL accounts for an estimate of 3% for cancer-related deaths and is the seventh leading cause of new cancer cases in the United States.¹⁰ In 2020, there were 74,200 diagnosed NHL cases and 19,970 deaths from this disease.¹¹

Acute lymphoblastic leukemia (ALL) is one of the most common types of cancer in the white blood cells by overproducing immature lymphocytes in the bone marrow diagnosed in the pediatric population.¹² Children who have ALL have a high number of lymphoblasts/lymphocytes. When this occurs, the number of cancerous cells outnumber the

number of white blood cells. ALL is a B-cell lymphoma disease that occurs from somatic genetic alterations, which include chromosome number change/rearrangement.¹³ Symptoms of ALL are anemia, bruising, bleeding, and fatigue. ALL is the most common cancer in children and young adults, with around 54.3% of new cases under 20.¹⁴ ALL accounts for around 20% of pediatric cancer for children.¹⁵ ALL occurs mainly in children, representing 80% of cases; however, adults can be susceptible to this disease with a low cure rate of 40%.²⁶ According to the National Cancer Institute, there were over 6,100 new cases of ALL and 1,500 deaths in 2020 in the US.¹⁷

Treatment can bring 95% complete remission of patients, and since 1948, there has been a significant 80% increase in survival rate in children.^{18,19} However, the survival rate can drastically decrease on patients who do not respond to initial chemotherapy treatment.

Adolescent or young adults with standard-risk ALL often receive three drugs for the first month of treatment as first-line therapy. Patients with standard-risk ALL would typically receive the chemotherapy drugs L-asparaginase and vincristine and the steroid drug dexamethasone.^{20,21} Treatment will vary according to the cancer risk. Patients who are relapsed or refractory need to use a second-line therapy that consists of chemotherapies such as blinatumomab and clofarabine combination (etoposide and cyclophosphamide).²² Patients who are refractory or relapsed after receiving two or more lines of systemic therapy can use tisagenlecleucel that is considered the last treatment option.

Tisagenlecleucel is indicated for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.^{23,24} Tisagenlecleucel was also approved for relapsed or refractory acute

lymphoblastic leukemia and for treating pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL).^{25,26} Tisagenlecleucel is given as a single dose with a wholesale acquisition cost (WAC) of \$475,000.²⁷ Despite the high cost of new ALL treatments, studies assessing their cost-effectiveness are lacking.

Cost-effective analysis of tisagenlecleucel compared to other salvage chemotherapy treatments for relapsed-refractory ALL has not been published. Due to the limitation of clinical trials and the high cost of CAR T-cell therapies, questions have been raised on their economic and clinical value in clinical practice.²⁸

2. OBJECTIVES

The objective of this study is to evaluate the cost-effectiveness of tisagenlecleucel; clofarabine, etoposide, cyclophosphamide; and blinatumomab for the treatment of relapse-refractory ALL for adolescent and young adult patients from the U.S. health care payer perspective.

3. HYPOTHESIS

We hypothesize that tisagenlecleucel is the most cost-effective alternative for treating RR-ALL for adolescent and young adult patients.

4. MATERIALS AND METHODS

4.1. Data Sources

Clinical data were collected from the FDA databases, RedBook online, National Institutes of Health (NIH) research database, PubMed database, and ClinicalTrials.gov.^{29,30} ClinicalTrials.gov is managed by the United States National Library of Medicine and the National Institutes of Health. ClinicalTrials.gov includes information from over 200 countries, with more than 329,000 trials to date.³¹

Tisagenlecleucel and salvage chemotherapy treatment AWP and WAC data were collected from the RedBook online. The information in the RedBook includes the name of the product, active ingredient, brand or generic status, price start date, orange book code, formulation, route of administration, dosage unit, average wholesale price (AWP), and wholesale acquisition cost (WAC).³² Drug manufacturers report the AWP and the WAC. These prices do not represent the actual net acquisition cost paid in the U.S. but are used for pharmacy reimbursement purposes. Other cost information was collected from previously published studies.

4.2 Methods

4.3 Partitioned Survival Model

A cost-effectiveness model using the U.S. health care payer's perspective was constructed by using TreeAge Pro (Healthcare Version) version 2021 software. The partitioned survival model (Figure 1) will consist of a cohort for specific states: remission, refractory or relapsed, and death based on overall survival.

Figure 1. States of the partitioned survival model

The partitioned survival model baseline assumptions are that patients had a previous history of chemotherapy and enter the model at ten years of age. The primary study outcome was the number of life-years gained over the study time horizon. The incremental life-years gained were estimated as the difference in life-years gained between the therapeutic alternatives.

The study includes direct healthcare costs related to the alternatives. Indirect costs were excluded from the analysis. All costs were adjusted to 2020 U.S. dollars using all urban consumers, not seasonally adjusted, U.S. city average, all items, consumer price index (CPI). Costs and outcomes were discounted at a 3% annual discount rate.

The cost and life-years gained over the time horizon were estimated for each treatment. A cost-effectiveness ratio (CER) was employed to calculate the cost per life-year gained for each treatment alternative. The lowest cost per life-year treatment was considered as the reference therapy. When a treatment had a greater cost and effectiveness in relation to the reference, an incremental cost-effectiveness ratio was performed to determine the additional cost to obtain one life-year.

The impact of parameter uncertainty was explored by a one-way sensitivity analysis on each model parameter. A probabilistic sensitivity analysis was conducted to investigate the combined impact of uncertainty of the variables included in the analysis. Random values were drawn from the chosen distributions as a second-order Monte-Carlo simulation of 1000 patients to estimate the mean and 95% confidential intervals (CI) of overall survival probabilities. All parameters in the model will have correspondingly appropriate distributions. Costs were randomly drawn from a gamma distribution; the hazard ratio was randomly sampled from a lognormal distribution. Likewise, binominal data, such as adverse events, were randomly drawn from a beta distribution.

4.4. Treatment Strategies

The FDA approved three products approved by the FDA for the treatment of ALL in pediatric patients (Table 1).

Table 1. Tisagenlecleucel, blinatumomab, and clofarabine FDA-Approved Indications

Generic Name (Approval Date)	Pediatric ALL Indications
Tisagenlecleucel (August 30, 2017)	Indicated for the treatment of Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL) patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.
Blinatumomab (September 1, 2016)	Indicated for the treatment of relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.
Clofarabine (December 12, 2004)	Indicated for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. This indication is based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with clofarabine injection.

The treatment dosages for tisagenlecleucel, blinatumomab, and clofarabine are described in Table 2.

Tisagenlecleucel Treatment Process

To prepare tisagenlecleucel, the patient undergoes leukapheresis to obtain peripheral blood mononuclear cells. Leukapheresis treatment lasts 3 to 6 hours, and within 24 hours, the blood cells are cryopreserved (Table 3).³² Ex vivo preparation is next conducted for tisagenlecleucel with autologous T cells. The autologous T cells are transduced to activate T cells by a lentiviral vector. The process of preparing tisagenlecleucel takes approximately 45 days, and during this time, patients undergo bridging therapy to stop disease progression.³² Lymphodepleting chemotherapy is received by patients two weeks before the infusion of tisagenlecleucel so the patient can help the proliferation of tisagenlecleucel throughout the body.

Table 2. Treatment dosages for tisagenlecleucel, blinatumomab, and clofarabine

Name	Therapy	Source
Tisagenlecleucel	3.1x10 ⁶ /kg (0.2-5.4 x 10 ⁶ /kg) transfused viable T cells.	Maude et al. (2018)
Bridging chemotherapy (Given to 87% of patients prior to CART)	Methotrexate (15mg I.T. x1); Hydrocortisone (15mg I.T. x1) and cytarabine (30mg I.T. weekly until CSF clears) Cytarabine (300mg/ m ² IV x 1) and etoposide (150mg/ m ² IV x 2) peg asparaginase (25000 units/ m ² IV x 1)	Lin et al. (2018)
Lympho-depleting chemotherapy (given to 96% of patients prior to CART)	Fludarabine (30mg/ m ² IV x 4), Cyclophosphamide (500mg/ m ² IV x 2)	Maude et al. (2018)
Lympho-depleting chemotherapy (given to 4% of patients prior to CART)	Cytarabine (500mg/ m ² IV x 2) and etoposide (150mg/m ² IV x 3)	Maude et al. (2018)
Blinatumomab	5ug/m ² /d x 7 days, then 15ug / m ² / d	Stackelberg et al. (2016)
Clofarabine Combination	clofarabine (400mg/ m ² IV x 9days), etoposide (100mg / m ² IV X 9 days), cyclophosphamide (440mg / m ² x 9 days)	Hijiya et al. (2009)

Table 3. Treatment timeline of tisagenlecleucel

Treatment	Dosage
<u>Bridging chemotherapy</u> Days 1-2	Methotrexate (15mg I.T. x1); Hydrocortisone (15mg I.T. x1) and cytarabine (30mg I.T. weekly until CSF clears); Cytarabine (300mg/ m ² IV x 1) and etoposide (150mg/m ² IV x 2) peg asparaginase (25000 units/ m ² IV x 1)
<u>Lymphodepleting chemotherapy</u> Days 3-17	Fludarabine (30mg/ m ² IV x 4), Cyclophosphamide(500mg/ m ² IV x 2)
<u>Tisagenlecleucel</u> Day 20	3.1x10 ⁶ /kg (0.2-5.4 x 10 ⁶ /kg) transfused viable T cells.

Blinatumomab and Clofarabine combination

Patients who receive blinatumomab and clofarabine and are in remission also receive post-induction chemotherapy after one year to continue to be in remission (Tables 4 and 5).

Table 4. Treatment timeline for blinatumomab

Cycle	Dosage
<u>Introduction Cycle 1</u> Days 1-7 Days 8-28 Days 29-42	5ug/m ² /d/day 15ug/m ² /d/day 14-day treatment-free interval
<u>Induction Cycle 2</u> Days 1-28 Days 29-42	15ug/m ² /d/day 14-day treatment-free interval
<u>Consolidation Cycles 3-5</u> Days 1-28 Days 29-42	15ug/m ² /d/day 14-day treatment-free interval
<u>Continued Cycles 6-9</u> Days 1-28 Days 19-84	15ug/m ² /d/day 56-day treatment-free interval

Table 5. Treatment timeline for clofarabine combination

Cycle	Dosage
<u>Cycle 1</u> (9 consecutive days)	clofarabine (400mg/ m ² IV x 9days), etoposide (100mg / m ² IV X 9 days), cyclophosphamide (440mg / m ² x 9 days)
<u>Cycle 2</u> (9 consecutive days)	clofarabine (400mg/ m ² IV x 9days), etoposide (100mg / m ² IV X 9 days), cyclophosphamide (440mg / m ² x 9 days)

4.5 Outcomes

Survival data were derived from three clinical trial sources Hijiya et al. (2009), Lin et al. (2018), Stackelberg et al. (2016), a study assessing the survival of ALL patients in the 10-14 years old range and survival for the general population³³.

Tisagenlecleucel overall survival, continued remission, and event-free survival were obtained from Maude et al. (2018). There were two sets of data used for tisagenlecleucel:

- **Efficacy analysis set:** Includes patients that used the drug and excludes patients that were enrolled in the study but did not qualify for getting the drug because of death, changes in health status that resulted in exclusion, or problems manufacturing the drug.
- **Enrolled set:** includes all the patients enrolled in the clinical trial.

Blinatumomab clinical trial overall survival, continued remission, and event-free survival were obtained from Stackelberg et al. (2016). Clofarabine combination clinical trial overall survival curve, continued remission, and event-free survival were obtained from Hijiya et al. (2009).

Kaplan-Meier curves were created for the probability of overall survival, continued remission, and event-free survival for tisagenlecleucel, blinatumomab, and clofarabine. Kaplan-Meier curves were created because the estimates of survival data can deal with differing survival times since not all patients continue throughout the whole study. Also, Kaplan-Meier curves give a "time to an event" at the respective time interval.

4.6 Adverse Events

The probability and cost of adverse events were collected from the literature (Table 6).

Table 6. Cost and probabilities per patient for all treatment strategies.^{12,14,24}

Cost and Probabilities	Tisagenlecleucel Probabilities of Adverse Events	Blinatumomab Probabilities of Adverse Events	Clofarabine Probabilities of Adverse Events	Cost of Patient
Acute Kidney Injury	0.08	0	0.16	\$682.03
ALT or AST Increased	0.1	0.16	0.4	\$1,544.79
Anemia	0.4	0.36	0.64	\$4,526.60
Coagulopathy	0	0	0.12	\$296.53
Cytokine Release Syndrome	0.46	0.06	0	\$9,043.81
Decreased Appetite	0.09	0	0.2	\$445.90
Febrile Neutropenia	0.35	0.17	0.6	\$7,273.80
Fluid Overload	0.05	0	0	\$30.02
Gingival Bleeding	0	0	0.12	\$154.67
Hepatomegaly	0	0	0	\$0
Hyperbilirubinemia	0.11	0	0.12	\$209.23
Hypertension	0	0.06	0	\$41.16
Hypokalemia	0.08	0.17	0.36	\$1,322.66
Hypophosphatemia	0.08	0	0.12	\$306.26
Hypotension	0.17	0	0.24	\$818.76
Hypoxia	0.11	0	0	\$98.97
Increased Lipase	0	0	0.2	\$275.98
Leukopenia	0.12	0.1	0.16	\$286.82
Nausea	0	0	0.12	\$111.64
Neutropenia	0.04	0.17	0.52	\$4,279.79
Overall Neurological Events	0.13	0.04	0	\$323.20
Pleural Effusion	0.04	0	0	\$51.27
Pulmonary Edema	0.06	0	0.12	\$192.22
Pyrexia	0.1	0.14	0.16	\$260.28
Rash	0	0	0	\$0
Respiratory Distress	0.04	0.01	0	\$13.34
Thrombocytopenia	0.05	0.21	0.64	\$4,416.20
Typhils	0	0	0.12	\$60.01
Veno Occlusive Disease	0	0	0.12	\$259.44

4.7 Costs

Costs were acquired from the Red Book, Centers for Medicare and Medicaid Services, and adjusted to 2020 dollars by the consumer price index (CPI). The direct medical costs include drug administration, drug product, follow-up care, and adverse events (Tables 7-11).

Table 7. Tisagenlecleucel healthcare costs

Pre-tisagenlecleucel		Cost	Source
Bridging chemotherapy	Drug and administration at the hospital	\$15,000.00	Lin et al. (2018)
Lymphodepleting chemotherapy (fludarabine and cyclophosphamide) 96% patients	Drug and administration at hospital	\$1,781.49	CMS (2018)
Lymphodepleting chemotherapy (cytarabine and etoposide) 4% of patients	Drug and administration at the hospital	\$807.78	CMS (2018)
Treatment cost	Drug	\$475,000.00	Red Book (2021)
	Adverse events	\$42,769.98	CMS (2018)
	IVIG treatment	\$28,818.24	Red Book (2018); Lin et al. (2018)
	Drug Administration at hospital	\$6,331.28	CMS (2018); Lin et al.(2018)
	Health care costs after treatment per month	\$8,056.01	
Total Cost		\$578,564.78	

Table 8. Clofarabine combination healthcare costs

		Cost	Source
Treatment Cost	Drug	\$37,400.00	Lin et al. (2018)
	Adverse events	\$54,252.52	Lin et al. (2018); CMS (2018)
	Administration at hospital	\$24,342.68	Lin et al. (2018)
	Health care costs after treatment per month	\$1,964.88	Lin et al. (2018)
Total Cost		\$117,960.08	

Table 9. Blinatumomab healthcare costs.

		Cost	Source
Treatment Cost	Drug	\$43,700.00	Lin et al. (2018)
	Adverse events	\$16,919.80	Lin et al. (2018); CMS (2018)
	Administration at hospital	\$8,187.00	Lin et al. (2018)
Total Cost		\$68,806.80	

Table 10. Cost of palliative chemotherapy for relapsed/refractory patients.

		Cost	Source
Palliative Chemotherapy	Drug	\$2,881.82	Lin et al.

Table 11. Cost of individual grade 3-4 adverse events for each treatment strategy.

Adverse Event	Tisagenlecleucel Cost	Blinatumomab Cost	Clofarabine Cost
Acute Kidney Injury	\$1,706.04	\$0	\$3,412.08
ALT or AST Increased	\$790.21	\$1,264.33	\$3,160.84
Anemia	\$2,591.02	\$2,331.92	\$4,145.63
Coagulopathy	\$0	\$0	\$2,472.47
Cytokine Release Syndrome	\$19,342.28	\$2,522.91	\$0
Decreased Appetite	\$834.78	\$0	\$1,855.07
Febrile Neutropenia	\$4,980.92	\$2,419.30	\$8,538.71
Fluid Overload	\$600.65	\$0	\$0
Gingival Bleeding	\$0	\$0	\$1,289.62
Hepatomegaly	\$0	\$0	\$0
Hyperbilirubinemia	\$868.99	\$0	\$947.99
Hypertension	\$0	\$686.40	\$0
Hypokalemia	\$642.04	\$1,364.33	\$2,889.16
Hypophosphatemia	\$1,178.58	\$0	\$1,767.87
Hypotension	\$1,610.02	\$0	\$2,272.97
Hypoxia	\$900.21	\$0	\$0
Increased Lipase	\$0	\$0	\$1,380.66
Leukopenia	\$688.76	\$573.96	\$918.34

Table 11. Cost of individual grade 3-4 adverse events for each treatment strategy (Cont.)

Nausea	\$0	\$0	\$930.83
Neutropenia	\$569.25	\$2,419.30	\$7,400.22
Overall Neurological Events	\$2,272.37	\$699.19	\$0
Pleural Effusion	\$1,282.46	\$0	\$0
Pulmonary Edema	\$641.07	\$0	\$1,282.15
Pyrexia	\$471.79	\$660.51	\$754.86
Rash	\$0	\$0	\$0
Respiratory Distress	\$313.94	\$78.49	\$0
Thrombocytopenia	\$484.29	\$2,034.01	\$6,198.89
Typhils	\$0	\$0	\$500.39
Veno Occlusive Disease	\$0	\$0	\$2,163.20
TOTAL	\$42,769.66	\$17,054.65	\$54,281.95

5. RESULTS

5.1 Patient Characteristics

The patient characteristics varied according to the clinical trial. Tisagenlecleucel patients were between 3 to 21 years of age (Table 12). There were 47% females and 53% males in the clinical trial. There were 92 patients enrolled in the study, and 75 underwent infusion

Table 12. Patient population of tisagenlecleucel clinical trial data (ELIANA).¹²

Patient Population tisagenlecleucel	Efficacy Analysis Set (n=107)	Enrolled Set (n=92)	Underwent Infusion (n=75)
0-45 days before receiving tisagenlecleucel			
Dropout/Censored	-	10 (11)	-
Death	-	7 (8)	-
After receiving tisagenlecleucel			
Dropout/Censored	-	-	16 (21)
Death	-	-	11 (15)
Age, years			
3 to 21	107 (100)	92 (100)	75 (100)
Sex			
Female	-	-	35 (47)
Male	-	-	40 (53)
Status			
Relapse/Refractory	-	-	9 (12)
Remission	-	-	61 (81)
Prior HSCT	-	-	46 (61)

Table 13. Patient population of blinatumomab clinical trials (n=70). ²⁴

Variable	n (%)
Sex	
Male	47 (67)
Female	25(33)
Age group, years	
<2	10 (14)
2 to 6	20 (29)
7 to 17	40 (57)
Previous HSCT	
Yes	40 (57)
No	30 (43)
Previous Relapses	
0	2 (3)
1	31 (44)
2	29 (41)
≥ 3	8 (11)
Status	
Relapse/Refractory	39 (56)
Remission	27 (39)
Dropout/Censored	16 (23)
Death	27 (39)

Blinatumomab patient age range was less than 2 years to 17 years (Table 13). The patient population of blinatumomab was 67% male and 33% female, with 70 total patients enrolled.

Clofarabine combination patients were between 1 year to 21 years of age (Table 14). The patient population was 64% male and 36% female, with 25 patients enrolled.

Table 14. Patient population of clofarabine with etoposide and cyclophosphamide clinical trials (N=25).¹²

Characteristic	n (%)
Age (years)	
Median	14
Range	1 to 21
Sex	
Male	16 (64)
Female	9 (36)
Prior regimens	
Median	2
Range	1 to 3
1 regimen	4 (16)
2 regimen	14 (56)
3 regimen	15 (60)
Status	
Relapse/Refractory	15 (60)
Remission	7 (28)
Prior HSCT	4 (16)
Dropout/Censored	2 (8)
Death	7 (28)

5.2 Outcomes

Tisagenlecleucel Kaplan-Meier plot (Figure 2) 95% confidence interval at month 26 was 0.421[0.203, 0.626]. Blinatumomab Kaplan-Meier plot (Figure 3) 95% confidence interval at month 26 was 0.246[0.146, 0.359]. Clofarabine combination (Figure 4) 95% confidence interval at month 36 was 0.211[0.0533, 0.439]. The partitioned model survival curves are displayed in figures 5-7.

Figure 2. Tisagenlecleucel overall patient survival.¹²

Figure 3. Blinatumomab overall patient survival.²⁴

Figure 4. Clofarabine overall patient survival.¹²

Figure 5. Partitioned survival model curve of tisagenlecleucel.

Figure 6. Partitioned survival model curve of blinatumomab.

Figure 7. Partitioned survival model curve of clofarabine combination.

5.3. Cost-Effectiveness and Incremental Cost-Effectiveness

In the base case scenario, tisagenlecleucel effectiveness was 19.284 years, blinatumomab was 12.580 years, and clofarabine combination was 7.566 years. Blinatumomab and tisagenlecleucel were both undominated, and the clofarabine combination was dominated (Table 15).

A partitioned survival analysis model followed the patient cohort through time as they moved through relapsed/refractory or remission states for tisagenlecleucel, blinatumomab, and clofarabine combination. The cost-effectiveness analysis showed that clofarabine was not cost-effective (Figure 8).

Table 15. Incremental cost, incremental effectiveness, ICER for tisagenlecleucel, blinatumomab, and clofarabine combination

Drugs	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	ICER
Excluding Dominated					
Blinatumomab	\$71,701		12.580		
Tisagenlecleucel	\$591,751	\$520,050	19.284	6.704	\$77,573
All Therapies					
Blinatumomab	\$71,701		12.580		
Clofarabine	\$139,225	\$67,524	7.566	-5.014	-\$13,467
Tisagenlecleucel	\$591,751	\$520,050	19.284	6.704	\$77,573

Figure 8. Cost-effectiveness analysis results for all treatments.

5.4 Probabilistic Sensitivity Analysis

The PSA was conducted using the 95% confidence intervals for the overall survival and remission for all treatments. Clofarabine was dominated while tisagenlecleucel and blinatumomab remained the strategy with the higher cost and effectiveness. The PSA found that tisagenlecleucel was more cost-effective 63.1% and blinatumomab 35.8% of the time.

The PSA results found that tisagenlecleucel and blinatumomab were both undominated, and clofarabine combination was dominated. The PSA found that tisagenlecleucel was cost-effective 63.1% of the time with a willingness to pay \$100,000. Even though tisagenlecleucel was more cost-effective, blinatumomab was more cost-effective 35.8% of the time (Figure 9-12).

The Monte Carlo acceptability at the WTP of 100,000 showed that tisagenlecleucel was more cost-effective 63.1% of the time when compared to blinatumomab (35.8%) and clofarabine (1.9%) (Figure 13). According to the cost-effectiveness acceptability curve for the WTP, tisagenlecleucel was more favorable at a WTP higher than \$80,000. The blinatumomab WTP was more favorable below a WTP of 80,000, and clofarabine was not favorable under any WTP.

Figure 9. One-way cost-effectiveness sensitivity analysis of tisagenlecleucel

Figure 10. One-way cost-effectiveness sensitivity analysis of blinatumomab

Figure 11. Monte Carlo acceptability at WTP of 100,000 for all treatment alternatives

Figure 12. Cost-effectiveness acceptability curve of tisagenlecleucel, blinatumomab, and clofarabine.

Figure 13. Monte Carlo probability distribution INMB of tisagenlecleucel vs. blinatumomab.

6. DISCUSSION

Our analysis indicates that tisagenlecleucel has higher overall survival than blinatumomab and clofarabine combination in patients with ALL.

This study presented that the effectiveness for tisagenlecleucel was 19.284 and had an ICER of \$77,573 for an additional L.Y. gained. Blinatumomab had an effectiveness of 12.580, and the dominated treatment clofarabine had an effectiveness of 7.566. Tisagenlecleucel had the highest cost in the partitioned survival model, with \$591,751 and an ICER of \$77,573.

Tisagenlecleucel and blinatumomab were both undominated, and the clofarabine combination was dominated for the base case analysis. The probabilistic sensitivity analysis confirmed that tisagenlecleucel and blinatumomab were undominated, and the clofarabine combination was dominated.

According to the probabilistic sensitivity analysis, tisagenlecleucel was the most cost-effective alternatives 63.1% of the time. These results are similar to those of other studies that also found that tisagenlecleucel was more cost-effective the majority of the time (Furzer et al., 2020). Clofarabine was dominated by tisagenlecleucel and blinatumomab and was the least cost-effective as found in previously published studies (Locatelli et al, 2009).

The available evidence about the cost, efficacy, and safety of tisagenlecleucel, blinatumomab and clofarabine is very limited. There is a need for more studies evaluating the long-term effect of the available therapies for the treatment of ALL to get the evidence necessary for the appropriate utilization of those expensive drugs.

7. LIMITATIONS

This study has some limitations. The model evaluates differences of alternative therapy pathways from a set of assumptions and does not portray the progression of RR-ALL patients in clinical practice. Patients can develop RR-ALL during their lifetime. The available data only contains outcomes for up to 34 months. Since the clinical trials are still ongoing, other clinical information on outcomes and safety was collected from published studies from the United States and other countries. The clinical trials used in this study had different disease states, previous treatments, and patient demographic characteristics. The difference is significant for age because survival rates decline with the increase in age.³⁰

The patient characteristics included in this study were different for the clinical trials of the products tisagenlecleucel, blinatumomab, and clofarabine. The clinical trials for blinatumomab and clofarabine included patients less than 2 years of age, unlike while the clinical trials for tisagenlecleucel included patients starting at 3 years of age. The disease states of the patients included in the clinical trials were also different, with tisagenlecleucel clinical trials having a higher percentage of patients in remission at the start of the study (Table 14). Non-health care and indirect costs were excluded from the analysis. The life years were not adjusted by the quality of life (quality-adjusted life years) due to the limitations of the clinical trials and lack of information about the quality of life.

8. CONCLUSIONS

The base case showed that tisagenlecleucel effectiveness was the highest at 19.284, and blinatumomab was the second-highest at 12.580. Tisagenlecleucel was cost-effective with an ICER of \$77,573. Clofarabine was dominated and was the worst out of the three treatment strategies for cost-effectiveness. The results of the PSA showed that tisagenlecleucel was always not the most cost-effective. Blinatumomab was more cost-effective when it was 35.8% higher than the base case. Tisagenlecleucel was more cost-effective at a higher WTP, and blinatumomab was more cost-effective at a lower WTP. Tisagenlecleucel was more cost-effective 63.1% of the time, and blinatumomab was more cost-effective 35.8% of the time.

7. REFERENCES

1. Carlson L, Ho P, Smith M, et al: Pediatric phase I drug tolerance: A review and comparison of recent adult and pediatric phase I trials. *J Pediatric Hematology Oncology* 1996;18:250-256, 1996
2. Lin, J., Lerman, B., Barnes, J., Boursiquot, B., Tan, Y., Robinson, A., Goldhaber-Fiebert, J. Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Relapsed or Refractory Pediatric B-Cell Acute Lymphoblastic Leukemia. *J. Clin. Oncol* 2018;10;36(32):3192-3202.
3. National Cancer Institute. Acute Lymphocytic Leukemia - Cancer Stat Facts. Available at: <https://seer.cancer.gov/statfacts/html/aly1.html> (Accessed January 8, 2021).
4. Locatelli F, Testi AM, Bernardo ME, et al. clofarabine, cyclophosphamide and etoposide as single-course reinduction therapy for children with refractory/multiple relapsed acute lymphoblastic leukaemia. *Br J Haematol* 2009;147(3): 371-378.
5. Abramson JS, Palomba ML, Gordon LI, et al. C.R. rates in relapsed/refractory (R/R) aggressive B-NHL treated with the CD19- directed CAR T-cell product JCAR017 (TRANSCEND NHL 001) [abstract]. *J Clin Oncol* 2017;35: Suppl 15: 7513.
6. Awasthi R, Mueller KT, Yanik GA, et al Considerations for tisagenlecleucel dosing rationale [abstract]. *J Clin Oncol* 2018;36(15 suppl):e15056.
7. Awasthi R, Pacaud L, Waldron E, et al. Tisagenlecleucel cellular kinetics, dose, and immunogenicity in relation to clinical factors in relapsed/refractory DLBCL. *Blood Adv* 2020;4(3):560-572.

8. Centers for Medicare & Medicaid Services. Available at:
<https://www.cms.gov/Regulations-and-Guidance/Administrative-Simplification/Code-Sets> (Accessed March 1, 2021).
9. Cheson B, Vena D, Foss F, et al: Neurotoxicity of purine analogs: A review. *J Clin Oncol* 1994;12:2216- 2228.
10. Gardner RA, Finney O, Annesley C, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. *Blood* 2017; 129:3322-31.
11. Hirschfeld S, Ho P, Smith M, et al: Regulatory approvals of pediatric oncology drugs: Previous experience and new initiatives. *J Clin Oncol* 2003;21:1066-1073.
12. Hijiya, N., Gaynon, P., Barry, E., Silverman, L., Thomson, B., Chu, R., Carroll, W. A multi-center phase I study of clofarabine, etoposide and cyclophosphamide in combination in pediatric patients with refractory or relapsed acute leukemia. *Leukemia* 2009;23, 2259–2264.
13. Cordo V, Meijerink J. T-cell Acute Lymphoblastic Leukemia: A Roadmap to Targeted Therapies. *Blood Cancer Discov* 2001;2: 19–31.
14. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med* 2018;378(5):439-448.
15. Mueller KT, Waldron E, Grupp SA, et al. Clinical pharmacology of tisagenlecleucel in B-cell acute lymphoblastic leukemia. *Clin Cancer Res* 2018; 24(24):6175-6184.
16. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. *N Engl J Med* 2015;373 (16): 1541–52.

17. Milone MC, Fish JD, Carpenito C, et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. *Mol Ther* 2009;17(8):1453-1464.
18. Lee DW, Stetler-Stevenson M, Yuan CM, et al. safety and response of incorporating CD19 chimeric antigen receptor T cell therapy in typical salvage regimens for children and young adults with acute lymphoblastic leukemia [abstract]. *Blood* 2015;126: 684.
19. Novartis. Prescribing information (Kymriah). East Hanover, NJ: Novartis Pharmaceuticals Corp., 2021.
20. IBM Micromedex – RedBook, 2021.
21. National Cancer Institute (NCI) (2018). Childhood Acute Lymphoblastic Leukemia Treatment. National Cancer Institute (NCI). Available at: <https://www.cancer.gov/types/leukemia/hp/child-all-treatment-pdq> (Accessed March 21, 2021)
22. Wheeler K, Chessells JM, Bailey CC, et al: Treatment related deaths during induction and in first remission in acute lymphoblastic leukaemia: MRC UKALL X. *Arch Dis Child* 1996;74:101-107.
23. Porter DL, Hwang WT, Frey NV, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia . *Sci Transl Med* 2015;7: 303ra139.
24. Von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *J Clin Oncol* 2016; 34:4381-9.

25. Chan K: Acute lymphoblastic leukemia. *Curr Probl Pediatr Adolesc Health Care* 2002;32:40-49.
26. Chessells J, Veys P, Kempinski H, et al: Long- term follow-up of relapsed childhood acute lymphoblastic leukaemia. *Br J Haematol* 2003;123:396-405.
27. Mansson E, Flordal E, Liliemark J, et al: Down regulation of deoxycytidine kinase in human leukemic cell lines resistant to cladribine and clofarabine and increased ribonucleotide reductase activity contributes to fludarabine resistance. *Biochem Pharmacol* 2003;65:237-247.
28. Mueller KT, Maude SL, Porter DL, et al. Cellular kinetics of CTL019 in relapsed/refractory B-cell acute lymphoblastic leukemia and chronic lymphocytic leukemia. *Blood* 2021;130(21):2317-2325.
29. Saarinen-Pihkala UM, Heilmann C, Winiarski J, et al. Pathways through relapses and deaths of children with acute lymphoblastic leukemia: role of allogeneic stem-cell transplantation in Nordic data. *J Clin Oncol* 2006;24(36):5750- 5762.
30. Turtle C.J., Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. *J Clin Invest* 2016; 126:2123-38.
31. Yamauchi T, Nowak B, Keating M, et al: DNA repair initiated in chronic lymphocytic leukemia lymphocytes by 4-hydroperoxycyclophosphamide is inhibited by fludarabine and clofarabine. *Clin Cancer Res* 2001;7:3580-3589.
32. Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1). Clinicaltrials.gov. Available at:

<https://clinicaltrials.gov/ct2/show/NCT02348216?term=Zuma-1&draw=2&rank=1>
(Accessed March 1, 2021).

33. Social Security. Actuarial Life Table, 2017. Available at:

<https://www.ssa.gov/oact/STATS/table4c6.html> (Accessed March 1, 2021).

34. Furzer J, Gupta S, Nathan PC, Schechter T, Pole JD, Krueger J, Pechlivanoglou P.

Cost-effectiveness of Tisagenlecleucel vs Standard Care in High-risk Relapsed

Pediatric Acute Lymphoblastic Leukemia in Canada. *JAMA Oncol* 2020;1;6(3):393-401.