Technology in Cancer Research & Treatment
Volume 21: 1-9

DOI: 10.1177/15330338221132927
journals.sagepub.com/home/tct
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Adverse Cardiac Effects of CAR T-Cell Therapy: Characteristics, Surveillance, Management, and Future Research Directions

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Abstract

This review summarizes the current literature on the adverse cardiac effects of CAR T-cell therapy. Case reports and series suggest that major adverse cardiovascular events are not uncommon after CAR T-cell therapy; however, limited data exist regarding incidence, pathophysiology, and prevention strategies related to CAR T-associated cardiovascular events. As cellular therapy advances and the indications for its use continue to expand, it is essential to better understand its associated cardiovascular toxicities. Biomarkers, cardiac imaging, longitudinal data from larger populations, and translational research are all essential areas for further research. Interestingly, CAR T-cell therapy can also be used to reverse cardiac fibrosis in murine models. Altogether this underscores the need to broadly understand how T-cells, endogenous and engineered, may impact cardiovascular diseases.

Keywords

CAR T-cells, bispecific T-cell engager, cardiotoxicity, cardio-oncology

Abbreviations

CAR, chimeric antigen receptor; BiTE, bispecific T-cell engager; ALL, acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; MHC, major histocompatibility complex; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; BCMA, B-cell maturation antigen; CVAs, cerebrovascular accidents; MI, myocardial infarctions; FDA, food and drug administration; ECG, electrocardiogram; MACE, major adverse cardiovascular events; hsTropT, high-sensitivity troponin T; NTproBNP, N-terminal pro-B natriuretic peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukins; MMP, matrix metalloproteinases; MRI, cardiac magnetic resonance imaging; TNFα, tumor necrosis factor α; GLS, global longitudinal strain; GDMT, guideline-directed medical therapy.

Received: June 7, 2022; Revised: September 17, 2022; Accepted: September 27, 2022.

Introduction

Immunotherapy is now a well-established pillar of cancer therapy in addition to standard chemotherapy, surgery, and radiation. The discovery of tumor-mediated immunosuppression and its relationship with malignancy progression paved the way for T cell-activating strategies. The success of checkpoint inhibitors led to a paradigm shift in oncology and direct therapeutic use of T-cells for therapy is now quickly evolving.

Chimeric antigen receptor T-cells (CAR T-cells) are T lymphocytes that have been genetically engineered to produce a specific T-cell receptor. Chimeric antigen receptors (CARs) have undergone many iterations of stepwise advancement and were first approved by the Food and Drug Administration (FDA) in 2017 for relapsed/refractory B-cell Acute Lymphoblastic Leukemia (B-ALL) in children and young adults, and diffuse large B-cell lymphoma (DLBCL) in adults.[1] In particular the unique advantage of this system is that unlike innate T cells, CAR T-cells can recognize antigens

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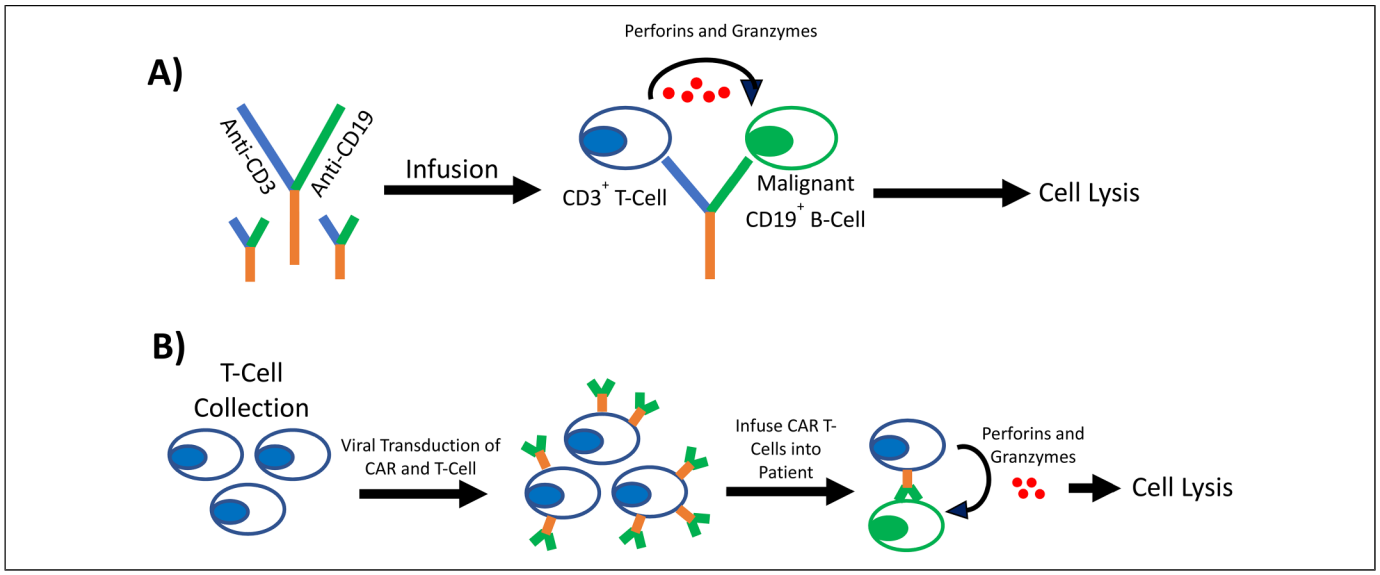

Figure 1. **(A)** administration process for BiTEs: bispecific antibodies with two different single-chain variable fragments against CD3 and CD19 are infused into a patient. These antibodies bind to both T-cells and malignant CD19 + B-cells simultaneously. This promotes T-cell cytotoxic activity. The T-cells release proteins like perforins and granzymes which initiate tumor cell lysis. **(B)** Administration process for CAR T-cells: T-cells are collected from peripheral blood and transduced with the gene encoding for the chimeric antigen receptor. These newly modified T-cells are then infused into the patient where they bind malignant tumor cells and release perforins and granzymes to cause tumor cell lysis.

without a presentation from the major histocompatibility complex (MHC). Furthermore, the chimeric receptor combines both antigen-binding and T-cell activating functions to allow for immune activation, tumor cell recognition, and destruction. Essentially T cells are isolated from either a patient's own blood (autologous) or from a healthy donor (allogeneic), genetically engineered to express a specific CAR, and then infused into the patient.[2] Prior to infusion patients often receive a lymphodepleting chemotherapy regimen most commonly including fludarabine and cyclophosphamide.[3] This promotes selective expansion of the adoptively transferred T-cells over endogenous lymphocytes. The target antigen is relatively specific to cancer cells to avoid the destruction of healthy cells and as the CAR T-cells detect their target antigen they become further activated and proliferate *in vivo* in order to treat malignancy (Figure 1).

Other types of T-cell therapies are also currently being developed, including bispecific T-cell engager (BiTE) antibodies. BiTE therapies are synthetic antibodies that bind two different antigens: one is a tumor-specific antigen and the other is an antigen that allows binding to endogenous immune cells. This simultaneous binding of T-cells and tumor cells allows for more efficient tumor cell lysis. Compared to CAR T-cell therapy which requires successful leukapheresis, T-cell isolation, viral transduction, and patient conditioning, BiTE therapy can be available off the shelf and does not require lymphodepleting chemotherapy (Table 1).[3,4] Blinatumomab is the first BiTE antibody to be FDA approved. It redirects CD3 + T-cells to CD19 + leukemic blasts and is approved for the treatment of relapsed/refractory B-cell precursor acute lymphoblastic leukemia (BCP-ALL) and BCP-ALL with minimal residual disease.[3] A single-arm trial blinatumomab showed a complete remission rate of 32% and the median duration of response was 6.7 months.[5]

CAR T-cells are given typically as a single infusion and the T-cells can persist and expand in patients. However, blinatumomab has an *in vivo* half-life of 2–4 hours and requires continuous intravenous infusion over 28 days per cycle.[4] The benefit of this approach is however that the infusion can be stopped at any time to reverse immune activation and immune-related adverse events. On the other hand, CAR T-cells have the potential to engraft long-term and create a constant pool of T cells that can quickly respond to disease recurrence before it becomes clinically evident.

Table 1. Comparison of BiTEs and CAR T-cells.

Characteristics	BiTEs	CAR T-Cells
Current available products	Blinatumomab	Axicabtagene ciloleucel Brexucabtagene autoleucel Tisagenlecleucel Lisacabtagene maraleucel Idecabtagene vicleucel Ciltacabtagene autoleucel
Target antigens	CD3 and CD19	CD19 or BCMA
Product type	Protein antibody	Virus transduced T-cells
Effector cells	Endogenous T-cells	Exogenous engineered T-cells
Pre-treatment chemotherapy	None	Lymphodepletion
Administration	Continuous infusion for cycle duration	One time

As CAR T-cells become activated, proliferate, and carry out their cytotoxic functions there can often be a significant release of inflammatory cytokines that cause known side effects such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Severe CRS has been associated with a higher disease burden and is typically treated with supportive care, corticosteroids, and tocilizumab (anti-IL6 monoclonal antibody).[6] In this review, we aim to summarize existing evidence on the monitoring, detection, and management of cardiac injury among patients receiving cellular therapies and provide areas of need for future research.

Overview of Current FDA-Approved CAR T-Cell Therapies

CAR T-cell therapy has been most extensively studied for advanced B-cell hematologic malignancies including B-ALL, B-cell non-Hodgkin lymphoma, and multiple myeloma. Currently, there are six CAR T-cell products approved by the FDA. These include axicabtagene ciloleucel (anti-CD19),[7] brexucabtagene autoleucel (anti-CD19),[8] tisagenlecleucel (anti-CD19),[9] lisocabtagene maraleucel (anti-CD19),[10] idecabtagene vicleucel (anti-B cell maturation antigen),[11] and ciltacabtagene autoleucel (anti-B cell maturation antigen)[12] (Table 2).

Axicabtagene ciloleucel (axi-cel) is approved for relapsed/refractory DLBCL and follicular lymphoma in adults.[13] In the initial phase 2, multicenter study axi-cel showed an overall response rate of 82%, complete response rate of 54% at 6 months, and an overall survival rate of 52% at 18 months.[14] Brexucabtagene autoleucel is approved for relapsed/refractory mantle cell lymphoma (MCL) and B-ALL. Its phase 2 study showed an overall response rate of 93%, a complete response rate of 67% at 6 months, and an overall survival rate of 83% at 12 months.[15] Tisagenlecleucel is approved for relapsed/refractory B-cell ALL in children and young adults and also for relapsed/refractory DLBCL in adults. In its phase 2 study for relapsed/refractory B-cell ALL there was an overall survival rate of 76% at 12 months.[16] In another phase 2 study for relapsed/refractory DLBCL there was an overall response rate of 52%, complete response rate of 40%, and a relapse-free survival rate of 65% at 12 months.[17] Lisocabtagene maraleucel is approved for relapsed/refractory large B-cell lymphoma. Its phase 1 study showed an overall response rate of 73%, a complete response rate of 53%, and an overall survival rate of 58% at 12 months.[18] Idecabtagene vicleucel is approved for relapsed/refractory multiple myeloma.[19,20] Its phase 2 study showed an overall response rate of 73%, a complete response rate of 33%, and an overall survival rate of 78% at 12 months.[20] Ciltacabtagene autoleucel is approved for relapsed/refractory multiple myeloma and its phase 1b/2 study showed an overall response rate of 97%, a complete response rate of 67%, and an overall survival rate of 80% at 12 months.[21]

Newer research is constantly building on the CAR T-cell concept to target additional malignancies including solid tumors and even expanding the concept into non-malignant diseases such as autoimmune diseases.[22,23] As indications and applications of CAR T-cell therapy continue to expand, it is crucial to better understand treatment-associated toxicities and how to prognosticate and manage them effectively. Conversely, given recent experimental findings suggesting a potential role of certain CAR T-cell approaches in reversing cardiac fibrosis, it is likewise essential to learn from current CAR T-cell approaches to inform the potential development of cardiovascular immunotherapeutics.[24]

Adverse Cardiac Effects

Cardiovascular toxicities are not uncommon among patients undergoing CAR T-cell therapy.[25] A recent pharmacovigilance study of the FDA adverse event reporting system reported 2.8% tachyarrhythmias, 2.6% cardiomyopathies, 1.8% cardiogenic

Table 2. Summary of Current FDA-Approved CAR T-Cell Therapies and Cardiac Toxicities from Package Inserts.

Drug	Target antigen	Target disease	Patient population (relapsed/refractory disease)	Incidence of reported cardiac toxicity
Tisagenlecleucel	CD19	B-cell ALL	Children and young adults	Tachycardia (26%), cardiac failure (7%), cardiac arrest (4%)
		DLBCL	Adults	Tachycardia (13%), arrhythmia (6%)
Axicabtagene ciloleucel	CD19	DLBCL	Adults	Tachycardia (43%–57%), arrhythmia (14%–23%), cardiac failure (1%–6%), cardiac arrest (4%)
		Follicular lymphoma	Adults	Tachycardia (44%), arrhythmia (21%), cardiac failure (2%)
Brexucabtagene autoleucel	CD19	Mantle cell lymphoma	Adults	Tachycardia (45%), bradycardia (10%), non-ventricular arrhythmias (10%)
		B-cell ALL	Adults	Tachycardia (63%), arrhythmia (15%), cardiac failure (4%)
Lisocabtagene maraleucel	CD19	DLBCL	Adults	Tachycardia (25%), arrhythmia (6%), cardiomyoopathy (1.5%)
Idecabtagene vicleucel	BCMA	Multiple myeloma	Adults	Tachycardia (19%), atrial fibrillation (4.7%), cardiomyopathy (1.6%)
Ciltacabtagene autoleucel	BCMA	Multiple myeloma	Adults	Tachycardia (27%), arrhythmia (8%), chest pain (7%)

shock, 1.7% pleural disorders, 0.4% pericardial diseases, and 1.6% venous thromboembolic events.[26] However, higher rates have been reported among the initial Phase I-III trials where approximately 10–30% of patients experienced a decline in left ventricular ejection fraction.[2] This likely represents an underestimate of the major adverse cardiovascular events (MACE) given that many trials excluded patients with significant cardiovascular comorbidities.

Major adverse cardiovascular events include arrhythmias, cardiomyopathy/heart failure, cerebrovascular accidents (CVAs), and myocardial infarctions (MI). A retrospective study from Steiner *et al* reported that 16% of patients developed at least one MACE within thirty days of CAR T-cell treatment.[27] Age greater than 60 years, earlier CRS start, CRS grade greater than or equal to 3, longer duration of CRS, and need for tocilizumab were all significantly associated with increased thirty-day risk of MACE.[27] Alvi *et al* also reported that of 137 patients studied, 55 patients experienced CRS grade 2 or higher and within that cohort 24 patients had a positive troponin after treatment. Among patients with a positive troponin after treatment, eight patients had newly reduced ejection fraction. In this study, five patients also experienced new arrhythmias and six patients experienced cardiovascular death.[28] Lefebvre *et al* showed that approximately 21% of patients experienced a MACE. With regards to arrhythmias, tachyarrhythmias are more common than bradyarrhythmias, and Goldman *et al* reported atrial fibrillation to be more common than ventricular arrhythmias.[26] Not many studies have examined the incidence of electrocardiogram (ECG) changes; however, a study of cardiac dysfunction among pediatric CAR T-cell recipients showed that 18% of patients with hypotension requiring inotropic support had new ST segment changes.[29] Other studies have also reported asymptomatic prolongation of the QTc interval [30] and new-onset supraventricular tachycardia, and atrial fibrillation or flutter.[28,31] Furthermore, chest pain has not been consistently studied but the FDA package insert for ciltacabtagene autoleucel does report chest pain as an adverse event occurring in approximately 8% of patients.[12] Of note, BiTE therapy can also be associated with cardiovascular adverse events. For example with blinatumomab, CRS was reported for 12% of the patients and the most common cardiovascular adverse events included hypertension (5–8%), hypotension (12–14%), and sinus tachycardia (5–6%). Serious events such as MI, atrial arrhythmias, congestive heart failure, and cardiac arrest are overall rare (<0.5%).[32] While the exact rates of MACE either with CAR T-cells or BiTEs may vary, studies across multiple large centers, trials, and registries show that cardiovascular adverse events are not uncommon and it is important for both cardiologists and oncologists to understand this entity.

Surveillance and Management of Adverse Cardiac Effects

Currently, there are no established guidelines regarding risk stratification of CAR T-cell recipients for early detection and treatment of cardiovascular toxicities. Based on available data we propose careful pre-treatment screening of cardiovascular comorbidities using a baseline ECG, chemistry panel, troponin, B-Type Natriuretic Peptide (BNP), and transthoracic echocardiogram with global longitudinal strain (GLS). High-risk patients could include those greater than 60 years of age, those with elevated baseline troponin or BNP, those with demonstrated left ventricular dysfunction (baseline ejection fraction <55% or baseline abnormal GLS), or those with two or more high-risk co-morbidities. These include hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, heart failure, history of arrhythmia, moderate to severe coronary artery disease, history of cardiotoxic chemotherapy such as anthracyclines, or history of previous chest radiation.[33] Patients identified as high-risk individuals for cardiovascular toxicities based on the above criteria should be referred to a cardio-oncologist for cardiac status evaluation prior to CAR T-cell treatment. While time to optimize medications may be limited due to the often aggressive nature of the malignancy requiring CAR T-cell therapy, a thorough risk assessment by a cardio-oncologist may help develop personalized clinical management strategies in anticipation of a possible cardiovascular adverse event for a higher-risk patient. We suggest that this includes a baseline ECG, baseline echocardiogram with strain, monitoring with telemetry if a history of arrhythmias, checking serum biomarkers such as troponin or BNP at days 0, 3, and 7 post CAR T-cell infusion and having a low threshold to repeat an echocardiogram with strain for assessment of early myocardial dysfunction if new heart failure symptoms, elevation in biomarkers, and/or high-grade CRS. Patients who develop high-grade CRS ($\geq$ grade 2) after CAR T-cell infusion should be considered high-risk for cardiac toxicities such as new or worsening heart failure or new or worsening arrhythmias. These patients should be monitored closely with additional cardiac biomarkers, ECG, or echocardiography. Ultimately these patients should also follow up with a cardio-oncologist after any adverse event for close surveillance and further management.

Alongside corticosteroids and/or tocilizumab to treat CRS, in patients with evidence of cardiotoxicity GDMT or antiarrhythmic therapy should be utilized when clinically indicated. Currently, IL-6 inhibition with tocilizumab is the first-line treatment for severe CRS. Corticosteroids are primarily reserved for refractory CRS and are rapidly tapered after the CRS improves. This is primarily due to concerns about potential negative effects of corticosteroids on CAR T-cell efficacy though recent data suggest that high-dose dexamethasone and methylprednisolone may not have an impact on CAR T-cell efficacy or endurance.[34] Nonetheless, not much research has been done regarding the ability of prophylactic GDMT, corticosteroids, or tocilizumab to affect CAR T-cell-induced cardiac toxicities.

Similar to how patients undergo a perioperative risk assessment to facilitate informed decision-making, it will be useful to develop risk assessment tools for cardiac adverse events after CAR T-cell therapy. Currently, patients planned for noncardiac surgeries undergo stratification to provide a risk versus benefit calculation of surgical intervention weighed against the

possibility of cardiac morbidity and mortality.[35] One commonly used risk calculator includes the revised cardiac risk index (RCRI) and the score helps delineate the percentage risk of major cardiac complications based on a variety of factors including kidney disease, diabetes requiring insulin use, history of ischemic heart disease, history of congestive heart failure, and others.[36] Though this certainly varies in the context of emergency, urgent, and elective surgeries, it provides a helpful framework for both clinicians and patients.[37] Currently there is insufficient data to construct such a calculator for CAR T-cell-associated cardiac toxicity, but in the future, it will be helpful to consistently collect additional data points so a stepwise algorithm may be developed. Since CAR T-cell therapy is often undertaken in urgent to an emergent situation, a certain degree of cardiac toxicity will likely have to be tolerated but as indications and uses for cellular therapy expand, a more precise periprocedure risk calculator will help inform awareness, earlier detection, and management, especially for high risk patients. It is necessary for clinical trial design to incorporate a systematic collection of data including details regarding medical comorbidities and preexisting cardiovascular risk factors and also data regarding cardiac function including baseline and interval ECGs, echocardiograms, and biomarker measurements.

Future Research Directions of CAR T-Cell Therapy

A key research area in CAR T-cell treatment cardiotoxicity is to understand which clinical variables are associated with post-treatment cardiotoxicity. Biomarkers, cardiac imaging, study design, and translational research are all critical areas for research needs (Figure 2).

Biomarkers

Future studies are needed to define the role of cardiac biomarker monitoring in patients undergoing CAR T-cell treatment. While other studies have examined biomarkers predictive of severe CRS including interferon-gamma, IL6, sgp130, and sIL6R, few studies exist with regard to biomarkers predictive of CAR T-cell cardiotoxicity.[38–40] Hu *et al* conducted a prospective study of 40 patients receiving CAR T-cell treatment and measured high-sensitivity troponin T (hsTropT) and N-terminal pro-B natriuretic peptide (NTproBNP) at baseline, day 1, day 7, and day 21 after CAR T-cell treatment with the hypothesis that an elevation of troponin could indicate damage to myocardium similar to its utility in ischemic cardiomyopathy and that an elevation of NTproBNP could be a surrogate for cardiac strain similar to its use in heart failure. Highly sensitive TropT did not vary significantly over the course of treatment, but NTproBNP was progressively elevated compared to baseline on days 1 and 7.[41] However, this study was limited by sample size and was not powered to assess the correlation between NTproBNP and likelihood or timeframe of developing a MACE. Other retrospective studies have noted a role for elevation in serum troponin in identifying patients at high risk for cardiac events post CAR T-cell infusion.[42–44] In particular, Alvi *et al* noted that of patients who had both

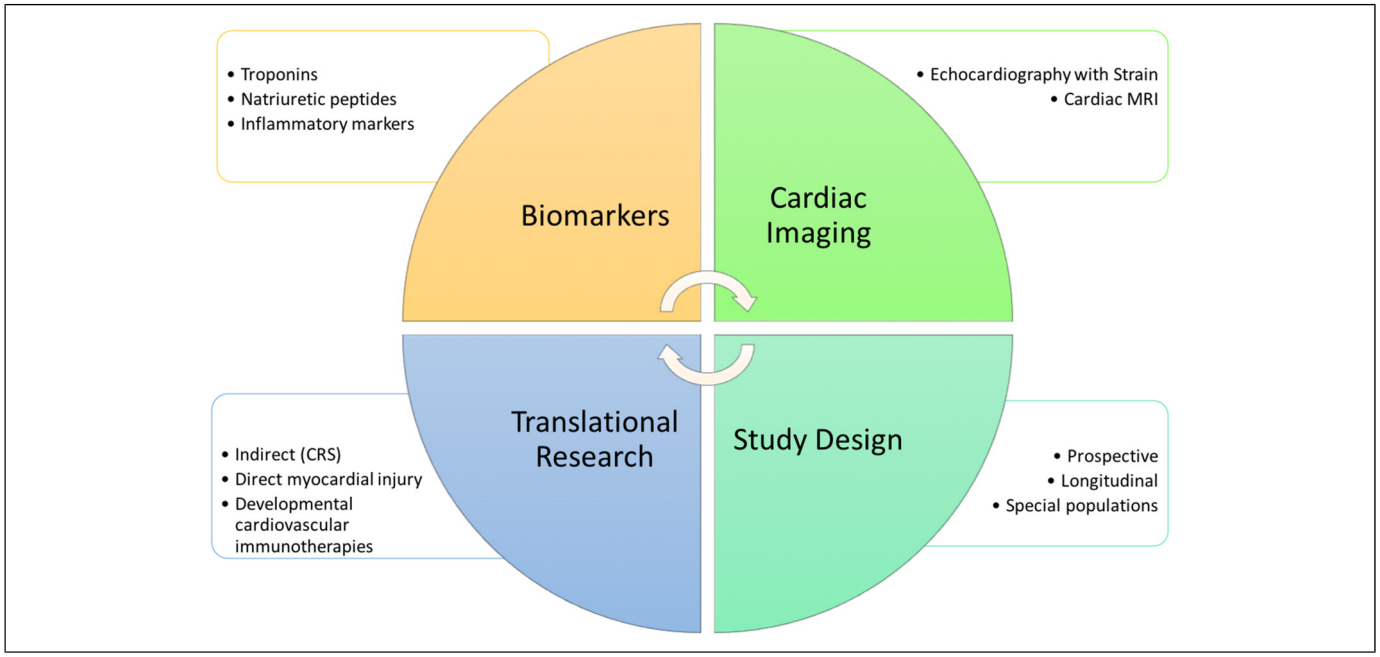

Figure 2. Future research directions for CAR T-cell-associated cardiotoxicities. As indications and applications of CAR T-cell therapy expand there are several key areas of future research. These areas include biomarkers to help predict impending cardiac injury, cardiac imaging to help risk stratify patient populations prior to receiving CAR T-cell therapy, translational research with attention to cytokine release syndrome (CRS) and the underlying pathophysiology driving cardiac injury, and improved study design with attention to cardiac toxicities.

pre- and post- CAR T-cell treatment troponin measurements, more than half of the patients had an elevation in serum troponin post CAR T-cell treatment (29/54, 54%) and 95% of high grade CRS (≥2) events were preceded by an elevated troponin.[28] Furthermore, very little is known about the value of inflammatory biomarkers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, and other inflammatory cytokines such as interleukins (IL) or matrix metalloproteinases (MMP) in association with MACE. These markers are often measured in conjunction with assessing CRS but the overall timing and pattern of their rise and fall has not been well characterized in the context of cardiac toxicity.[38,45] As surrogates of systemic inflammation, they may be useful to trend during the treatment course. Ultimately more systematic research with larger sample sizes and pre-defined time points is needed to fully characterize their utility in relation to cardiotoxic adverse events.

Cardiac Imaging

Another prospective area of research is the utility of various imaging modalities in assessing CAR T-cell toxicities. To date, few studies have systematically employed serial echocardiograms to assess cardiac function. Ganatra *et al* reported new or worsening cardiomyopathy in 10% of CAR T-cell recipients but in this study serial echocardiograms were primarily done for patients experiencing higher-grade CRS or at the discretion of the treating physician. This may underestimate the true incidence of reduced ejection fraction and a prospective study with long-term, serial echocardiography would be informative for the future.[46] Although changes in left ventricular ejection fraction are the primary parameter to detect cardiomyopathy, novel echocardiographic techniques using speckle-tracking strain are also emerging as a tool for screening and monitoring cardiotoxic therapies. Subclinical left ventricular dysfunction can be detected by GLS measurements and can be a useful additive to ejection fraction and other echocardiographic parameters.[47,48] Shalabi *et al* showed that among 14 patients with strain measurements at baseline and during CRS, 9 patients had a relative reduction in GLS > 15%.[49] However, this is a small sample size among pediatric patients and additional studies are warranted. Cardiac magnetic resonance imaging (MRI) has also yet to be studied in the context of CAR T-cell cardiotoxicity. Cardiac MRI can often provide additional diagnostic data over echocardiograms and is useful to rule-out myocarditis but may be difficult to obtain quickly, especially in the acute toxicity period.

Study Design

Furthermore, longitudinal studies of the cardiotoxic effects should also be undertaken. Data so far suggests that decreased left ventricular ejection fraction related to cardiotoxicity in many cases may recover but very little systematic longitudinal monitoring exists for these cases. For example, one study of pediatric patients showed that persistent dysfunction at 6-month follow-up was rare, but this was limited by a sample size of 10 patients that had documented echocardiographic dysfunction among a total study population of 98 patients.[29] Additional serial longitudinal GLS measurements may also be a more sensitive way to detect subtle, persistent abnormalities. Ultimately despite the apparent recovery, questions of whether these CAR T-cell-associated cardiotoxic events may increase risk for future cardiac events given their long-term engraftment remain unanswered.[46] Given the limited follow-up and relatively small sample sizes of single-center studies it is crucial that cardiovascular toxicities be assessed in larger, prospective studies.

Special populations, such as pediatric and young adults receiving CAR T-cell treatment may have unique long-term cardiac sequelae and require monitoring.[49] Fitzgerald *et al* studied 39 pediatric and young adult patients undergoing CAR T-cell treatment for relapsed/refractory ALL. This study identified grade 3–4 CRS in 18 subjects and found that 10 suffered vasogenic shock requiring a vasoactive agent which took a median of 4 days to resolve.[50] Another study by Burstein *et al* showed that 24 of 98 patients experienced hypotension requiring inotropic support and 10 patients showed worsened echocardiographic systolic function. Factors associated with hypotension requiring inotropic support included higher pretreatment blast percentage on bone marrow biopsy, and baseline lower ejection fraction or diastolic dysfunction.[29]

Translational Research

Several studies have focused on the correlation between CRS and cardiotoxicity. Emerging research suggests that vascular endothelial activation can contribute to the development of CRS and ICANS.[51,52] Therefore, blockade of tumor necrosis factor α (TNFα) and IL-1β may have therapeutic potential.[51] However, the role of endothelial activation, TNFα, and IL-1β in CAR T-cell-associated cardiac events has yet not been explored. CRS has also been hypothesized to play a role in CAR T-cell cardiotoxicity. Perhaps the acute onset, widespread immune and inflammatory activation precipitate a critical illness or stress-induced cardiomyopathy though more research in this area is needed. Research does suggest that early treatment with tocilizumab (anti-IL6 receptor antagonist) may help mitigate cardiotoxicity and research by Alvi *et al* showed that cardiovascular event risk increased 1.7-fold with each 12-hour delay to tocilizumab.[28] Direct cardiac injury is also another hypothesis. A case report of melanoma-associated antigen 3 (MAGE-A3) CAR T-cells showed cardiac histopathologic analysis with evidence of cardiac myonecrosis and T-cell infiltration in two patients who died from cardiogenic shock.[53] The cardiac toxicity in this case represented a cross-reactivity of the T-cell receptor to an unintended target antigen, titin, a sarcomeric protein expressed in cardiomyocytes. Another example of on-target, off-tumor toxicity includes possible cross-reactivity between anti-mesothelin CAR T-cells with normal mesothelin expressed on serous cells of the pleura and

pericardium causing pleuropericarditis, though this was not shown in a recent phase I trial.[54]

Insights for Developmental Cardiovascular Immunotherapies

While CAR T-cell therapy may be associated with cardiovascular toxicities, recent research has also shown success in utilizing CAR T-cell therapy to attenuate cardiac fibrosis in murine models.[24] While previous CAR T-cells targeting fibroblast activation protein (FAP) were used in a mouse model of hypertensive cardiac injury,[55] Rurik *et al* developed a unique method to generate transient CAR T-cells *in vivo* to bypass the need for *ex vivo* cell manufacturing and to minimize long-term side effects of persistently inhibiting the anti-fibrotic response. In this study targeted lipid nanoparticles were able to reprogram T-cells and analysis of a murine model of heart disease showed that the approach was able to reduce fibrosis and restore cardiac function.[24]

Other developing cardiovascular immune therapies include engineered CAR Treg cells directed against atherosclerosis-relevant epitopes to suppress local inflammation and developing tolerogenic Treg-based vaccines to prevent and treat cardiovascular diseases.[56] Overall this highlights how an improved understanding of T-cell biology in cardiovascular disease can be leveraged for both better management of cardiovascular adverse events and to expand CAR T-cell use for directed immunotherapy of cardiovascular diseases.

Conclusions

A better understanding of patient characteristics before and after undergoing CAR T-cell therapy will help inform improved therapy selection, prognosis, and management of patients receiving cellular therapies. There are several areas of future research needs, including biomarkers, cardiac imaging, longitudinal studies, special attention to sub-populations and translational research on mechanisms of cardiotoxicity. Increasing knowledge of the adaptive immune response and a better understanding of both engineered and non-engineered T-cell function in cardiovascular tissues can help inform future cardiovascular immunotherapies. Furthermore, as cellular therapies move beyond T-cells and expand into chimeric antigen NK cells and macrophages, it is important to keep in mind potential cardiotoxicities and incorporate cardiac parameters prospectively into the design of clinical trials. This includes routine data collection about cardiac function at prespecificed intervals by assessing laboratory and imaging parameters through BNP, troponin, electrocardiography, and echocardiography with GLS. While this may not mitigate the risk of MACE entirely, it would help better understand the pathophysiology and evolution of cardiac injury after cellular therapies and could improve strategies for early detection and management.

Acknowledgments

None

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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