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# TREATMENTS FOR ACUTE LYMPHOBLASTIC LEUKEMIA: A COMPARISON BETWEEN TISAGENLECLEUCEL AND CLOFARABINE

# TRATAMENTOS PARA LEUCEMIA LINFOBLÁSTICA AGUDA: UMA COMPARAÇÃO ENTRE TISAGENLECLEUCEL E CLOFARABINA

CARMONA, Rocío Guadalupe[1#]; MONTIVERO, Malena[1#]; QUATTROCCHI, Georgina[1#]; ZARELLI, Valeria[1,2]; GIAI, Constanza[1,3]; QUINTERO, Cristián Andrés[1,3,*]

[1] Facultad de Farmacia y Bioquímica. Universidad Juan Agustín Maza, Mendoza, Argentina.

[2] Laboratorio de Genética, Ambiente y Reproducción. Universidad Juan Agustín Maza, Mendoza, Argentina.

[3] Laboratorio de Biología Molecular y Celular. Universidad Juan Agustín Maza, Mendoza, Argentina.

*Corresponding author: cquintero@umaza.edu.ar

# These authors contributed equally

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## ABSTRACT

**Background:** Acute lymphoblastic leukemia (ALL) is a heterogeneous hematological malignancy predominantly affecting individuals under 20 years of age. Traditional chemotherapy, such as clofarabine, has shown efficacy; however, novel immunotherapeutic strategies like tisagenlecleucel (Kymriah®) have significantly altered the treatment paradigm. **Aim:** This study aimed to perform a comparative analysis of tisagenlecleucel, a CAR-T cell therapy, and clofarabine, a second-generation purine nucleoside analog, evaluating their mechanisms of action, therapeutic benefits, limitations, and clinical applicability across diverse patient populations. **Methods:** A systematic comparative evaluation was conducted, encompassing pharmacological characteristics, mechanisms of action, treatment protocols, efficacy, safety profiles, and clinical indications of both agents. The analysis considered pharmacokinetic and pharmacodynamic data and included patient demographic variables. **Results:** Tisagenlecleucel demonstrated high efficacy in refractory B-cell ALL, with durable responses and a blood half-life of 128 days, but with notable immune-related adverse effects such as cytokine release syndrome. Clofarabine, effective across a broader patient population, acts via multiple antitumor mechanisms but carries significant toxicity risks, including infection and sepsis. **Discussion:** The therapies present distinct clinical profiles: tisagenlecleucel offers targeted immunotherapy with high specificity but requires specialized infrastructure and management of immune toxicities. Clofarabine is more widely accessible and applicable, but is associated with conventional chemotherapy-related side effects. Treatment accessibility and cost differ markedly between the two. **Conclusions:** Therapy selection should be personalized based on patient-specific factors and institutional resources. Tisagenlecleucel is ideal for pediatric and young adult patients with relapsed/refractory B-cell ALL in CAR-T-capable centers, while clofarabine remains a viable option for broader ALL populations, particularly when genetic therapies are not feasible. Further research is needed to optimize therapeutic strategies and improve access to advanced treatments.

**Keywords**: *tisagenlecleucel, clofarabine, Acute lymphoblastic leukemia.*

## RESUMO

**Introdução:** A leucemia linfoblástica aguda (LLA) é uma neoplasia hematológica heterogênea que afeta predominantemente indivíduos com menos de 20 anos de idade. A quimioterapia tradicional, como a clofarabina, tem demonstrado eficácia; no entanto, estratégias imunoterapêuticas inovadoras como o tisagenlecleucel (Kymriah®) alteraram significativamente o paradigma de tratamento. **Objetivo:** Realizar uma análise comparativa

 
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do tisagenlecleucel, uma terapia com células CAR-T, e da clofarabina, um análogo de nucleosídeo de purina de segunda geração, avaliando seus mecanismos de ação, benefícios terapêuticos, limitações e aplicabilidade clínica em diversas populações de pacientes. **Métodos:** Foi conduzida uma avaliação comparativa sistemática, abrangendo características farmacológicas, mecanismos de ação, protocolos de tratamento, eficácia, perfis de segurança e indicações clínicas de ambos os agentes. A análise considerou dados farmacocinéticos e farmacodinâmicos e incluiu variáveis demográficas dos pacientes. **Resultados:** O tisagenlecleucel demonstrou alta eficácia na LLA de células B refratária, com respostas duradouras e meia-vida sanguínea de 128 dias, mas com efeitos adversos relacionados ao sistema imunológico notáveis, como a síndrome de liberação de citocinas. A clofarabina, eficaz em uma população de pacientes mais ampla, atua através de múltiplos mecanismos antitumorais, mas carrega riscos significativos de toxicidade, incluindo infecção e sepse. **Discussão:** As terapias apresentam perfis clínicos distintos: o tisagenlecleucel oferece imunoterapia direcionada com alta especificidade, mas requer infraestrutura especializada e manejo de toxicidades imunológicas. A clofarabina é mais amplamente acessível e aplicável, mas está associada a efeitos colaterais convencionais relacionados à quimioterapia. A acessibilidade ao tratamento e o custo diferem marcadamente entre os dois. **Conclusões:** A seleção da terapia deve ser personalizada com base em fatores específicos do paciente e recursos institucionais. O tisagenlecleucel é ideal para pacientes pediátricos e adultos jovens com LLA de células B recidivada/refratária em centros capazes de realizar terapia CAR-T, enquanto a clofarabina permanece uma opção viável para populações mais amplas de LLA, particularmente quando terapias genéticas não são viáveis. Mais pesquisas são necessárias para otimizar estratégias terapêuticas e melhorar o acesso a tratamentos avançados.

**Palavras-chave**: *tisagenlecleucel, clofarabina, leucemia linfoblástica aguda.*

## 1. INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematological malignancy characterized by the proliferation of immature lymphoid cells—specifically B-cell lymphoblasts in B-cell ALL. These malignant cells infiltrate the bone marrow, spread to the peripheral blood and other organs, disrupt normal hematopoiesis, and can lead to organ failure and death if left untreated (Agencia Española de Medicamentos y Productos Sanitarios, 2019).

Initially, clofarabine monotherapy was employed. This purine nucleoside analog interferes with DNA replication and RNA transcription in leukemic cells, thereby inhibiting their proliferation and inducing apoptosis. More recently, Kymriah® (tisagenlecleucel), a gene therapy involving genetically modified autologous T cells, has emerged as an alternative treatment.

This review compares the two therapeutic approaches in terms of their mechanisms of action, clinical advantages, and limitations, with the aim of evaluating their relative efficacy in the treatment of ALL.

## 2. METHODS

A systematic review of the literature in PubMed and Scielo was performed to search for publications describing the use tisagenlecleucel and clofarabine for the treatment of acute lymphoblastic leukemia, collecting and analyzing data. In order to do so, we used the following words/terms in combination: tisagenlecleucel AND treatments AND acute lymphoblastic leukemia. The exclusion criteria consisted of limiting papers on the use of any of those drugs from 2009 to 2023. The work was made as a task for the subject Biotecnología, belonging to the Pharmacy and Biochemistry career, and the extension and number of citations were restricted to the indication of the catherdra.

## 3. RESULTS AND DISCUSSION

### 3.1. Results

### 3.1.1Tisagenlecleucel

*3.1.1.1 Pharmacology*

Tisagenlecleucel (Kymriah®) is a gene therapy involving T cells extracted from the patient. These cells are genetically modified ex vivo using a viral vector to express chimeric antigen receptors (CAR-T), enabling the T cells to recognize and destroy cells expressing the CD19 antigen. This includes both malignant and healthy B lymphocytes (1).

*3.1.1.2 Treatment Process:*

1. T-cell extraction: Blood draw followed by leukapheresis.
2. Genetic modification: Ex vivo enhancement of immune response.

3. Reinfusion: Modified T cells are reinfused to target cancer cells.

The therapy is indicated for pediatric and young adult patients up to 25 years old with refractory B-cell ALL (Agencia Española de Medicamentos y Productos Sanitarios, 2019).

*3.1.1.3 Structure and Mechanism of Action*

CAR-T receptors are produced by transfecting T cells with a lentiviral vector. The receptor's structure includes:

- **CD3-zeta signaling domain:** Essential for T-cell activation against tumor cells.
- **CD8-α transmembrane domain** (from human receptors) and **CD137 (4-1BB) costimulatory domain:** Enhance T-cell persistence and expansion in vivo.
- **Murine-derived single-chain variable fragment (scFv):** Binds to CD19, an antigen highly expressed on B lymphocytes in ALL patients (2,3).

CD19 regulates B lymphocyte proliferation and activation, making it a critical target in B-cell ALL.

*3.1.1.4 Pharmacodynamics*

After reinfusion, modified T cells interact with CD19, releasing antitumor cytokines and signaling the targeted cell. Cytokines also promote T-cell expansion and selectivity for CD19, increasing treatment efficacy and toxicity (1,3).

*3.1.1.5 Pharmacokinetics and Metabolism*

Tisagenlecleucel is administered intravenously, with immediate availability. Post-reinfusion, cellular expansion follows a biexponential decline due to tissue distribution. The average blood half-life is 128 days, depending on dose, proliferation, and cell viability. Dosage recommendations:

- Patients ≤50 kg: 0.2–2.5 × $10^6$ or 0.1–2.5 × $10^8$ transduced T cells.
- Patients >50 kg: 1.0–2.5 × $10^8$ transduced T cells (1, 2).

*3.1.1.6 Advantages*

- Applicable to various cancers.
- Innovative therapy using modified T cells.
- High complete response rate (4, 5).

*3.1.1.7 Disadvantages*

- Adverse effects: cytokine release syndrome.
- Severe risks: exaggerated immune response leading to complications such as severe fever and cerebral edema (4, 5).

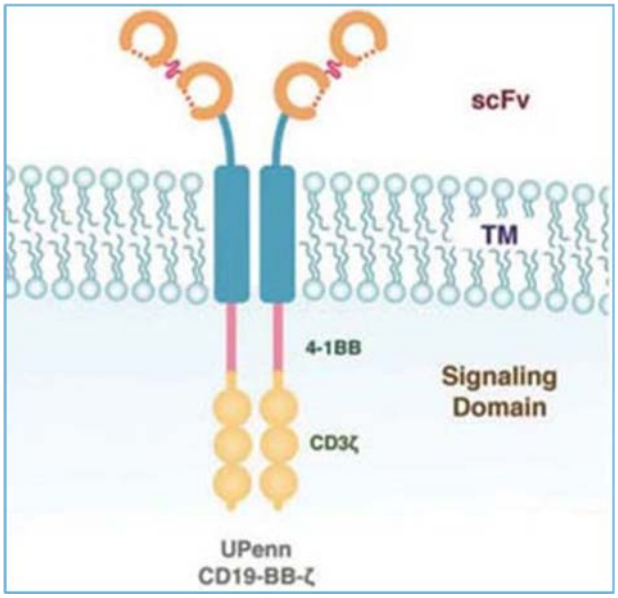


**Figure 1.** *Schematic diagram of the CAR-T receptor. Tisagenlecleucel possesses a CD137 (4-1BB) costimulatory domain (pink), a signalling CD3-zeta domain (pale orange) and a murine scFv (dark orange) in addition to spacer and transmembrane domains (light blue). Modified from (Leahy et al., 2018).*

### 3.1.2 Clofarabine

*3.1.2.1 Pharmacology*

Clofarabine is a second-generation purine nucleoside analog, designed for higher efficacy and reduced extramedullary toxicity compared to fludarabine and cladribine (Jeha et al., 2023). It is toxic to both non-dividing and rapidly proliferating lymphocytes. Clofarabine resists phosphorylation cleavage and remains stable in acidic environments (7).

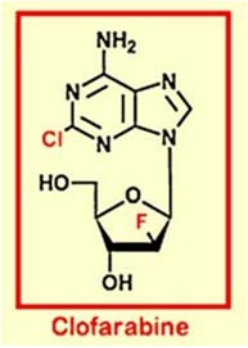


***Figure 2.*** *Molecular structure of Clofarabine: 2-chloro-2'-arabino-fluoro-2'-desoxyadenosine. Modified from (7)*

Approved by the FDA in 2004 (Clolar™) and the European Commission in 2006 (Evoltra®), clofarabine is actively investigated for other cancers and age groups. It is primarily used for pediatric ALL patients with relapsed or refractory disease after at least two prior regimens (Agencia Española de Medicamentos y Productos Sanitarios, 2023).

*3.1.2.2 Mechanism of Action*

Clofarabine is progressively phosphorylated by deoxycytidine kinase (dCK), monophosphate kinase, and diphosphate kinase to its active form, clofarabine triphosphate (clofarabineTP), which acts via three mechanisms (6-8):

1. Inhibition of DNA polymerase (α and ε): Competes with dATP, halting DNA synthesis and repair.
2. Ribonucleotide reductase inhibition: Depletes dNTP pools.
3. Mitochondrial membrane disruption: Induces apoptosis, including in non-proliferating lymphocytes.

*3.1.2.3 Pharmacokinetics*

Pharmacokinetics vary with weight. An intravenous infusion of 52 mg/m² daily for five consecutive days provides similar exposure across weights. Dosage is calculated based on actual body surface area. Treatment cycles repeat every 2–6 weeks, depending on hematopoietic recovery (RAN ≥0.75 × 10⁹/L) and baseline organ function. Dose reduction by 25% may be required for significant toxicity (8).

*3.1.2.4 Advantages*

- Effective for ALL patients.
- Can be combined with other treatments.
- Fewer severe effects compared to Kymriah® (Ramiz et al., 2023).

*3.1.2.5 Disadvantages*

- High toxicity with increased risk of severe adverse effects.
- Treatment-related infections.
- Severe sepsis with potential mortality (Ramiz et al., 2023).

### 3.2. Discussions

In this study, treatments based on Tisagenlecleucel and Clofarabine for ALL were contrasted, considering aspects such as mechanism of action, efficacy, advantages, disadvantages, and their clinical impact across diverse subgroups of patients.

Both treatments represent significant advances in the management of ALL, although they have different applications and toxicity profiles. Tisagenlecleucel has been identified as a more innovative option, but it is associated with a higher financial cost. Conversely, clofarabine has been identified as a viable alternative for cases that have relapsed. The development of accessible therapies that carry a reduced risk of complications remains a significant objective in the treatment of ALL.

## 4. CONCLUSIONS

Choosing between treatments depends on leukemia type, patient age, health status, and previous treatment response. Kymriah® is effective for B-cell ALL, while clofarabine is used for both ALL and acute myeloid leukemia. Regarding age, Kymriah® is suitable for pediatric and adult patients, while clofarabine is more commonly used in pediatric patients. Access to genetic treatments like Kymriah® is currently limited due to high costs compared to non-genetic alternatives. Finally, clofarabine is often employed in relapsed cases or when CAR-T therapy is not an option.

## 5. DECLARATIONS

### 5.1. Study Limitations

This comparative review has several limitations that should be acknowledged. The literature search was restricted to two databases (PubMed and Scielo) and publications from 2009-2023, potentially excluding relevant studies from other sources or time periods. As an academic coursework project, the scope and depth of analysis were constrained by institutional requirements regarding length and citation limits. The absence of direct head-to-head clinical trials comparing tisagenlecleucel and clofarabine necessitated indirect comparisons based on separate studies with potentially different patient populations and methodologies. Additionally, the rapidly evolving nature of CAR-T cell therapy means newer data may have emerged since the completion of this analysis. Cost-effectiveness comparisons were limited due to variable pricing across healthcare systems and the lack of comprehensive economic analyses in the available literature.


### 5.2. Acknowledgements

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### 5.4. Competing Interests

The authors declare no financial, professional, or personal conflicts of interest that could have influenced the content or conclusions of this review. All authors are affiliated solely with academic institutions and have no commercial relationships with pharmaceutical companies manufacturing the treatments discussed in this analysis.



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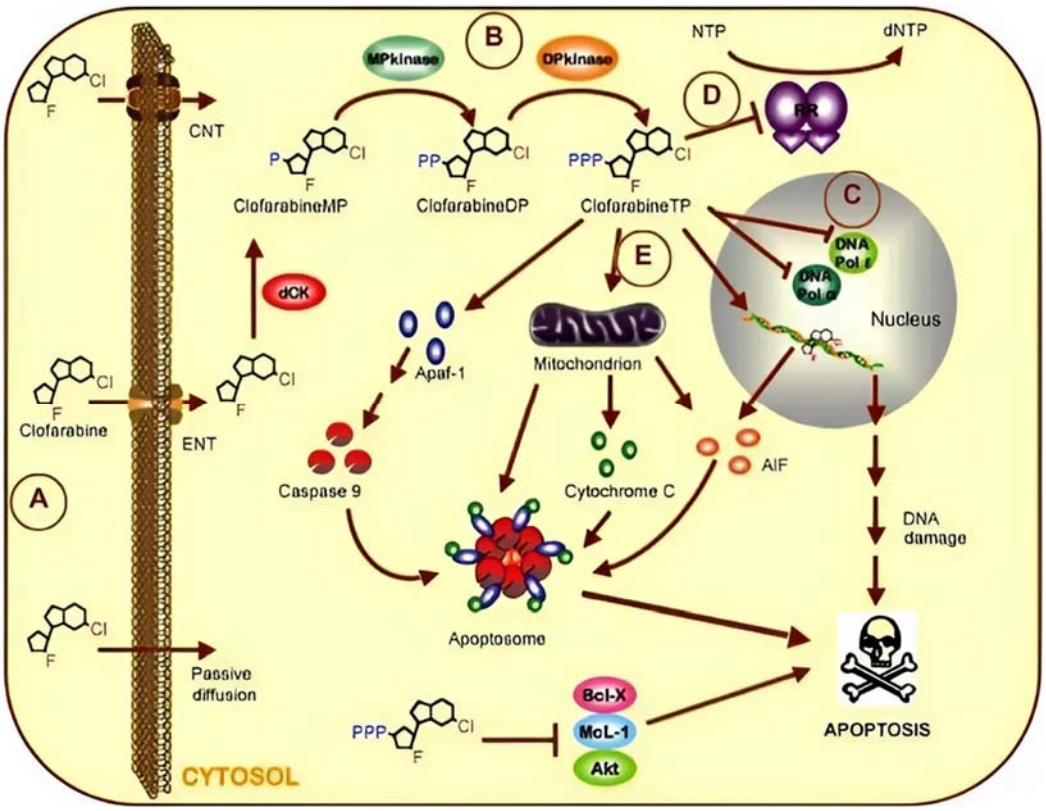


***Figure 3.*** *Mechanism of action of Clofarabine. (A) Entrance of Clofarabine to the cell through three possible pathways: active/facilitated transport by nucleoside transporters or passive diffuison. (B) Progressive phosphorylation by dCK, MPkinase, and DPkinase. (C) Inhibition of DNA polymerase (α and ε). (D) Ribonucleotide reductase inhibition. (E) Mitochondrial membrane disruption. Modified from (Zhenchuk et al., 2009).*