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Review Article

Autologous Anti-CD19 CAR T-Cells immunotherapy in relapsed/refractory acute lymphoblastic leukemia patients. A systematic review and meta-analysis

Imunoterapia de CAR T-Cells Anti-CD19 no tratamento de leucemia linfoblástica aguda refratária/recidivante. Revisão sistemática e metanálise

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ABSTRACT: *Introduction*: Acute Lymphoblastic Leukemia (ALL) is the most prevalent malignancy in children; however, when the neoplasm becomes refractory/relapses (R/R) the cure possibilities are practically null. *Objectives*: To analyze the Anti-CD19 Chimeric Antigen Receptors (CAR) T-Cells immunotherapy efficacy in the treatment of R/R ALL, providing evidence about the efficacy and safety of the therapy for the analyzed group. *Methods*: The study consisted of a systematic review and meta-analysis based on the analysis of indexed articles. The searches were carried out with the terms: "acute lymphoblastic leukemia", "CAR T", and "CD19-specific chimeric antigen receptor". *Results*: Only 18 of the 94 articles obtained initially met the inclusion criteria and were selected for review, totaling 637 patients. Thus, it was observed in the responses that approximately 81% of the patients achieved a Complete Response; 7% did not respond; the neoplasm relapsed in 17% of the cases; and 6.1% of the patients died. The main side effects found were Cytokine Release Syndrome (CRS), Severe Cytokine Release Syndrome, and Neurotoxicity, present in 36.3%, 29%, and 24% of patients, respectively. *Conclusion*: Anti-CD19 CAR T-Cells immunotherapy is an effective therapy, capable of producing high rates of complete remission in R/R ALL treatment.

Keywords: Immunotherapy; Chimeric antigen receptors; CD19 antigens; B-cell leukemia.

RESUMO: *Introdução:* A Leucemia Linfoblástica Aguda (LLA) é a neoplasia maligna mais prevalente em crianças; entretanto, quando se torna refratária/recidivante (R/R) as possibilidades de cura são praticamente nulas. *Objetivos:* Analisar a eficácia da imunoterapia de Receptores de Antígenos Quiméricos anti-CD19 no tratamento da LLA R/R, fornecendo evidências sobre a efetividade e segurança da terapia para o grupo analisado. *Métodos:* O estudo consistiu em uma revisão sistemática e metanálise baseada em artigos indexados. As pesquisas foram realizadas com os termos: "*acute lymphoblastic leukemia*", "*CAR T*", and "*CD19-specific chimeric antigen receptor*". *Resultados:* Dos 94 artigos obtidos, apenas 18 atenderam inicialmente aos critérios de inclusão e foram selecionados para revisão, totalizando 637 pacientes. Assim, observou-se nas respostas que aproximadamente 81% dos pacientes obtiveram resposta completa; 7% não responderam; a neoplasia recidivou em 17% dos casos; e 6,1% dos pacientes morreram. Os principais efeitos colaterais encontrados foram síndrome de liberação de citocinas, síndrome de liberação grave de citocinas e neurotoxicidade, presentes em 36,3%, 29% e 24% dos pacientes, respectivamente. *Conclusão:* A imunoterapia com células CAR T anti-CD19 é uma terapia eficaz, sendo capaz de produzir altas taxas de remissão completa no tratamento de LLA R / R.

Palavras-chave: Imunoterapia; Receptores de antígenos quiméricos; Antígenos CD19; Leucemia de células B.

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INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the most prevalent neoplasm in pediatrics, accounting for 26.8% of childhood cancers and 78.6% of leukemias. Although treatment based on chemotherapy protocols lead to complete remission in 80-95% of patients, when the disease becomes refractory/relapses (R/R), chances of cure are practically null[1,2].

In this scenario, autologous Anti-CD19 Chimeric Antigen Receptors (CAR) T-Cells immunotherapy has shown revolutionary success enabling a complete response achievement. Since its first application in April 2012, clinical trials have been conducted trying to incorporate this immunotherapy as an alternative to traditional treatment regimens. Despite being a well-explored topic in the literature, the present systematic review and meta-analysis accomplishes the idea of gathering current evidence in R/R ALL, quantifying autologous Anti-CD19 CAR T-Cells effectiveness and side effects rates[3,4].

METHODS

Search Strategy

The study consisted of a systematic review from original articles indexed from January 2015 to February 2021, totaling 2515 articles, without going through any filter and without removing duplicates, indexed in the PubMed, Cochrane Library, Embase, Web of Science and LILACS databases, as well as in the Grey Literature through Google Scholar, and published studies in the Journals BLOOD, NATURE, Journal of the American Medical Association (JAMA) and New England Journal of Medicine (NEJM). Searches for original articles were conducted based on English terms related to the topic. Based on PRISMA-2020 (Preferred Reporting Items for Systematic Review and Meta-analysis Protocols), articles were selected independently, subject to agreement between two or more authors[5].

Selection Criteria

The study included original articles published from 2015 to 2020 with an experimental design (clinical trials, randomized or not), as well as controlled trials and Cohort studies corresponding to the search terms pre-determined by the authors. For the selection of articles published in the journals, the terms “acute lymphoblastic leukemia”, “CAR T”, and “CD19-specific chimeric antigen receptor” were used as MeSH terms, title/abstract and text-wide free terms to optimize the findings in the databases. Articles that analyzed the efficacy of Anti-CD19 CAR-T Cells in malignant B-cell pathologies, not considering ALL, were excluded and that evaluated the efficacy of other modalities of CAR T-Cells, not corresponding to autologous Anti-CD19 CAR T-Cells. Also, observational studies with cross-sectional analysis, literature reviews, systematic reviews, and academic thesis were disregarded.

Initial Review of Studies

After selection through the title of the search results and removal of duplicates, 67 articles remained. Then, through the screening of abstracts, 35 more articles were removed, leaving 32 for full-text evaluation. The remaining studies were submitted to the eligibility criteria, which selected a total of 18 compatible articles for the extraction of data suitable for review. At each stage, articles were chosen based on the agreement between two or more authors. Disagreeing articles regarding inclusion were submitted to a discussion between two or more authors. The Flow-diagram of the literature selection process is shown in Figure 1.

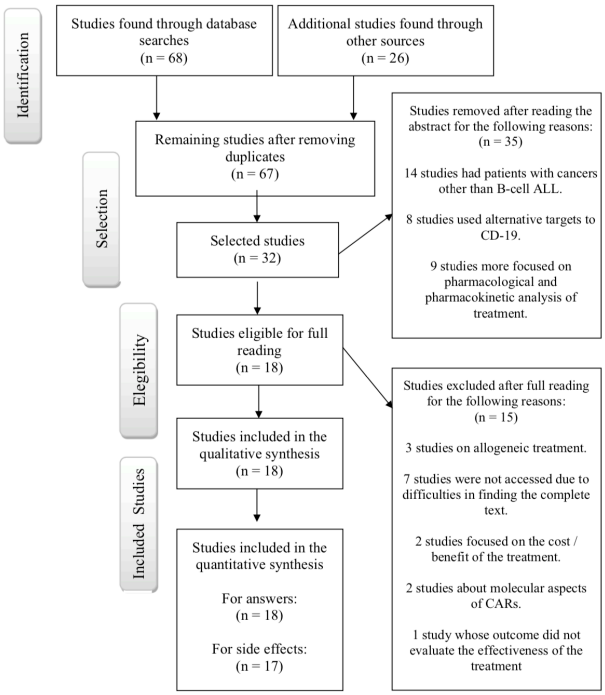


Figure 1. Flow-diagram of the literature selection process

Data Organization

Data extraction was carried out independently by two authors, and disagreements were resolved through a third author. Subsequently, the extracted data was discussed among the 7 authors for the organization of a table with the following topics: name of the author, year of publication, type of study, costimulatory domain, genetic transfer method, Time of Persistence in the organism, pre-conditioning (Lymphodepletion), dosage of CAR-T Cells administered, Responses and Side Effects.

Assessment of study quality and risk of bias

Two authors independently assessed the quality of studies (risk and bias) using the tool for assessing the quality of diagnostic accuracy studies (QUADAS-2). According to the QUADAS-2 user guidelines, some items have been modified for this study[6]. In domain 1 (patient selection), the questions "Was a consecutive or random sample of patients included?" and "Did the study avoid inappropriate exclusions?". In domain 2 (index test), the items "Were the results of the index test interpreted without knowledge of the results of the reference standard?" and "If a limit was used, was it pre-specified?" were replaced by the item "Was the method described to determine the outcome of patients after treatment administration been described?". In domain 3 (reference standard), the item "Is the reference standard suitable for classifying the target condition?". In domain 4 (flow and time), the item "Did all patients receive autologous Anti-CD19 CAR-T Cells?" was used. The QUADAS-2 Tool is shown in Table 1.

Based on the QUADAS-2 guidelines, the research and data found in the studies were assessed individually for each item according to the following classification scale: high risk of bias, low risk of bias, or non-specific. Any disagreement was resolved by the discussion between two authors[7].

The study is registered in the PROSPERO platform, confirming its originality and validation: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=168551.

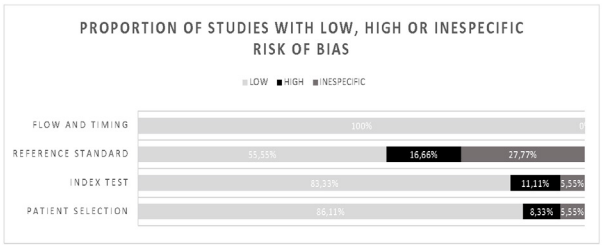
Table 1. Assessment of study quality and risk of bias. A) Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) Tool. B) Results of the methodologic assessment by using the QUADAS-2 Tool

QUADAS-2 Tool

A)

QUADAS-2 Tool								
AUTHOR, YEAR OF PUBLICATION	MEDIAN AGE (YEARS)	SEX	QUADAS					
			1	2	3	4	5	
Park et al., 2018	44 (23 - 74)	NE						
Lee et al., 2015	14.7 (5 - 27)	14M/7F						
Hu et al., 2016	32 (7 - 57)	NE						
Gardner et al., 2017	12.3 (1.3 - 25.4)	21M/23F						
Callahan et al., 2017	(1 - 14)	NE						
Turtle et al., 2016	40 (20 - 73)	27M/5F						
Grupp SA et al., 2016	12 (3 - 23)	NE						
Buechner et al., 2017	12 (3 - 23)	NE						
Daniel W. Lee et al., 2015	(4 - 25)	14M/3F						
Curran et al., 2015	15 (3 - 22)	NE						
Maude et al., 2016	(2.4 - 24)	NE						
Grupp SA et al., 2018	(3 - 21)	NE						
Weng et al., 2018	23.3 (16 - 34)	2M/1F						
Hu et al., 2018	31.6 (8 - 57)	6M/11F						
Gardner et al., 2016	NE	NE						
Grupp SA et al., 2015	11 (4 - 24)	NE						
Pan et al., 2018	13.3 (2 - 68)	32M/19F						
Dai et al., 2018	(15 - 65)	4M/5F						
1. Was a sample of consecutive or random patients included?								
2. Did the study avoid inappropriate exclusions?								
3. Has the method been described for determining the outcome of patients after administration?								
4. Is the reference standard suitable for classifying the target condition?								
5. Did all patients received autologous Anti-CD19 CAR T-Cells?								
According to the QUADAS-2 Tool guidelines, each item was assessed with the answers "Yes", "No" or "Unspecified"								
YES								
NO								
UNSPECIFIED								

B)



Statistical analysis

The R 3.5.0 software was used to perform the statistical analysis in the meta-analysis. The software has the statistical tool "Meta package" that can be used to improve the functionality of R Software in the execution of the meta-analysis. Thus, for the preparation of the analysis of this study, the "Metaprop" was used, a "Meta package" model designed especially for proportion meta-analysis.

The "Metaprop" performed some special binomial data procedures, allowing the exact calculation of the binomial test and scoring based on the confidence interval. Thus, it was possible to include proportions close to 0 or 100% in the meta-analysis. Then, the Logit transformation was used to calculate the rate of Complete Response, Absence of Response, Relapse, Death, CRS, sCRS, and Neurotoxicity events.

The Cochran Q test and Higgins I^2 statistics were used to perform the homogeneity test in the eligible studies. A p-value ≤ 0.1 and / or $I^2 \geq 50\%$ indicates significant heterogeneity. Thus, in the presence of heterogeneity, the data must have been calculated by the "Randomized Model Effect"[8].

Potential heterogeneity factors for each analysis including "Costimulatory Domain", "genetic transfer method (Vector)", "Time of Persistence in the organism", "pre-conditioning (Lymphodepletion)" and "dosage of CAR-T Cells administered" were assessed by meta-regression analysis.

All analysis was performed using software R 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria), Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), and MedCalc software (MedCalc Software, Ostend, Belgium).

RESULTS

Study characteristics

Eighteen articles were included in this study, totalizing 637 patients. Of these articles, patients differ in various types and stages of study: 462 patients were in interventional type studies, 99 were in prospective cohorts, and 76 were in retrospective cohorts. The major findings of the studies are shown in Table 2.

Table 2. CAR T-Cells research in Refractory / Relapsed Acute Lymphoblastic Leukemia

Author, Year	Participants	Study type	Costimulatory Domain	Genetic Transfer Method (Vector)	Time of persistence in the organism (days)	Pre-Conditioning (Lymphodepletion)	Dosage of car T-Cells Administrade	Responses	Side effects
Park et al., 2018	53	Interventional - Phase I	CD3/CD28 beads	Retroviral	7-138	Cyclophosphamide and Fludarabine; Cyclophosphamide; Cyclophosphamide and Etoposide	3×10^6 (1 - 3×10^6) cells/kg	44 CR 12 NR 25 Relapses 1 Death	45 CRS 14 sCRS 23 Neurotoxicity
Lee et al., 2015	20	Interventional - Phase I	CD3/CD28 beads	Retroviral	3-168	Cyclophosphamide and Fludarabine	1 x 10^6 (0.03 - 3.6 × 10^6) cells /kg	14 CR 7 NR 2 Relapses	10 CRS 6 sCRS 9 Neurotoxicity 120 Others
Hu et al., 2016	15	Interventional - Phase I	CD19 specific CAR/4-1BB/CD3-ζ	Lentiviral	30-281	Cyclophosphamide and Fludarabine	3.7 x 10^6 (1.1 - 9.8 x 10^6) cells /kg	12 CR 2 NR 6 Relapses 6 Deaths	4 CRS 6 sCRS 5 Neurotoxicity
Gardner et al., 2017	43	Interventional - Phase I/II	CD3/CD28 beads	Lentiviral	14-840	Cyclophosphamide and Fludarabine; Cyclophosphamide	1.0 × 10^6 (0.5 × 10^6 - 10.0 × 10^6) cells /kg	40 CR 3 NR 18 Relapses	9 sCRS 9 Neurotoxicity
Callahan et al., 2017	59	Retrospective cohort	NI	NI	NI	Cyclophosphamide and Fludarabine	NI	55 CR 27 Relapses	NI
Turtle et al., 2016	30	Interventional - Phase I/II	CD3/CD28 beads	Lentiviral	25-300	Cyclophosphamide and Fludarabine; Cyclophosphamide; Cyclophosphamide and Etoposide	2 x 10^6 (0.2 - 20 x 10^6) cells /kg	27 CR 9 Relapses 6 Deaths	25 CRS 7 sCRS 15 Neurotoxicity
Grupp SA et al., 2016	57	Interventional - Phase II	NI	Lentiviral	NI	Cyclophosphamide and Fludarabine	2.9 x 10^6 (0.2 - 4 x 10^6) cells /kg	29 CR 2 NR 2 Deaths	15 sCRS 7 Neurotoxicity 31 Others
Buechner et al., 2017	63	Interventional - Phase II	NI	Lentiviral	NI	Cyclophosphamide and Fludarabine	3.0 X 10^6 (0.2 - 5.4 X 10^6) cells/kg	52 CR 5 NR 6 Deaths	15 CRS 24 sCRS 9 Neurotoxicity
Daniel W. Lee et al., 2015	39	Prospective cohort	CD3/CD28 beads	Retroviral	NI	Cyclophosphamide and Fludarabine	1 × 10^6 cells /kg	23 CR 2 Relapses	8 CRS 5 sCRS
Curran et al., 2015	9	Interventional - Phase I	CD3/CD28 beads	NI	7-60	NI	(1 - 3 × 10^6) cells /kg	5 CR	2 CRS 3 sCRS
Maude et al., 2016	30	Interventional - Phase I	CD3/CD28 beads	Lentiviral	NI	NI	NI	26 CR 4 NR 3 Relapses	24 CRS 4 sCRS 9 Neurotoxicity
Grupp SA et al., 2018	79	Interventional - Phase II	CD19 specific CAR/4-1BB/CD3-ζ	Lentiviral	720	Cyclophosphamide and Fludarabine	3.0 × 10^6 (0.2 - 5.4 x 10^6) cells /kg	65 CR 19 Relapses 13 Deaths	61 sCRS 10 Neurotoxicity
Weng et al., 2018	3	Interventional - Phase I	CD3/CD28 beads	Lentiviral	17-92	Cyclophosphamide and Fludarabine	0.5 × 10^6 (0.05 - 1 x 10^6) cells /kg	3 CR	2 CRS 1 sCRS
Hu et al., 2018	17	Retrospective Cohort	CD19 specific CAR/4-1BB/CD3-ζ	Lentiviral	NI	Cyclophosphamide and Fludarabine	4,03 (1,3 x 10^6 - 9,4 x 10^6) cells /kg	15 CR	9 CRS 8 sCRS 17 Neurotoxicity 14 Others
Gardner et al., 2016	7	Interventional - Phase I	CD19 specific CAR/4-1BB/CD3-ζ	Lentiviral	22	Cyclophosphamide and Fludarabine	(1 x 10^7 - 2 × 10^6) cells /kg	7 CR 2 Relapses	2 sCRS 2 Neurotoxicity
Grupp SA et al., 2015	53	Interventional - Phase I	CD3/CD28 beads	Lentiviral	30-780	Cyclophosphamide and Fludarabine	4.3 x 10^6 (1 - 17.4 x 10^6) cells /kg	50 CR 3 NR 20 Relapses	47 CRS
Pan et al., 2018	51	Prospective cohort	CD3/CD28 beads	Lentiviral	< 60	Cyclophosphamide and Fludarabine	1X10^5 (0.05 - 14 X 10^5) cells /kg	45 CR 3 NR 9 Relapses 7 Deaths	37 CRS 14 sCRS 10 Neurotoxicity
Dai et al., 2018	9	Prospective cohort	CD19 specific CAR/4-1BB/CD3-ζ	Lentiviral	NI	Cyclophosphamide, Etoposide and Vincristine; Vincristine, Cyclophosphamide and Daunorubicin	5.3 x 10^6 (3 - 12.7 x 10^6) cells /kg	4 CR 2 NR 5 Deaths	1 CRS 3 sCRS 2 Neurotoxicity 15 Others

Meta-Analysis of Responses Rates

Eighteen studies including 637 patients with Acute Lymphoblastic Leukemia, were selected for the evaluation of response rates after administration of the therapy involving the Anti-CD19 CAR T-Cells. The rate of responses in patients undergoing therapy with CAR T-Cells showed significant differences between the studies analyzed, ranging from 44 to 100% (Complete Response), 0 to 35% (No Response), 0 to 47.2% (Relapses), and 0 to 55.5% (Deaths).

The average of responses and the 95% confidence intervals for each of the studies analyzed are shown in Figure 2.

Homogeneity tests indicate that these studies have significant heterogeneity: Complete Response (CR) (I^2 = 73.5%, p <0.05), No Responses (I^2 = 76.5%, p <0.05), Relapses (I^2 = 89.82%, p <0.05), Deaths (I^2 = 79%, p <0.05). Thus, the "random-effect model" was used to perform the calculations and statistical analysis.

The study concludes that patients who receive the therapy with Autologous Anti-CD19 CAR T-Cells can achieve approximately 81% (95% Confidence Interval (CI): 73.9 to 87%) of Complete Responses, 7% (95% CI: 3.2 – 11%) of No Responses, 17% (95% CI: 8.6 – 27.2%) of Relapses, and 6.1% (95% CI: 2.6 – 11%) evolved to Death. The Meta-Analysis of Responses Rates are shown in Figure 2.

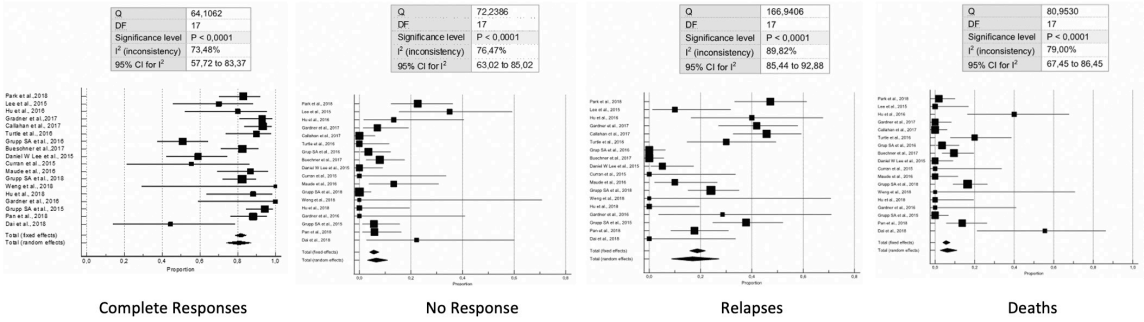


Figure 2. *Meta-Analysis of Responses Rates. A) Complete Responses. B) No Response. C) Relapses. D) Deaths*

Meta-Analysis of Side Effects Rates

Seventeen studies, including 578 patients with Acute Lymphoblastic Leukemia, were selected to assess the side effects of Anti-CD19 CAR T-Cells treatment. The rate of side effects in patients undergoing therapy with CAR T-Cells was shown to differ greatly between the studies analyzed, ranging from 0 to 88.7% of CRS; 0 to 77.2% of sCRS; and 0 to 100% of Neurotoxicity.

The average of Side Effects and the 95% confidence intervals for each of the studies analyzed are shown in Figure 3.

Homogeneity tests indicate that these studies have significant heterogeneity: CRS (I^2 = 96.7%, p <0.05); sCRS (I^2 = 89.5%, p <0.05); Neurotoxicity (I^2 = 90.9%, p <0.05). Thus, the "random-effect model" was used to perform the calculations and statistical analysis.

The study concludes that the average of side effect in the treatment of Anti-CD19 CAR T-Cells in patients diagnosed with Acute Lymphoblastic Leukemia is approximately 36.3% (95% CI: 16.7 – 58.7%) for CRS; 29% (95% CI: 18.1 – 41.4%) for sCRS; and 24% (95% CI: 13.2 – 36.6%) for Neurotoxicity. The Meta-Analysis of Side Effects Rates are shown in Figure 3. Study of Callahan et al., 2017 was disregarded for the analysis of side effects since it did not have side effects as its objective of study[9]. Thus, no inference can be made.

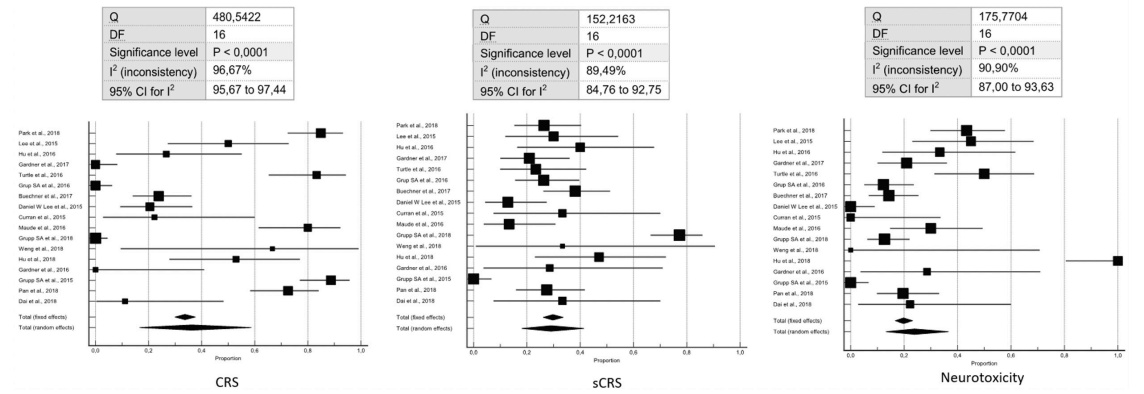


Figure 3. Meta-Analysis of Side Effects Rates. A) Cytokine Release Syndrome (CRS). B) severe Cytokine Release Syndrome (sCRS). C) Neurotoxicity

Sources of heterogeneity

The results of the heterogeneity analysis showed that heterogeneity also existed due to other factors. The result of the meta-regression analysis between the responses obtained in the studies and the different factors showed that the complete response is significantly associated with

lymphodepletion in cyclophosphamide and fludarabine (p = 0,01); the lack of response is closely associated with the vector used as a method of genetic transfer (p = 0.04); and the number of deaths is related to Lymphodepletion (p = 0.001), the Costimulatory Domain - CD3 / CD28 beads or CD19 specific CAR / 4-1BB / CD3-ζ - used (p = 0.04) and the dose used (p = 0.04). As for side effects, the result of the meta-regression analysis revealed that there is a relevant association of the costimulatory domain used with the CRS (p = 0.03) and sCRS (p = 0.01) levels obtained. The Meta-regression to assess the sources of heterogeneity is shown in Table 3.

Table 3. Source of heterogeneity. Meta-regression

		p- value						
		Complete Response	**No Response**	**Relapses**	**Deaths**	**CRS**	**sCRS**	**Neurotoxicity**
Variable	Costimulatory Domain	0,75	0,77	0,88	0,03	0,03	0,01	0,21
	Genetic Transfer Method (Vector)	0,25	0,04	0,79	0,28	0,58	0,46	0,86
	Time of Persistence in the Organism	0,64	0,43	0,29	0,68	0,15	0,25	0,42
	Pre-conditioning (Lymphodepletion)	0,02	0,16	0,26	0,001	0,42	0,89	0,86
	Dosage of CAR T-Cells Administrated	0,31	0,56	0,89	0,04	0,75	0,54	0,39

DISCUSSION

The infusion of CAR T-Cells in a uniform 1:1 ratio between CD4 + and CD8 + proved to be the most effective correlation in cell dosage. The inclusion of fludarabine (Flu) in lymphodepletion with cyclophosphamide (Cy) promotes the greater expansion of CD4 + and CD8 + and functional persistence of CAR T-Cells, culminating in a greater number of complete responses, in addition to the fact that patients undergoing Flu had fewer relapses[10,11].

Compared to allogeneic treatment, there was no difference in complete response rates when patients were first exposed to the treatment. However, autologous CARs induced greater spikes in expansion and had more cases of severe CRS than the allogeneic group[12]. 50% of patients who relapsed to treatment with murine CAR T-Cells had a complete response to autologous treatment[13].

According to Gardner et al., 2016 patients with complete MRD-negative remission with 19-28z T-Cells infusion had an overall survival of 20.7 months (14.1 months longer than MRD-positive patients). In the same study, the event-free mean in MRD-negative patients (12.5 months) was four times that of MRD-positive patients (3.1 months). Low Disease Burden (LDB) patients had significantly longer event-free survival and overall survival than those with High Disease Burden (HDB). Even a robust expansion of CAR T-Cells leading quickly to high rates of remission may not be enough to prevent relapses, especially in patients with HDB, in these cases treatment with low doses of CAR T-Cells may be more indicated to minimize toxic effects[14].

"Classic" CRS, containing fever, capillary fragility, and hypotension requiring intensive treatment, is common in patients undergoing treatment, however, they respond quickly to tocilizumab and dexamethasone[11]. ALL with multiple relapses were more likely to have grade 3 CRS and there is no consensus on effective treatment strategies in this patient profile[8]. The mechanisms that induce neurotoxicity are not yet clear, however, this is a significant side effect, causing proportionally high deaths in recent clinical trials[11].

It was concluded that the peak expansion of CAR T-Cells in vivo is the best predictor of short-term response and toxic effects[11]. On long-term response, in contrast, disease burden pretreatment was found to be a useful predictor of the duration of remission and survival. There was no correlation between the persistence of 19-28z CAR T-Cells and the durability of remissions[11]. Rapid loss of CTL019 cells (less than three months) is associated with an increased risk of relapse[15].

Symptoms associated with Neurotoxicity and CRS

Despite the favorable results that CAR-T therapy has brought throughout the studies, the treatment is not free from adverse effects. The main adverse effects of treatment are cytokine release syndrome (CRS) and neurotoxicity. CRS found even in a severe form in some studies (grades 3, 4 and 5 - indicating hospitalization accompanied by limited ability to care for oneself, risk of life and death, respectively), is a systemic inflammatory response, related to the increased activation of T cells and, consequently, to the increase in the number of cytokines, manifesting itself in the form of tachycardia, fever, and myalgia; can lead to death if not properly controlled, due to multiple organ failure[16,17]. Neurotoxicity is an adverse effect related to changes in central nervous system functions, the main symptoms of which are encephalopathy, seizures, aphasia, tremors, and delirium; its pathophysiology is still unknown. Both adverse effects are correlated[18].

In addition to the two main adverse effects listed above, others are also likely to occur. These effects can affect different systems of the patient's organism and occur in different degrees of severity. The research

included in this review reported the following changes: QT prolongation, hypotension, hypertension, cardiac arrest and left ventricular dysfunction, anemia, febrile neutropenia, prolonged TAP, lymphocytopenia, thrombocytopenia, leukopenia, neutropenia, thrombocytopenia, and coagulopathy, elevated ALT, elevated AST and increased serum bilirubin, rash, ulcers in the oral and genital mucosa, hydro electrolytic disorders (hypophosphatemia, hypokalemia, and hyponatremia), pulmonary edema, tumor lysis syndrome, systemic capillary leak syndrome, fever, pain, edema, hypoxia, acute renal failure, increased CPK, hyperglycemia and multiple organ failure[19-21].

These other adverse effects found were not better analyzed in the graphs and tables of this article due to the low prevalence of their occurrences. The order of the list above does not reflect the prevalence or importance of the adverse effects.

Confounding Factors and Limitations

The limitations found during the study were the small number of patients in some studies and lack of description about age, race, ethnicity, among other individual characteristics. The qualitative absence of these factors prevented greater correlations from being established, such as the relationship between complete response rate and age. The variations between the CAR T-Cells treatments themselves, such as dose, lymphodepletion, and time of persistence in the organism can also be considered limitations for a more assertive approach regarding results since most studies did not specify the treatment submitted and the response of each patient.

CONCLUSIONS

Given the study limitations and the lack of individuals description, literature requires studies that can provide more information about the patients involved in the studies, in order to provide qualitative analytical data so that greater correlations are established between individual, treatment, and response.

Despite the adverse effects described, especially CRS and neurotoxicity, Anti-CD19 CAR T-Cells immunotherapy presents itself as a promising and highly effective therapy, capable of producing high rates of complete remission in the treatment of R/R ALL. This legacy is beginning to consolidate now and opens new perspectives so that in the coming years it will be possible to take advantage of new technologies and data increasingly encouraging.

This review corroborates with previous studies, reporting that treatment with CAR T-Cells induces high rates of remission and complete responses. Its most frequent side effects are managed effectively; although many patients develop CRS, only a few dies. In conclusion, CAR T-Cells treatment is an innovative treatment whose best time to be indicated is still an open question. It is imperative to perform new clinical trials that might address this question. Once the best time of indication is defined, CAR T-Cells effectiveness will be fully comprehended.

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