Title

T-cell Immunotherapy and Cardiovascular Disease: Chimeric Antigen Receptor T-cell and Bispecific T-cell Engager Therapies.

Journal

Heart failure clinics, 18(3)

ISSN

1551-7136

Authors

Stein-Merlob, Ashley F
Ganatra, Sarju
Yang, Eric H

Publication Date

2022-07-01

Peer reviewed

T-cell Immunotherapy and Cardiovascular Disease

Chimeric Antigen Receptor T-cell and Bispecific T-cell Engager Therapies

Ashley F. Stein-Merlob, MD[a,b,1], Sarju Ganatra, MD[c,2,3,*], Eric H. Yang, MD[a,b,2,4,*]

KEYWORDS

• Cardiotoxicity • Immunotherapy • Chimeric Antigen Receptor (CAR) T-cell therapy
• Bispecific T-cell engager (BiTE) therapy • Cardio-Oncology

KEY POINTS

- Chimeric antigen receptor (CAR) T-cell therapy and bispecific T-cell engager (BiTE) therapies are novel immunotherapies for the treatment of refractory or relapsed leukemia, lymphoma, and multiple myeloma.
- An adverse effect of CAR T-cell and BiTE therapy is the development of cytokine release syndrome (CRS), ranging from mild flu-like symptoms to severe hemodynamic collapse, and can be associated with cardiotoxicity.
- Cardiotoxic manifestations of CAR T-cell therapy include hypotension, cardiomyopathy, heart failure, arrhythmia, myocardial injury, circulatory collapse, and cardiac arrest.
- Cardiovascular evaluation before CAR T-cell therapy, particularly for patients at increased risk of adverse cardiovascular events, should include evaluating for coronary ischemia and/or significant structural heart disease, as well as the optimization of preexisting or suspected cardiovascular disease in the anticipation of potential hemodynamic changes with high-grade CRS.
- Treatment of cardiotoxicity and high-grade CRS includes supportive care, anti-IL-6 agent such as tocilizumab and possibly corticosteroids.

INTRODUCTION

T-cell-based immunotherapy, including chimeric antigen receptor (CAR) T-cell and bispecific T-cell engager (BiTE) therapies, has transformed the field of oncology and particularly the treatment of relapsed or refractory lymphoma and leukemia. Immunotherapies harness the antitumor properties of the patient's native immune system to treat a wide variety of malignancies. In CAR T-cell therapy, T-cells are engineered *in vitro* to express a tumor-targeted antigen and then infused to target malignant cells.[1] BiTE therapy uses an engineered antibody with 2 antigen-binding sites that targets both a tumor-cell specific antigen and a native T-cell specific antigen (CD3) to

[a] Division of Cardiology, Department of Medicine, University of California at Los Angeles, Los Angeles, CA, USA; [b] Division of Cardiology, Department of Medicine, UCLA-Cardio-Oncology Program, University of California at Los Angeles, Los Angeles, CA, USA; [c] Cardio-Oncology Program, Division of Cardiovascular Medicine, Department of Medicine, Lahey Hospital and Medical Center, Burlington, MA, USA
[1] Present address: 650 Charles E. Young Dr. South, A2-237 CHS, Los Angeles, CA 90095-1679.
[2] Authors have contributed equally.
[3] Present address: 41 Mall Road, Burlington, MA 01805, USA.
[4] Address: 100 Medical Plaza, Suite 630, Los Angeles, CA 90095.
* Corresponding authors.
E-mail addresses: sarju.ganatra@lahey.org (S.G.); ehyang@mednet.ucla.edu (E.H.Y.)
Twitter: @A_SteinMerlob (A.F.S.-M.); @SarjuGanatraMD (S.G.); @datsunian (E.H.Y.)

Heart Failure Clin 18 (2022) 443–454
https://doi.org/10.1016/j.hfc.2022.02.008

colocalize these cells.[2,3] Although early clinical trials did not reveal significantly associated cardiotoxicity, with the growing use of immunotherapy in real-world, high-risk populations there has been greater recognition of off-target adverse effects including cardiotoxicity.

The scientific basis of CAR T-cell therapy has been in development for 3 decades with the first CAR T-cells engineered in the early 1990s. The most widely studied, and first FDA-approved, CAR T-cell therapies are directed at the B-lymphocyte antigen CD19. There are now 4 FDA-approved CD19-directed CAR T-cell therapies, 2 of which have been approved since 2020. These therapies, axicabtagene ciloleucel,[4] brexucabtagene autoleucel,[5] tisagenlecleucel,[6] and lisocabtagene maraleucel,[7] are approved for the treatment of relapsed or refractory hematologic malignancies including B-cell acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and mantle cell lymphoma (Fig. 1). In early 2021, idecabtagene vicleucel was the first B-cell maturation antigen (BCMA) targeted CAR T-cell therapy approved for treatment-refractory multiple myeloma.[8] To date, there is only one FDA-approved BiTE therapy, blinatumomab, for B-cell precursor ALL in multiple populations (see Fig. 1).[9]

MECHANISMS OF CHIMERIC ANTIGEN RECEPTOR T-CELL AND BISPECIFIC T-CELL ENGAGER THERAPIES

CAR T-cell immunotherapy uses genetically engineered cells to induce tumor-cell apoptosis by targeting tumor-specific antigens (Fig. 2, Panel A). Production of these specialized cells requires first isolating T-cells from human blood originating from the patient themselves (autologous) or from a healthy donor (allogeneic). Leukocytes are isolated via leukapheresis and specific T-cells are expanded using IL-2 and anti-CD3 antibodies. Subsequently, the T-cells are purified and a gene that encodes an engineered CAR is transduced using a retroviral vector.[1] The patient receives lymphodepletion chemotherapy (ie, fludarabine, cyclophosphamide) before the infusion of the engineered CAR T-cells. Once infused, CAR T-cells proliferate and attack cells that contain the target antigen. However, this response can be accompanied by significant cytokine production and release, leading to cytokine release syndrome (CRS) which causes cardiotoxicity likely through direct and indirect mechanisms of cardiac injury.

Bispecific T-cell engager (BiTE) molecules are fusion proteins of linked single-chain variable fragments (scFv) with 2 different antigen-binding sites—one directed against the CD3 receptor, which leads to downstream activation of cytotoxic T lymphocytes, and another directed specifically at antigens of malignant cells. The linked BiTE protein colocalizes these cells, leading to cell linkage with cytolytic synapses to initiate selective cell lysis and death (Fig. 2, Panel B).[2,3]

CYTOKINE RELEASE SYNDROME

The presentation of CRS ranges from mild flu-like symptoms, including fever, fatigue, headache, arthralgia, and myalgia, to severe, hemodynamically unstable presentations, including hypotension, systemic inflammatory response, coagulopathy,

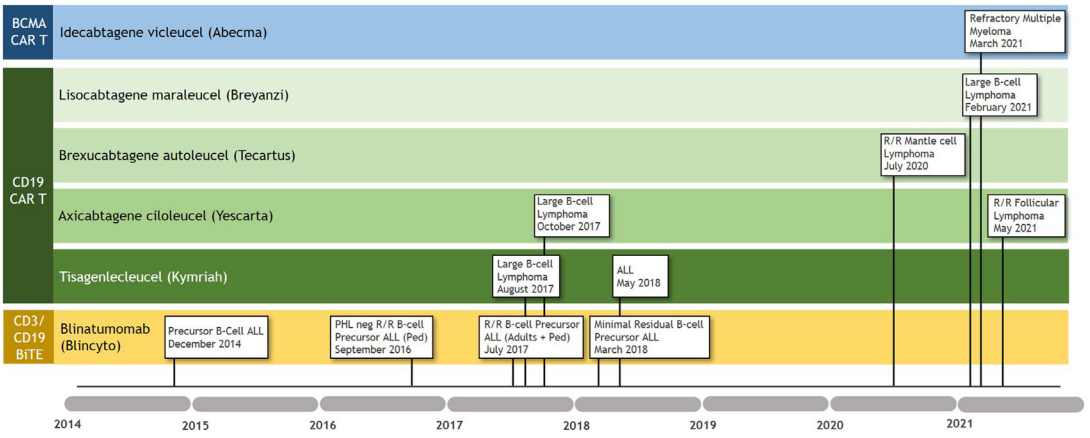

Fig. 1. Timeline of FDA-approval of chimeric antigen receptor (CAR) T-cell and bispecific T-cell engager (BiTE) therapies. Blinatumomab is the only FDA-approved BiTE therapy with multiple indications since 2014. There are 5 FDA-approved CAR T-cell therapies with 4 CD19-and one BCMA-targeted agent. There has been a significant increase in FDA approvals in 2020 to 2021. ALL = acute lymphoblastic leukemia; BCMA = B-cell maturation antigen; R/R = relapsed or refractory.

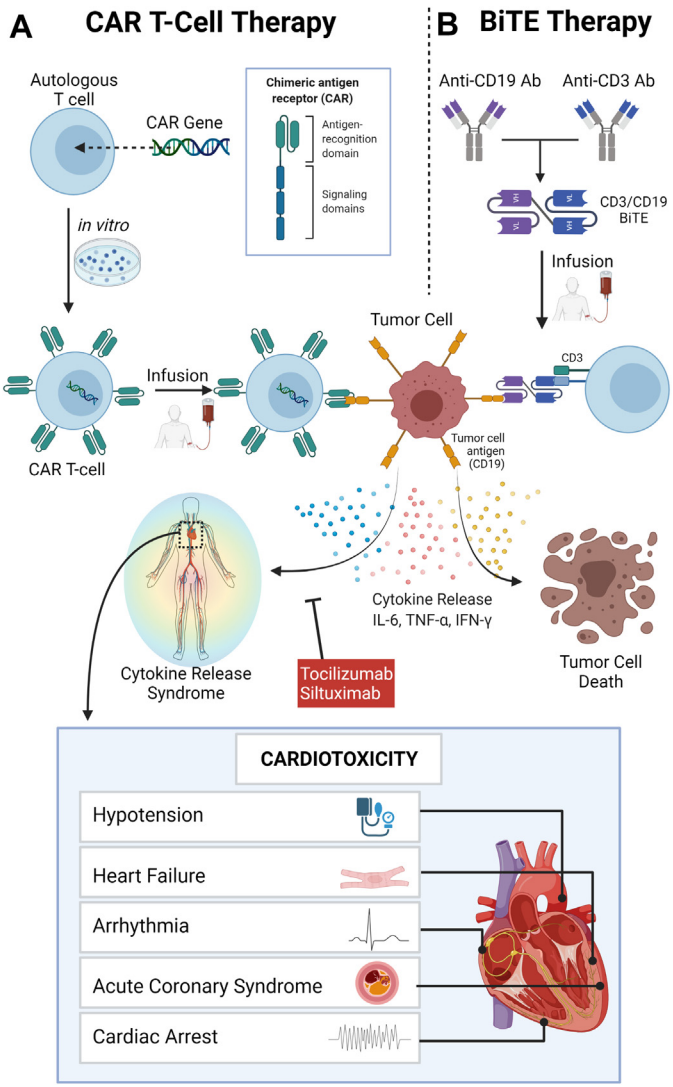

Fig. 2. Mechanism of chimeric antigen receptor (CAR) T-cell and bispecific T-cell engager (BiTE) therapies and cardiotoxicity. (*A*) Mechanism of CAR T-cell therapy. Autologous or allogenic T-cells are isolated and transfected *in vitro* with a gene encoding a chimeric antigen receptor that binds with an antigen expressed on tumor cells, most commonly the CD19. Engineered CAR T-cells are infused and then target antigen-positive tumor cells. Binding of the CAR and tumor cell antigen leads to tumor cell apoptosis. (*B*) Mechanism of BiTE therapy. The BiTE molecule links 2 scFv that bind a tumor antigen, such as CD19, and the T-cell antigen CD3. On binding these 2 antigens, the linked peptide brings the tumor and T-cell into close physical proximity. This activates the T-cell to cause tumor cell apoptosis. With both CAR T-cell and BiTE therapy, the T-cell activation that leads to tumor cell lysis initiates a cascade of cytokine release, including IL-1, IL-6, IFN-γ, and TNF-α. This inflammatory response can trigger CRS, a systemic disorder characterized by fever, hypotension, and multiorgan involvement. The most common treatment of CRS is tocilizumab, an anti-IL6 monoclonal antibody. CRS has been associated with cardiotoxicity including hypotension, heart failure, arrhythmia, acute coronary syndrome, and cardiac arrest. (Created with BioRender.com.)

multiorgan failure, and circulatory shock. CRS in CAR T-cell and BiTE therapy occurs through multiple mechanisms. Cytokines are released by infused CAR T-cells, activation of local "bystander" immune cells, and byproducts of CAR T-cell induced tumor cell apoptosis.[10] In particular, proliferation of CAR T-cells at the site of the targeted tumor cells leads to *in situ* cytokine production and systemic inflammatory response. It is thought that the release of cytokines changes the tumor microenvironment and provides additional antitumor effects beyond the direct cytotoxic effect of CAR T-cells of BiTE molecules.[3] Subsequent increases in vascular permeability and endothelial dysfunction causes hypotension, hypoxia, and multiorgan damage. Breakdown of the blood–brain barrier allows CAR T-cells, endogenous T-cells, and monocytes to translocate into the cerebrospinal fluid and central nervous system, potentially leading to immune effector cell-associated neurotoxicity syndrome (ICANS).[10]

A variety of cytokines are implicated in the inflammatory cascade of CRS. The key mediator of CRS is thought to be IL-6 [11]. It was initially hypothesized that CAR T-cells directly increased IL-6 levels in CRS, but later studies found IL-6 production primarily by macrophages and monocytes. IL-6 antagonism has been the major focus for the treatment of CRS. Lymphodepletion therapy increases interleukin (IL)-2, IL-7, and IL-15, which synergistically leads to CAR T-cell proliferation and increased survival.[12] Macrophages, activated CAR T-cells, endothelial cells and fibroblasts produce high levels of IL-1β, IL-1, and granulocyte–macrophage colony-stimulating factor (GM-CSF) before the onset of CRS.[12] Tumor necrosis factor (TNF)

exhibits direct tumoricidal activity while also mediating inflammation in CRS by activating T-cells, macrophages, and other immune cells. High levels of Interferon-γ, produced by activated T-cells, contribute to increased tissue permeability, including the blood–brain barrier, and have been associated with severe CRS.

The combination of sepsis-like stress of CRS and direct toxic effects of cytokines, particularly IL-6, is thought to contribute to myocardial dysfunction and subsequent cardiotoxicity.[13] Severe CRS also seems to trigger endothelial cell activation, including the upregulation of Ang-2 and von Willebrand factor, leading to clinical manifestations of capillary leakage, coagulopathy, and hypotension.[11,12]

MECHANISMS OF CARDIOTOXICITY

The mechanisms of cardiotoxicity from CAR T-cell and BiTE therapies are not well understood. Immunotherapy-related cardiotoxicities are thought to stem from several key mechanisms, including on-target, on-tumor effects (CRS), on-target, off-tumor effects (direct injury by T-cells of native tissue that share a common antigen with the tumor), and off-target, off-tumor effects (transduced T-cell unexpectedly attacks antigen other than intended tumor antigen).[14] The primary driver of CAR T-cell and BiTE-associated cardiotoxicity is thought to be "on-target, on-tumor" adverse effects of CRS, which is the most common adverse effect of CAR T-cell treatments. CRS stems from activated T lymphocytes, monocytes, macrophages, and endothelial cells releasing systemic inflammatory cytokines leading to multiorgan involvement. In contrast, the first investigational patient-administered CAR T-cell therapy directed to melanoma-associated antigen 3 (MAGEA3) had significant "off-target, off-tumor" cardiotoxicity due to cross-reactivity of the MAGEA3 and myocyte titin protein.[15,16] This cross-reactivity led to fatal, fulminant acute myocarditis in 2 patients, limiting the clinical use of this agent. At this time, there have been no significant "off-target, off-tumor" effects specifically reported for CAR T-cell therapy.

CLINICAL EVIDENCE OF CARDIOTOXICITY

Early clinical trials of CAR T-cell therapy with highly selective patient enrollment reported significant rates of CRS, although the overall incidence of serious cardiovascular events was low. Initial Phase 2 trials showed a CRS incidence of up to 93% (**Table 1**) and with severe (greater than or equal to Grade 3) CRS in up to 46% of patients.[17–22] The notable exception, however, was a pediatric study of relapsed and refractory acute lymphoblastic leukemia (ELIANA), which found an increased incidence of heart failure and cardiovascular death (2.7% and 4.0%, respectively).[17]

Subsequently, real-world institutional cohort studies have demonstrated significant incidences of cardiotoxicity not seen in Phase 2 trials despite similar rates of CRS. Cardiotoxicities include heart failure, arrhythmias, and myocardial infarction (see **Table 1**). In a single-center cohort study of 145 adult patients undergoing CD19-directed CAR T-cell therapy for DLBCL, ALL, and CLL, major adverse cardiac events (MACE) occurred in 21% of patients at a median of 11 days (interquartile range [IQR]: 6–151 days).[23] In the second study of 137 adult patients with DLBCL, transformed follicular lymphoma and multiple myeloma, there was a 12% incidence of MACE with median onset 21 days (IQR: 11–38 days).[24] The incidence of cardiovascular death was 4.3%,[24] the highest among clinical studies of cardiotoxicity (see **Table 1**). A cross-sectional analysis of the FDA Adverse Events Reporting System (FAERS), found that 19.7% of all adverse events reported to the FDA were cardiovascular related to the most reported cardiotoxicities being arrhythmia (77.6%), heart failure (14.3%), and myocardial infarction (0.5%). This may suggest that when CAR T-cell therapy is used more broadly under real-world conditions with higher risk patients, the incidence and impact of such cardiotoxicity is higher than previously estimated.

The development of heart failure with CD19-targeted CAR T-cell therapy was first noted in the pediatric population. In the pediatric trial of tisagenlecleucel in relapsed or refractory B-cell ALL (n = 75), there was a 2.7% incidence of symptomatic heart failure.[17] However, retrospectively, the incidence in the pediatric population has been as high as 10.8%, with reduced left ventricular ejection fraction (LVEF) in 41% of patients with hypotension requiring vasopressor support.[25] At time of discharge, 60% of these patients had persistent cardiac dysfunction. In the adult population, the incidence of symptomatic heart failure is as high as 15%.[23] Of 116 patients with relapsed or refractory non-Hodgkin's lymphoma with serial echocardiography during CD19-targeted CAR T-cell therapy, 10.3% (n = 12) developed new or worsening cardiomyopathy with an LVEF decline from 58% to 37% after a median duration of 12.5 days (range 2–24 days).[26] In long-term follow-up, LVEF improved in 75% of patients with reduced LVEF with normalization in half of the patients. In BiTE therapy, there are limited data on the incidence of heart failure. However, there is a case report of the development of fatal

Table 1
Major studies reporting chimeric antigen receptor (CAR) T-cell and bispecific T-cell engager (BiTE) cardiotoxicities

Study	Indication (n)	Therapy	CRS Any Grade (%)	CRS Grade 3–5 (%)	Adverse CV Event (%)									
					CV Death	Reduced LVEF	Symptomatic HF	ACS	Arrhythmia (all)	Atrial Fibrillation	Hypotension (all)	Hypotension (Vasopressors)	Cardiac Arrest	Other
A. Institutional Cohort Studies of Cardiotoxicity														
Burstein et al,[25] 2018	Pediatric ALL (2–27yo) (n = 93)	CD19-Directed CAR T	NA	25.8%	0	10.8						24	1.1	
Alvi et al,[24] 2019	DLBCL, MM, Transf. Follicular, Other (n = 137)	CD19-Directed CAR T	59%	4%	4.3	5.8	4.3		5.1	2.2			2.2	
Lefebvre et al,[23] 2020	DLBCL, ALL, CLL (n = 145)	CD19-Directed CAR T	72%	N/A	1.4		15.0	1.4	9.0	7.6		50.0	0.0	
Ganatra et al,[26] 2020	R/R NHL (n = 187)	CD19-Directed CAR T	83%	5.3%		10.3	5.2		7.0			7.0	0	
Qi et al,[31] 2021	MM, NHL, ALL (n = 126)	CD19-, CD20-, BCMA-Directed CAR T	81.7%	17.5%	1.6		11.9	7.1	5.6				0	
Brammer et al, 2021	R/R DLBCL, Mantle Cell or Follicular lymphoma (n = 90)	CD-19 Directed CAR T	88.9%	16.3%			1.1		12.2		87.8			Myocarditis (2.2%)
B. Single Therapy Investigational Phase 2 or 3 Studies														
TOWER Kantarjian, et al 2017	ALL (n = 271)	Blinatumomab, CD3/CD19 BiTE	14.2%	4.9%	0		0.4	0.4	0.8	0.4			0.4	HTN (6.4%)
ELIANA *Maude et al,[17] 2018*	Pediatrics, Young Adults R/R B-ALL (n = 75)	Tisagenlecleucel (CD19)	77%	46%	4.0		2.7					25		

(*continued on next page*)

Table 1
(*continued*)

Study	Indication (n)	Therapy	CRS Any Grade (%)	CRS Grade 3–5 (%)	Adverse CV Event (%)									
					CV Death	Reduced LVEF	Symptomatic HF	ACS	Arrhythmia (all)	Atrial Fibrillation	Hypotension (all)	Hypotension (Vasopressors)	Cardiac Arrest	Other
ZUMA-1 *Locke et al,*[18] *2018*	R/R B-ALL (n = 101)	Axicabtagene ciloleucel (CD19)	93%	11%	1.0						59	17	1.0	HTN (16%)
JULIET Schuster et al,[19] *2019*	R/R DLBCL	Tisagenlecleucel (CD19)	58%	21.5%	0							26		
ZUMA-2 Wang et al,[20] *2020*	R/R Mantle Cell lymphoma (n = 68)	Brexucabtagene autoleucel (CD19)	91%	15%							51	22		
Munshi et al,[21] *2021*	Refractory MM (n = 128)	Idecabtagene vicleucel (BCMA)	84%	5%							16	1.0		
TRANSCEND Abramson et al,[22] *2021*	R/R DLBCL (n = 269)	Lisocabtagene ***maraleucel*** (CD19)	42%	2%	0.3						22	3		HTN (14%)
C. Single Therapy Investigational Phase I Study														
Lee et al,[28] *2015*	Pediatrics, ALL or r/r NHL (n = 21)	Investigational CD19-Directed CAR T	76%	29%		5					19.0		5	QTc (5%), HTN (5%)
Shalabi et al,[44] *2020*	Pediatrics, Young Adults (R/R B-cell malignancies) (n = 52)	Investigational CD19-Directed CAR T	71%	17%		11.5						17.3	1.9	

(A) Retrospective single-institution cohort studies have provided the most detail regarding real-world cardiotoxicity of CAR T-cell therapies. Rates of heart failure, including reduced left ventricular ejection fraction (LVEF) and symptomatic heart failure, have been significantly higher than reported in early Phase 2 studies. (B) Important Phase 2 and Phase 3 single therapy CAR T-cell and BiTE therapy studies. The most commonly reported cardiotoxicity has been hypotension. ELIANA study was the notable exception for reporting significant rates of heart failure and cardiovascular death. (C) Phase I trials of investigation CAR T-cell therapies with reported cardiotoxicities. Colors indicate frequency of toxicity: red = greater than 10% incidence, yellow = 1 to 10% incidence, green = less than 1% incidence, gray = not reported

heart failure due to Blinatumomab administration in a 5-year-old boy with ALL. Further studies of heart failure in BiTE therapy, particularly with serial echocardiographic monitoring, are needed.

Arrhythmias have been reported with an incidence ranging from 5.1% to 12.2% (see **Table 1**). The most common arrhythmia is atrial fibrillation, followed by supraventricular tachycardia and rare nonsustained ventricular tachycardia.[23,24,27] Additionally, there have been multiple reports of QTc prolongation.[24,28]

Cardiotoxicity is a potentially fatal adverse effect of CAR T-cell therapy. In retrospective cohort studies, the incidence of cardiovascular death in adults undergoing CAR T-cell therapy ranges from 1.4% to 4.3%.[23,24] Notable, in a FAERS study of cardiotoxicity, the mortality in patients with cardiovascular adverse events was 30.1%.

Dedicated studies of cardiotoxicity in BiTE therapy are lacking. In the Phase 3 TOWER trial of blinatumomab, CRS and acute coronary syndrome occurred in 2.6% and 2.2% of patients, respectively.[29] A subsequent real-world study of blinatumomab showed grade 3 to 4 CRS in up to 19% of patients. Ongoing surveillance for adverse cardiovascular effects is warranted for this evolving immunotherapy.[30]

RISK FACTORS FOR CARDIOTOXICITY

CAR T-cell therapy-associated cardiotoxicity is often accompanied by other systemic toxicities, particularly CRS, neurotoxicity, and graft versus host disease.[18,31] In Alvi and colleagues, all patients who developed MACE had at least Grade 2 CRS. In a retrospective analysis, Grade 3 and 4 CRS conferred a significantly increased risk of developing cardiotoxicity with hazard ratios of 3.31 (95% confidence interval 1.55–7.09) and 9.79 (95% CI: 3.96–24.21), respectively.[23] Additionally, early onset of CRS was associated with an increased risk of developing cardiotoxicity.[31] Although one recent retrospective study casts doubt on this theory, showing no association between cardiotoxicity and CRS Grade 3 and above,[32] the predominating theory continues to be that most of the cardiotoxicity is related to the inflammatory cascade of CRS. Neurotoxicity, particularly immune effector cell-associated encephalopathy (ICANS)—previously called CAR T-cell related encephalopathy syndrome—has also been associated with cardiotoxicity (odds ratio, 1.76; 95% confidence interval, 1.20–2.60; $P = .004$).[33]

The risk of developing cardiotoxicity due to baseline cardiovascular disease and prior cancer treatments is still unclear. Prior radiation, anthracycline dose and other cardiotoxic chemotherapy has not been found to be associated with the development of cardiotoxicity or hypotension.[25,26] However, a major predictor of severe CRS in both CAR T-cell or BiTE therapy is preexisting disease burden before treatment.[12] Prior use of insulin, statins and aspirin have been associated with MACE, likely indicating higher baseline cardiovascular risk.[34] Renal dysfunction is also associated with the development of MACE.[31,34] Development of heart failure has been associated with increased age, hyperlipidemia and coronary artery disease.[26] Elevated troponin has been associated with the development of cardiotoxicity and may be an important marker to identify patients at risk of cardiotoxicity.[24]

Currently, there are limited data on the 3 newest CAR T-cell therapies that have been FDA approved since 2020 as they have not yet been included in published retrospective cohort studies. The most recent CD-19 targeted CAR T-cell therapy, lisocabtagene maraleucel (Beryanzi) has a different 4-1BB costimulatory domain, which was designed to reduce the incidence of CRS.[22] In the clinical trial, the overall incidence of CRS was similar to prior agents at 84%, but the rate of Grade 3 to 4 CRS was decreased significantly to 5%.[22] Idecabtagene vicleucel has a unique target, BCMA, and had a lower overall rate of CRS.[21] Further studies will be required to evaluate if this reduction in severe CRS contributes to a different cardiotoxicity profile.

CLINICAL MANAGEMENT

Pre-chimeric antigen receptor T-cell therapy cardiovascular workup

Currently, there is no standardized protocol for pretherapy cardiovascular evaluation. However, the expert consensus recommendation is that each patient should undergo a detailed cardiovascular examination along with obtaining an ECG. An echocardiogram should also be performed in all patients at baseline given the associated risk of cardiomyopathy and to rule out any significant valvular or other structural heart diseases.[35] If the patient has a prior history of cardiovascular disease, any significant cardiovascular symptoms, impaired exercise capacity, or any abnormality noted on initial workup, further risk stratification with functional stress testing may need to be considered to evaluate for underlying obstructive coronary artery disease or other structural heart diseases to ensure that the patient will be able to withstand the hemodynamic changes associated with a high-grade CRS (**Fig. 3**).[35,36]

Many patients who need to undergo CAR T-cell therapy have one or multiple cardiovascular

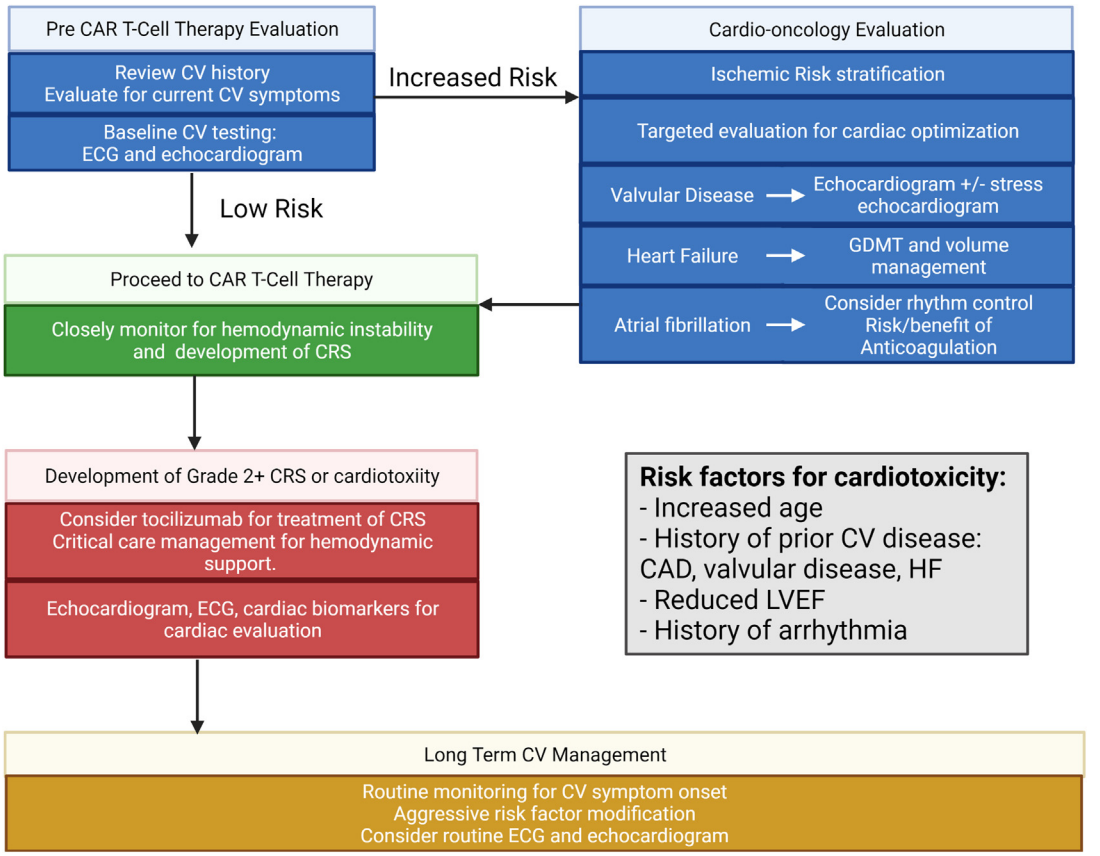

Fig. 3. Proposed algorithm for the management of cardiovascular risk and complications during chimeric antigen receptor (CAR) T-cell therapy. Before the initiation of CAR T-cell therapy all patients should undergo baseline evaluation to determine their level of cardiovascular risk. Patients with increased cardiovascular risk due to prior cardiovascular disease, current cardiovascular symptoms, or abnormal ECG or echocardiogram should be evaluated by a cardio-oncologist before the initiation of therapy. Ischemic evaluation should be pursued based on individual risk factors. Preexisting valvular heart disease, left ventricular dysfunction or arrhythmia should be medically optimized due to the potential for hemodynamic instability or cardiotoxicity during CAR T-cell therapy. Patients who develop CRS should be treated using the current standard of care with hemodynamic support and consideration of tocilizumab. Given the unknown long-term cardiovascular risks associated with CAR T-cell therapy, particular attention should be paid to aggressive risk factor modification and ongoing evaluation for the development of new cardiovascular toxicities after the completion of therapy. (Created with BioRender.com.)

comorbidities and are on medical therapies for those conditions.[26] Optimization of their preexisting cardiovascular conditions and their medications is crucial to minimize the CRS-associated adverse events. High-grade CRS is typically associated with hypotension, and hence it is important to consider either down titration or discontinuation of antihypertensive medications and diuretics.[35] Additionally, similar consideration should be given to antiplatelet and anticoagulation agents given the elevated risk of thrombocytopenia and, in turn bleeding events, on a case-by-case basis after weighing the risks and benefits.[35,37]

While the interaction between CAR T-cell therapy and preexisting cardiovascular conditions is not well established, patients with an uncorrected severe valvular disease or significant obstructive coronary artery disease are likely to suffer significant major adverse cardiovascular events even with transient hemodynamic changes associated with CRS. Although having a preexisting CVD may not be an absolute contraindication for receiving CAR T-cell therapy, such patients need to be identified, and their cardiovascular status should be optimized before CAR T-cell therapy so that they are able to withstand any potential hemodynamic instability during CRS.

Diagnosis

As the vast majority of adverse cardiovascular events with CAR T-cell therapy occur in the

context of CRS, prompt recognition of CRS is crucial. A high degree of suspicion and close surveillance with close monitoring of vital signs [especially heart rate and blood pressure (BP)] are required to recognize the CRS promptly and also to classify the severity. While the markers of inflammation such as C-reactive protein, ferritin, and IL-6 are typically elevated with CRS, it is not specific and could be elevated due to other conditions. Similarly, cardiac troponin can be elevated in the context of an adverse cardiovascular event or high-grade CRS. However, routine surveillance with serial cardiac troponin may not be required or helpful. An echocardiogram should be repeated in patients with cardiovascular symptoms, hemodynamic instability, and/or grade $\geq$ 2 CRS. For patients with CRS-associated hemodynamic instability, while considering CRS and associated cardiotoxicity, other possible etiologies, such as sepsis, tumor lysis syndrome, pulmonary embolism, or primary cardiac events should also be ruled out.

Management

The cornerstones of the management are supportive hemodynamic care along with targeted anti-IL-6 therapy and, if required, broader immunosuppression with corticosteroids.[35] Intravenous fluid resuscitation should be considered as a first-line intervention for patients with tachycardia and hypotension secondary to CRS, weighing the risk of vascular leak and pulmonary congestion. If hypotension persists, vasopressors should be considered. In select, very high-risk patients, invasive pulmonary artery monitoring may be required. In a unique example, a patient with DLBCL and anthracycline-induced cardiomyopathy underwent invasive continuous pulmonary artery pressure monitoring with implantable CardioMEMS. Invasive monitoring tailored diuretic dosing during acute decompensated heart failure, noncardiogenic pulmonary edema, intubation, vasopressor use, and arrhythmia.[38]

Given the central mechanistic role of excessive IL-6 in causing CAR T-cell therapy associated CRS as well as myocardial depression,[13] anti-IL-6 therapy is considered first-line therapy for high-grade CRS along with supportive care.[39] Tocilizumab is a monoclonal anti-IL-6 receptor antibody used in the management of CRS-related toxicity. Typically, 8 mg/kg intravenously is given, and this dose could be repeated up to 3 times 8 hours apart.[39] Shorter time from CRS onset to tocilizumab is shown to be associated with a lower rate of adverse cardiovascular events.[24] However, there is also an unproven concern that the anticancer efficacy of the CAR T-cell therapy may be reduced with the use of an anti-IL-6 agent. Hence, there is wide interinstitutional and interprovider variation in practice. While it is used generously with any grade CRS at some institutions, some experts believe that it should be reserved for patients with hemodynamic instability, such as hypotension requiring BP support for longer than 24 h, hypoxia, unstable arrhythmia, evidence of myocardial damage (increased troponin level), or new cardiomyopathy.

Siltuximab, another monoclonal antibody blocks IL-6 signaling by binding to IL-6 itself to prevent it from activating immune effector cells.[40] While it has not been studied extensively for the management of CRS, it has a higher affinity for IL-6 than tocilizumab. It can be considered in patients with refractory CRS to tocilizumab and corticosteroids. Unlike tocilizumab, siltuximab binds directly to IL-6 and not its receptors. Hence, it may decrease the IL-6 level in the central nervous system. In contrast, tocilizumab may potentially increase systemic and central nervous system IL-6 levels, which could precipitate or worsen neurotoxicity.[41]

Corticosteroids, by their broad immunosuppressive action, are effective in the treatment of CRS. However, given the concern of reduced CAR T-cell therapy efficacy with its use, they are often not used as a first-line agent and rather are considered second-line therapy for the management of CRS refractory to tocilizumab. Although corticosteroids are thought to potentially decrease CAR T-cell efficacy, this concern has been unfounded, and results from initial clinical trials did not show an association between the use of corticosteroids and cancer response rates.[41]

Prognosis

The long-term prognosis of patients who develop CAR T-cell therapy-associated adverse cardiovascular events remains unknown. A recent study of patients who developed CAR T-cell therapy-associated cardiomyopathy showed that LVEF recovered in 75% of patients with supportive care.[26] Long-term follow-up studies are needed to better understand cardiovascular effects of immune system modulation and continued circulation of CAR T-cells, particularly to assess if patients are at a higher risk of developing metabolic syndrome, hypertension, vascular disease, and cardiomyopathy after a latent period following CAR T-cell therapy.

In terms of patients cancer-related prognosis, there has been a theorized relationship between early immune-related toxicity and improved response to certain types of immunotherapy. In CAR T-cell therapy particularly, there has been

a reported association between increased progression-free survival and moderate CRS. However, no specific association was noted with cardiotoxicity in particular.[32] Future, large-scale studies will be needed to determine the prognostic significance of cardiotoxicity.

NOVEL CARDIOVASCULAR TARGETED CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPIES

In addition to the current oncologic applications of CAR T-cell therapy, preclinical studies have investigated the use of CAR T-cell therapy as a treatment of cardiovascular disease itself. In particular, antifibrotic CAR T-cells directed against fibroblast activated protein (FAP) have been used to target activated fibroblasts and prevent myocardial fibrosis in heart failure.[42,43] In addition to the traditional *in vitro* created FAP CAR T-cells, a novel method of *in vivo* CAR T-cell generation delivers mRNA packaged in CD5-targeted lipid nanoparticles (LNP)–different from the CD19 target used in cancer treatment—which can be intravenously injected. Using LNPs, mRNA is transported to lymphocyte cytoplasm and produces FAP CAR T-cells *in vivo*.[42] This method is based on the same technology as the LNP-mRNA COVID vaccines. Because mRNA is delivered to the cytoplasm, it does not integrate into the lymphocyte genome and thus creates a transient CAR T-cell. In a mouse model of pressure overload induced heart failure, FAP CAR T-cell treated mice using both methods of CAR T-cell production showed improvement in left ventricular systolic and diastolic function and left ventricular end-diastolic and end-systolic volumes. Histologic analysis showed a significant reduction in fibrosis. This promising and highly adaptable technology has the potential to target multiple traditional mechanisms and pathways of cardiovascular disease with the goal of translation to clinical care. In one preclinical study, FAP-targeted CAR T-cells were associated with cachexia and bone toxicity via effects on FAP mediated stromal cells in the bone marrow while having limited effects on the progression of various tumor types. Additionally, whether such FAP-directed CAR T-cell therapy is associated with CRS and cardiovascular complications similar to anti-CD-19 CAR T-cell therapy remain to be seen.

SUMMARY

Immunotherapy is a rapidly evolving field with frequent new applications of existing medications and a constant influx of novel, investigational therapies. Current CAR T-cell and BiTE therapies have been shown to cause infrequent, but potentially severe, cardiotoxicities that were not immediately apparent during initial clinical trials. As new immunotherapies enter the market, careful surveillance for emerging cardiotoxicities will be needed. Additionally, further studies and registry data are warranted to better understand the mechanisms, risk factors, and treatment of immunotherapy-associated cardiotoxicity.

CLINICS CARE POINTS

- All patients undergoing chimeric antigen receptor (CAR) T-cell or bispecific T-cell engager (BiTE) therapies should undergo baseline cardiovascular risk stratification and optimization of preexisting or suspected cardiovascular disease, particularly coronary artery disease, valvular disease, heart failure, and atrial fibrillation.
- Manifestations of CAR T-cell therapy-associated cardiotoxicity most commonly occur within the first few weeks after the initiation of therapy and can present as hypotension, cardiomyopathy, heart failure, arrhythmia, or myocardial injury.
- Patients undergoing CAR T-cell therapy who develop cytokine release syndrome (CRS) should be evaluated for cardiotoxicity with serum troponin levels, ECG, and echocardiogram.
- Cardiac biomarker elevation (ie, troponin) can be commonly seen in CAR T-cell therapy; however, in the presence of high-grade CRS, it can be associated with an increased risk of major adverse cardiovascular events.
- Early treatment of CRS with anti-IL-6 agents, such as tocilizumab, may lead to reduced rates of adverse cardiovascular events, but future research is needed.

DISCLOSURES

Dr E.H. Yang receives research funding from CSL Behring, Boehringer Ingelheim and Eli Lilly and Company (nonrelevant). Dr A.F. Stein-Merlob is supported by the National Institutes of Health Cardiovascular Scientist Training Program (T32 HL007895)

REFERENCES

1. Kalos M, Levine BL, Porter DL, et al. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with

advanced leukemia. Sci translational Med 2011; 3(95). 95ra73-95ra73.
2. Sedykh S, Prinz V, Buneva V, et al. Bispecific antibodies: design, therapy, perspectives. Drug Des Development Ther 2018;ume 12:195–208.
3. Slaney CY, Wang P, Darcy PK, et al. CARs versus BiTEs: A Comparison between T Cell–Redirection Strategies for Cancer Treatment. Cancer Discov 2018;8(8):924–34.
4. YESCARTA (axicabtagene ciloleucel) FDA Approval. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel. Accessed March 27, 2022.
5. TECARTUS (brexucabtagene autoleucel) FDA Approval. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/tecartus-brexucabtagene-autoleucel. Accessed August 31 2021.
6. KYMRIAH (tisagenlecleucel) FDA Approval. 2021. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/kymriah-tisagenlecleucel. Accessed August 31 2021.
7. BREYANZI (lisocabtagene maraleucel) FDA Approval. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel. Accessed August 31 2021.
8. ABECMA (idecabtagene vicleucel) FDA Approval. Available at: https://www.fda.gov/vaccines-blood-biologics/abecma-idecabtagene-vicleucel. Accessed August 31 2021.
9. FDA Approval letter for blinatumomab. Available at: *https://wwwaccessdatafdagov/drugsatfda_docs/nda/2014/125557Orig1s000Approvpdf*.
10. Morris EC, Neelapu SS, Giavridis T, et al. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nat Rev Immunol 2022 Feb;22(2):85–96.
11. Khadka RH, Sakemura R, Kenderian SS, et al. Management of cytokine release syndrome: an update on emerging antigen-specific T cell engaging immunotherapies. Immunotherapy 2019;11(10):851–7.
12. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. J ImmunoTherapy Cancer 2018;6(1).
13. Pathan N, Hemingway CA, Alizadeh AA, et al. Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. Lancet 2004;363(9404):203–9.
14. Baik AH, Oluwole OO, Johnson DB, et al. Mechanisms of Cardiovascular Toxicities Associated With Immunotherapies. Circ Res 2021;128(11):1780–801.
15. Cameron BJ, Gerry AB, Dukes J, et al. Identification of a Titin-Derived HLA-A1-Presented Peptide as a Cross-Reactive Target for Engineered MAGE A3-Directed T Cells. Sci Translational Med 2013; 5(197). 197ra103-197ra191.
16. Linette GP, Stadtmauer EA, Maus MV, et al. Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma. Blood 2013;122(6):863–71.
17. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 2018; 378(5):439–48.
18. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20(1):31–42.
19. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 2019; 380(1):45–56.
20. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med 2020;382(14):1331–42.
21. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med 2021;384(8): 705–16.
22. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet 2020;396(10254):839–52.
23. Lefebvre B, Kang Y, Smith AM, et al. Cardiovascular Effects of CAR T Cell Therapy. JACC: CardioOncology. 2020;2(2):193–203.
24. Alvi RM, Frigault MJ, Fradley MG, et al. Cardiovascular Events Among Adults Treated With Chimeric Antigen Receptor T-Cells (CAR-T). J Am Coll Cardiol 2019;74(25):3099–108.
25. Burstein DS, Maude S, Grupp S, et al. Cardiac Profile of Chimeric Antigen Receptor T Cell Therapy in Children: A Single-Institution Experience. Biol Blood Marrow Transplant 2018;24(8):1590–5.
26. Ganatra S, Redd R, Hayek SS, et al. Chimeric Antigen Receptor T-Cell Therapy-Associated Cardiomyopathy in Patients With Refractory or Relapsed Non-Hodgkin Lymphoma. Circulation 2020;142(17):1687–90.
27. Herrmann J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. Nat Rev Cardiol 2020;17(8):474–502.
28. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015;385(9967):517–28.
29. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med 2017; 376(9):836–47.

30. Apel A, Ofran Y, Wolach O, et al. Safety and efficacy of blinatumomab: a real world data. Ann Hematol 2020;99(4):835–8.
31. Qi K, Yan Z, Cheng H, et al. An Analysis of Cardiac Disorders Associated With Chimeric Antigen Receptor T Cell Therapy in 126 Patients: A Single-Centre Retrospective Study. Front Oncol 2021;11(2264).
32. Brammer JE, Braunstein Z, Katapadi A, et al. Early toxicity and clinical outcomes after chimeric antigen receptor T-cell (CAR-T) therapy for lymphoma. J ImmunoTherapy Cancer 2021;9(8):e002303.
33. Guha A, Addison D, Jain P, et al. Cardiovascular Events Associated with Chimeric Antigen Receptor T Cell Therapy: Cross-Sectional FDA Adverse Events Reporting System Analysis. Biol Blood Marrow Transpl 2020;26(12):2211–6.
34. Khunger A, Battel L, Wadhawan A, et al. New Insights into Mechanisms of Immune Checkpoint Inhibitor-Induced Cardiovascular Toxicity. Curr Oncol Rep 2020;22(7).
35. Ganatra S, Carver JR, Hayek SS, et al. Chimeric Antigen Receptor T-Cell Therapy for Cancer and Heart: JACC Council Perspectives. J Am Coll Cardiol 2019;74(25):3153–63.
36. Ganatra S, Parikh R, Neilan TG. Cardiotoxicity of Immune Therapy. Cardiol Clin 2019;37(4):385–97.
37. Dal'Bo N, Patel R, Parikh R, et al. Cardiotoxicity of Contemporary Anticancer Immunotherapy. Curr Treat Options Cardiovasc Med 2020;22(12).
38. Kanelidis AJ, Raikhelkar J, Kim G, et al. Cardio-MEMS-Guided CAR T Cell Therapy for Lymphoma in a Patient With Anthracycline-Induced Cardiomyopathy. JACC: CardioOncology 2020;2(3):515–8.
39. Le RQ, Li L, Yuan W, et al. FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. Oncologist 2018;23(8):943–7.
40. Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323–35.
41. Locke FL, Neelapu SS, Bartlett NL, et al. Preliminary Results of Prophylactic Tocilizumab after Axicabtageneciloleucel (axi-cel; KTE-C19) Treatment for Patients with Refractory,Aggressive Non-Hodgkin Lymphoma (NHL). Blood 2017;130(Supplement 1):1547.
42. Rurik JG, Tombácz I, Yadegari A, et al. CAR T cells produced in vivo to treat cardiac injury. Science 2022;375(6576):91–6.
43. Aghajanian H, Kimura T, Rurik JG, et al. Targeting cardiac fibrosis with engineered T cells. Nature 2019;573(7774):430–3.
44. Shalabi H, Sachdev V, Kulshreshtha A, et al. Impact of cytokine release syndrome on cardiac function following CD19 CAR-T cell therapy in children and young adults with hematological malignancies. J Immunother Cancer 2020;8(2).