Review Article

# CAR-T Cells Therapy: What Cardiovascular Adverse Effects Should We Expect?

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## Abstract

Immunotherapy has emerged as a specific treatment, guided by oncologic targets, that has given the false impression (to oncologists and hematologists) that it had no adverse effects, including cardiovascular complications. Chimeric antigen receptor (CAR) T-cell therapy has certainly benefited specific patients; in contrast, reports of adverse cardiovascular effects have emerged. In this paper, we conducted a narrative review of conceptual aspects, clinical applicability, the cytokine release syndrome, extracardiac AE and, above all, the cardiovascular AE of CAR-T cell therapy. CAR-T cell therapy has been approved by regulatory agencies in the United States, Europe and Brazil, initially for the treatment of hematological malignancies at advanced stages, after failure or refractoriness. Among extracardiac AE, cytokine release syndrome and, consequently, encephalopathy, macrophage activation syndrome or hemophagocytic lymphohistiocytosis stand out. The most frequently described cardiovascular AE are cardiomyopathies, myocarditis and ventricular dysfunction; tachyarrhythmias, changes in QT and other electrocardiographic changes; pleural and pericardial disease, and changes in biomarkers. Thus, prior to the therapy, it is recommended to perform clinical evaluation, electrocardiogram, echocardiogram, and troponin and B-type natriuretic peptide measurements. The patient should be monitored during treatment with continuous electrocardiogram, serial echocardiogram, and biomarkers. Patients with severe cardiovascular AE should be admitted to a cardiac intensive care unit.

## Introduction

Cancer treatment has evolved from surgery, radiotherapy and chemotherapy to a fourth and new pillar – immunotherapy.[1] Immunotherapy has emerged as a specific therapy, guided by oncologic targets, that has given the false impression (to oncologists and hematologists) that it had no adverse effects, including cardiovascular complications. However, with the use of this therapy, these effects not only occurred but were also found to be, in many cases, fatal. Another treatment modality, the chimeric antigen receptor (CAR) T-cell therapy, has undoubtedly benefited some patients. In other hand, case reports followed by cohort and pharmacovigilance studies have produced strong evidence of CAR-T cell therapy-induced cardiotoxicity. CART-cell is still an unknown topic for most cardiologists. Based on this, we conducted a brief, narrative review, of conceptual aspects, clinical applicability, cytokine release syndrome (CRS), extracardiac adverse effects, and above all, cardiovascular adverse effects related to CAR T-cell therapy.

## Keywords

Immunotherapy, Adoptive; Receptors, Chimeric Antigen; Neoplasms

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Manuscript received January 04, 2023, revised manuscript January 12, 2023, accepted January 12, 2023

**DOI:** https://doi.org/10.36660/abchf.20230002

## CAR T-cell therapy

### CAR-T cell: a new therapeutic modality

The immune system is an important tool in the fight against cancer, and several studies have demonstrated its activity even in pre-neoplastic stages. However, at diagnosis, the immune system activity is deficient or tolerant, allowing tumor expansion. In this context, the search for specific therapies that restore tumor control corresponds to the modern era of immunotherapy in onco-hematology.[2] Approximately ten years ago, a new antitumor therapy was successfully tested in childhood acute lymphoblastic leukemia (ALL), refractory to available therapies such as polychemotherapy and allogenic stem cell transplant. This new advanced cell therapy, developed by researchers from the University of Pennsylvania, consisted of collecting T cells from patients and changing of T cell receptors (TCR) by genetic engineering, to achieve high affinity and interact with specific targets expressed on the neoplastic cells, like CD19 present on B cells in ALL.[3] Following this laboratory stage, the patient was admitted to the hospital for pre-conditioning lymphodepletion, to receive a combination of immune suppressors, usually fludarabine and cyclophosphamide, and infusion of CAR-T cells. The patient was hospitalized from two to three weeks, during which the expansion and migration of CAR-T cells to tumor sites, as well as potential complications of the procedure occurred[4,5] (Figure 1).

## Clinical applicability

Pivotal phase 2 studies have tested the principle and proved its efficacy and toxicity, with the cure of several cases

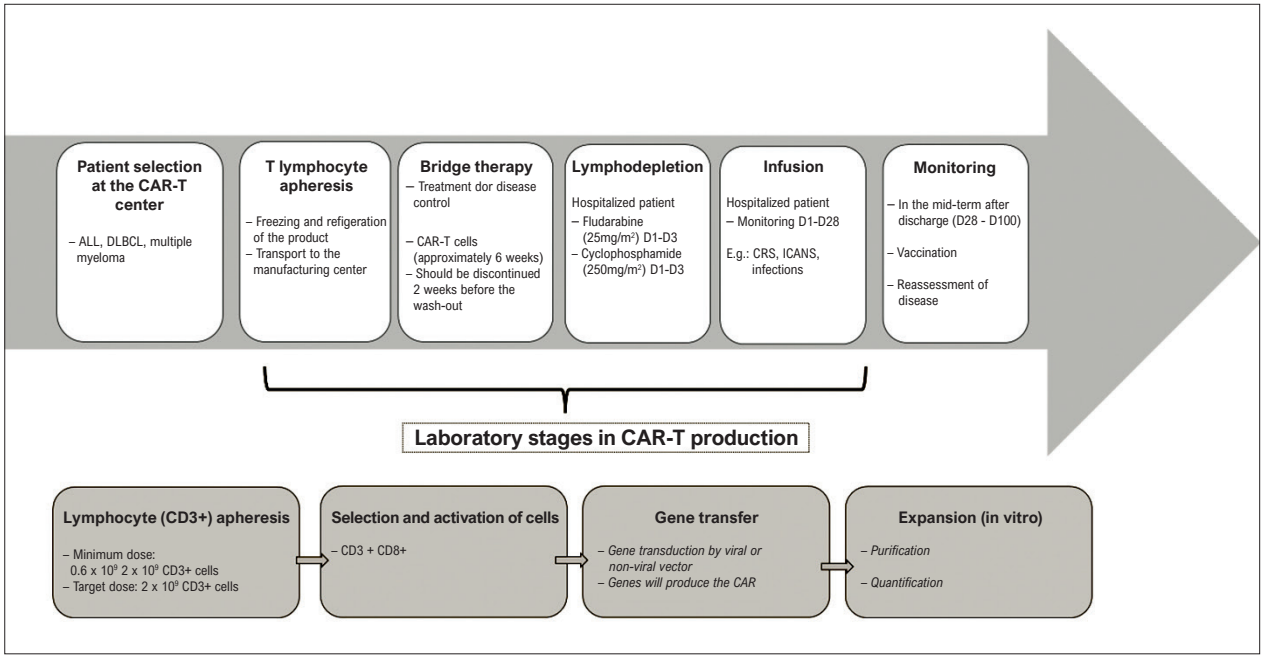


**Figure 1 –** *Stages of the chimeric antigen receptor (CAR) T-cell therapy. Adapted from Hartmannet al.,4 ALL: acute lymphoblastic leukemia; DLBCL: diffuse large B cell lymphoma; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; CAR: chimeric antigen receptor.*

of ALL and lymphomas, and control of relapsed and refractory multiple myeloma. A new therapeutic field has emerged, providing comfort and encouragement for patients with several incurable hematologic malignancies. An increasing amount of phase 2 and phase 3 studies have been testing strategies, molecules and therapeutic targets (Table 1).

## Cytokine release syndrome (CRS)

The CAR-T cell therapy has specific adverse events (AEs) that should be early recognized and monitored during hospitalization, usually in bone marrow transplant units, and by a trained multidisciplinary team for the effective management of these complications. CRS is a common complication, affecting up to 90% of patients under treatment, and occurring from the first 24 hours to two weeks after the infusion. This syndrome is attributed to the increased release of inflammatory cytokines, such as interleukin-6 (IL-6), interferon-gamma (IFNγ), tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1).[11] Risk factors for CRS include the type of disease treated, the manufactured CAR-T cell product, and the dose of CART cells. Due attention should be paid to fever, which is the first symptom of CRS and may appear already on the first day after infusion. Persistence of fever elevates the grade of this AE, and indicates immediate intervention with anti-interleukin 6 (tocilizumab). This drug is indicated to all patients with AE grade greater than 2, who then present, in addition to fever, hypotension of hypoxemia. For most patients who receive early treatment, AE will not progress to higher grades and subsequent clinical worsening and further need of vasopressors, mechanical ventilation or intensive care (Figure 2). Differential diagnoses of CRS include sepsis, tumor lysis syndrome, pulmonary thromboembolism and primary cardiac arrest or cardiogenic shock.[12]

In laboratory monitoring, it is also of great value to measure C-reactive protein and ferritin, which are increased in SLC, and fibrinogen, whose levels are low in SLC.[13]

## Extracardiac adverse effects

In the spectrum of CRS-associated complications, a new type of encephalopathy has been reported, the immune effector cell-associated encephalopathy (ICANS). In the KarMMa[9] e Cartitude-1[10] studies, ICANS was developed in 18% and 16% of patients, and was of grade ≥ 3 in 4% and 2.1%, with median time to onset of two and eight days, respectively.[9,10] In general, ICANS occurs after CRS, and clinically presents as different signs and symptoms including delirium, encephalopathy, aphasia, lethargy, difficulty in concentrating, agitation, headache, shivering, convulsions, and rarely, cerebral edema. This syndrome is usually reversible, has its own grading system, and must be followed by neurologists during all steps of the procedure. One of the earliest symptoms may be agraphia, and because of that all patients are encouraged to write their names as a form of assessment. Neuroimaging tests, electrocardiogram, support measures, in addition to anticonvulsants and corticosteroids may be required in some cases.

Among the frequently reported AEs are persistent cytopenias, sometimes characterized as macrophage activation syndrome or hemophagocytic lymphohistiocytosis that can be treated with Anakynra (not available in Brazil). The risk of infections is multifactorial, and related to neutropenia, T cell depletion, and persistent

**Table 1 – Pivotal studies on chimeric antigen receptor (CAR) T-cell therapy and cytokine release syndrome with clinical applicability**

| Clinical study/ Authors | Disease (*Relapsed or Refractory*) | CAR-T cell type | Target | CRS/n total (%) | CRS (%) *Grade 3-4* | Time of onset (median) |
|---|---|---|---|---|---|---|
| Juliet Schuster et al. [6] | Lymphoma* | Tisagenlecleucel Kymriah | CD19 | 64/111 (58) | 22 | 3 |
| Eliana Maude et al. [7] | ALL | Tisagenlecleucel Kymriah | CD19 | 58/75 (77) | 25 *(43 ICU admissions)* | 3 (1-22) |
| Zuma-1 Neelapu SS et al. [8] | Lymphoma* | Axicabtagene ciloleucel Yescarta | CD19 | 94/101 (93) | 13 | 2 (1-12) |
| KarMMa Munshi NC et al. [9] | Multiple myeloma | Idecabtagene vicleucel# Abecma | Anti-BCMA | 107/128 (84) | 5 | 1 (1-10) |
| Cartitude-1 Berdeja JG et al. [10] | Multiple myeloma | Ciltacabtagene autoleucel Carvykti | Anti-BCMA | 92/97 (95) | 5.4 | 7 (1-12) |

*# not approved in Brazil; CRS: cytokine release syndrome; ALL: acute lymphoblastic leukemia; * diffuse large B cell lymphoma; ICU: intensive care unit.*

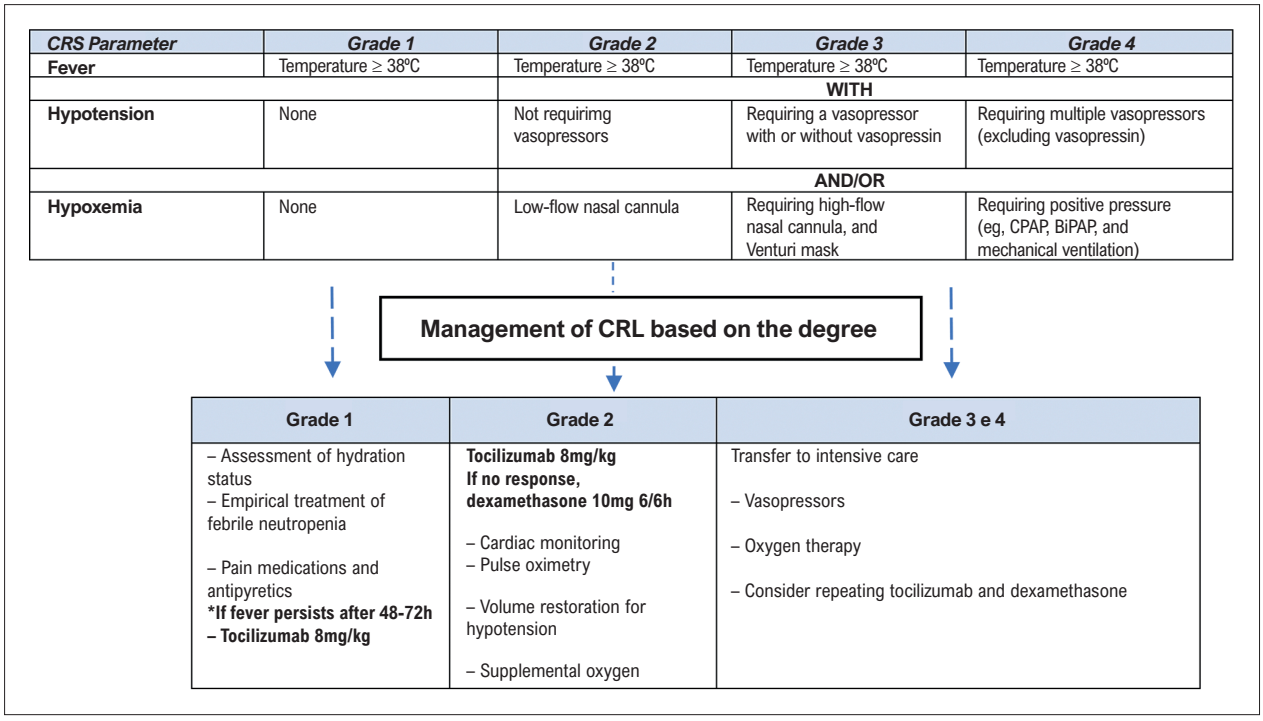


**Figure 2 –** *American Society for Transplantation and Cellular Therapy consensus on cytokine release syndrome grading and management. Adapted from Lee et al.,12 CRS: cytokine release syndrome.*

hypogammaglobulinemia.[10] All patients are vaccinated, starting three months after the procedure, including against SARS-CoV 19 and receive prophylaxis against *Pneumocitis carinii* with cotrimoxazol and against herpes simplex virus and herpes zoster with acyclovir. Patients with IgG <400mg/dL and those with repeated infections should receive intravenous immunoglobulin. Patient monitoring for viral infections such as cytomegalovirus, Epstein-Barr virus, HHV6 and adenovirus, and fungal infections with *Aspergilus* sp. and *Candida* sp. is recommended.[14]

## Current scenario of CAR-T cells in Brazil and the world

The CAR-T cell therapy has been approved by regulatory agencies in the North America, Europe and in Brazil (by ANVISA), for the treatment of advanced hematological malignancies, after failure or refractory treatment. There are ongoing phase 3 studies in hematology on earlier stages of the disease and myeloid neoplasms, as well as researches on solid tumors and autoimmune disorders. Several strategies, tumor targets and allogeneic cart T-cells have been explored, to reduce the time between cell production and treatment. This new modality of advanced cell therapy has expanded

and been patented as a pharmaceutical industry product with specific manufacturing centers distributed over the world. In Brazil, the first experiences have been made in bone marrow transplant units of onco-hematology centers. The first case reported were patients from international clinical studies, and the first cases of patients covered by the supplementary health care have also been reported. In addition to its high complexity, an obstacle to the implementation of CAR-T cell therapy is its high cost. The solution to improve the access to the therapy in China, Spain and Canada has been initiatives for an autonomous production. In Brazil, the group from Hemocentro in the city of Ribeirao Preto, and the Butantan Institute in Sao Paulo have developed research with own manufacturing and history of successful infusions.[15]

## Cardiovascular adverse effects of CAR-T cell therapy

CAR-T cell therapy is relatively new in oncology, and knowledge about adverse effects has been obtained primarily from case reports and subsequently from retrospective registry of patients at referral centers.

The cardiovascular adverse effects of CAR-T cells are not negligible. Lefrebve et al.[16] evaluated 145 adults undergoing CAR-T cell therapy and observed 41 (28.3%) events, including cardiovascular deaths, heart failure, acute coronary syndrome, ischemic stroke and new arrhythmias. The events occurred early, within a median of 11 days after the therapy was implemented. Elevated serum creatinine and CRS grades 3 and 4 were predictors of outcomes.

In 2019, Alvi et al.[17] studied 137 patients who received CAR-T cells in two hospitals in the USA. Troponin elevation was relatively frequent in patients with CRS who received CAR-T cells, who also had an increased risk for cardiovascular events subsequently. Patients with more severe CRS are at higher risk for severe adverse events.

Historically, cardiotoxicity has been associated with cardiomyopathy and heart failure. During CAR-T cell therapy, approximately 10% of patients develop cardiomyopathy, which was a level-2 predictor of CRS. The frequency of cardiomyopathy is higher among patients with cardiovascular risk factors. Nearly half of patients who develop ventricular dysfunction do not return to baseline function.[18] Adverse cardiovascular effects correlate not only with CRS but also with neurotoxicity.[19]

Data on larger number of patients come from the retrospective registry of pharmacovigilance of the adverse cardiopulmonary effects of the US Food and Drug Administration.[19-21] According to this registry,[21] of the 2,657 patients who received industrialized CAR-T cells, 546 (20.5%) had adverse effects, with an overlapping with CRS in 373 patients (38.3%). Lethality rate among patients who had cardiopulmonary adverse effects was 30.9%, and atrial fibrillation was the most common tachyarrhythmia reported. The main cardiovascular effects are listed in Table 2.

Some inferences can be drawn from these registries that are relevant from the perspective of clinical applicability: (a) to assess the risk of cardiotoxicity in candidates for CAR-T cell therapy; (b) to start the assessment with clinical history and physical examination; (c) to perform routine echocardiography to evaluate heart valve function and exclude valve diseases; (d) patients (candidates for the therapy) should have their cardiovascular status optimized by a cardiologist; (e) an early recognition and treatment of CRS reduces the risk of cardiotoxicity; (f) most cardiopulmonary adverse events have been reported in the first 30 days of treatment; and (g) patients who had received immune checkpoint inhibitor are at higher risk for CAR-T cell-associated cardiotoxicity.[21] The most commonly reported cardiovascular effects were severe arterial hypotension requiring inotropic support (4-33%); left ventricular systolic dysfunction (2-10%); pulmonary edema (4-6%); volumetric overload (5%); electrocardiographic changes; and biomarker changes, especially NT-ProBNP and troponin.[20]

**Table 2 – Cardiovascular adverse effects secondary to chimeric antigen receptor T-cell therapy according to notifications to the US Food and Drug Administration**

| Cardiopulmonary adverse effect | n and frequency (n total= 2,657) | Risk rate and 95% confidence interval |
|---|---|---|
| Tachyarrhythmias | 74 (2.8%) | 2.21 – 3.51 |
| Cardiomyopathies | 69 (2.6%) | 2.42 – 5.09 |
| Pleural disease | 46 (1.7%) | 2.92 – 5.23 |
| Pericardial disease | 11 (0.4%) | 1.25 – 4.09 |

*Font: Goldman et al.[21]*

## Consensual recommendations

Although CAR-T cell is a new therapy, there are already recommendations issued by specialist societies. We will first mention clinical practice guideline on immune effector cell-related adverse events of the Society for Immunotherapy of Cancer (SITC).[1] The authors used the definition and nomenclature of cardiotoxicity established by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), and considered as cardiovascular adverse effects secondary to CAR-T cells the following: (a) new arterial hypotension; (b) decompensated heart failure; (c) heart failure combined with new arrhythmias such as atrial fibrillation or flutter; (d) nonsustained ventricular tachycardia; (e) prolonged QTc interval in the presence or absence of drugs that prolong the QT interval or electrolyte disturbances; (f) narrow or wide QRS complex tachycardias; (g) pericarditis; and (h) myocarditis.[1] Echocardiography is an accurate and accessible method for measuring ventricular function before the CAR-T cell therapy is started.

The SITC recommends:[1]

- Baseline cardiac assessment prior to CAR-T cell therapy by transthoracic echocardiogram, and troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement;
- Troponin and LVEF should be monitored in patients who develop CRS of American Society for Transplantation and Cellular Therapy (ASTCT) grade ≥ 2;

- Patients with established and severe cardiovascular disease such as heart failure, previous myocardial infarction, and arrhythmias should be assessed and may be excluded from the CAR-T cell therapy;
- In evidence of cardiotoxicity, elevated troponin, decrease in LVEF or clinically significant arrhythmias, IL-6 blockade and/or steroids should be considered;
- Antiplatelet agents such as aspirin and clopidogrel should be discontinued prior to CAR-T cell therapy. However, high-risk patients who recently underwent a coronary revascularization, management decisions should be individualized, and made in conjunction with the cardiology team;
- Anticoagulants should be changed to short-acting agents. If platelet counts drop below 50,000/μL, all anticoagulants should be discontinued unless the patient has had a recent thrombosis. In these cases, the dose should be reduced, or platelet transfusions should be considered.

The European Society of Cardiology (ESC) recommends if clinical suspicion of cardiovascular complication:[22]

- Baseline electrocardiogram
- Continuous electrocardiographic monitoring
- Transthoracic echocardiogram
- Monitor cardiac troponin and B-type natriuretic peptide (BNP)
- Severe patients should be admitted to cardiac intensive care unit

## Conclusions

Cardiovascular adverse events secondary to the CAR-T cell are frequent and severe, and justify the screening, monitoring, and early diagnosis and intervention to improve the outcomes of survival and quality of life. Data on this topic, obtained by careful work, are still lacking to answer specific questions.

## Author Contributions

Conception and design of the research, Acquisition of data and Critical revision of the manuscript for important intellectual content: Martins WA, Magalhães Filho RJP, Galvão TFG; Analysis and interpretation of the data: Magalhães Filho RJP, Galvão TFG; Writing of the manuscript: Martins WA, Magalhães Filho RJP.

### Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

### Sources of funding

There were no external funding sources for this study.

### Study association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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