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PRIMERS IN CARDIO-ONCOLOGY

Cardiotoxicity of T-Cell Antineoplastic Therapies

JACC: CardioOncology Primer

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ABSTRACT

T-cell therapies, such as chimeric antigen receptor (CAR) T-cell, bispecific T-cell engager (BiTE) and tumor-infiltrating lymphocyte (TIL) therapies, fight cancer cells harboring specific tumor antigens. However, activation of the immune response by these therapies can lead to a systemic inflammatory response, termed cytokine release syndrome (CRS), that can result in adverse events, including cardiotoxicity. Retrospective studies have shown that cardiovascular complications occur in 10% to 20% of patients who develop high-grade CRS after CAR T-cell therapy and can include cardiomyopathy, heart failure, arrhythmias, and myocardial infarction. While cardiotoxicities have been less commonly reported with BiTE and TIL therapies, systematic surveillance for cardiotoxicity has not been performed. Patients undergoing T-cell therapies should be screened for cardiovascular conditions that may not be able to withstand the hemodynamic perturbations imposed by CRS. Generalized management of CRS, including the use of the interleukin-6 antagonist, tocilizumab, for high-grade CRS, is used to mitigate the risk of cardiotoxicity. (J Am Coll Cardiol CardioOnc 2022;4:616–623)

T-cell therapies, such as chimeric antigen receptor (CAR) T-cell, bispecific T-cell engager (BiTE), and tumor-infiltrating lymphocyte (TIL) therapies, have changed the treatment landscape for patients with a variety of malignancies.[1-3] However, these therapies can be associated with adverse cardiovascular effects. Although clinical trials included patients without significant cardiovascular comorbidities, real-world use of these therapies includes patients with pre-existing cardiovascular risk factors and disease, increasing the potential for associated cardiotoxicities. Hence, awareness and surveillance are crucial for early recognition and treatment of cardiotoxicity.

CAR T cells are patient-derived T cells that are genetically engineered to target a tumor-specific antigen, such as CD19 or BCMA (B-cell maturation antigen), to induce tumor-cell apoptosis.[1] BiTE molecules are fusion proteins 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 an antigen present on malignant cells.[2,4] TILs are isolated from the tumor site, stimulated

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HIGHLIGHTS

- MACE are reported at variable frequencies with different T-cell therapies.
- High-grade CRS is a significant risk factor for the development of MACE.
- Pre-therapy cardiovascular evaluation and optimization are necessary. Surveillance echocardiography should be considered with high-grade CRS.
- Treatment of cardiotoxicity and high-grade CRS includes supportive care, anti-IL-6 therapies, and possibly corticosteroids.

with interleukin (IL)-2, grown in vitro, and then infused back into the patient.[3] Although the target antigens are preidentified and T-cell therapies are manufactured to fight cancer cells harboring those antigens, activation of the immune response can cascade and lead to systemic inflammation and downstream adverse effects, including cardiotoxicity (**Figure 1**).

MECHANISMS AND MANIFESTATIONS OF CARDIOTOXICITY

The mechanisms underlying immune-mediated cardiotoxicity can be divided into 3 broad categories: 1) on-target, on-tumor effects that lead to cytokine release syndrome (CRS); 2) on-target, off-tumor effects: direct T-cell-mediated injury of recipient organs that share target antigens with the tumor; and 3) off-target, off-tumor effects: the T cells unexpectedly attack an antigen other than the intended tumor antigen (**Figure 1**).[2-4]

Information regarding T-cell therapy-associated cardiotoxicity is based primarily on experience with CAR T-cell therapy. Evidence thus far suggests that cardiotoxicity occurs mainly in the context of CRS and is correlated with CRS severity. However, it is unclear if cardiotoxicity is merely an epiphenomenon of CRS. Additionally, certain CAR T-cell constructs, such as those directed against melanoma-associated antigen-3, demonstrated cross-reactivity against titin, a striated muscle protein in the heart, to cause fatal, fulminant myocarditis.[5] Furthermore, lymphodepletion with potentially cardiotoxic agents such as cyclophosphamide and anthracyclines, given prior to some T-cell therapies, may also contribute to the development of adverse cardiovascular events.

Activation of the immune system by T-cell therapies leads to a surge in circulating cytokines and chemokines (such as IL-2, interferon-alpha, IL-6, and granulocyte-macrophage colony-stimulating factor) that originate from the infused cells themselves, from activation and recruitment of other local immune cells (such as monocytes, macrophages, and dendritic cells), and as a result of therapy-mediated tumor-cell lysis.[6] This surge in cytokines can lead to a systemic inflammatory response, called CRS, which is characterized by fever and one or more of the following presentations: hypotension, hypoxia, and organ toxicity. Although many grading systems exist, the system put forth by the American Society for Transplantation and Cellular Therapy is commonly used to grade the severity of CRS.[7] CRS has been reported in 70% to 90% of patients undergoing CAR T-cell therapy. Although CRS is mostly mild in severity (grade 1), some patients exhibit serious systemic adverse effects (grades 2-4), including cardiovascular complications such as cardiomyopathy, heart failure (HF), arrhythmias, myocardial infarction and vascular leak syndrome with associated circulatory collapse and multiorgan failure.[8-10]

Among the cytokines involved in the inflammatory cascade, IL-6 has been implicated as a key mediator of CRS and in the pathophysiology of T-cell therapy-associated cardiotoxicity.[9] IL-6 up-regulation activates the gp130/STAT3 signaling pathway to promote oxidative stress, leading to mitochondrial dysfunction and cardiac hypertrophy. The increase in reactive oxygen species also increases cardiomyocyte apoptosis. In addition, IL-6 alters Ca^{2+} handling and reduces myocardial contractility, potentially resulting in diastolic dysfunction and arrhythmias.[11]

INCIDENCE OF CARDIOTOXICITY

CAR T-CELL THERAPY. Clinical trials of CAR T-cell therapy have reported low rates of cardiotoxicity, possibly due to selective patient enrollment. However, subsequent retrospective cohort studies have noted major adverse cardiovascular events (MACE) in 10% to 20% of patients (**Table 1**).

A retrospective study of 145 patients receiving CAR T-cell therapy for a variety of hematologic malignancies, with median follow-up of 456 days, reported 15% incidence of HF, 7.5% incidence of atrial fibrillation with 2 events of other arrhythmias (supraventricular tachycardia and nonsustained ventricular tachycardia), 2 episodes of acute coronary syndrome,

ABBREVIATIONS AND ACRONYMS

BCMA = B-cell maturation antigen

BiTE = bispecific T-cell engager

CAR = chimeric antigen receptor

CRS = cytokine release syndrome

HF = heart failure

ICSR = individual case safety report

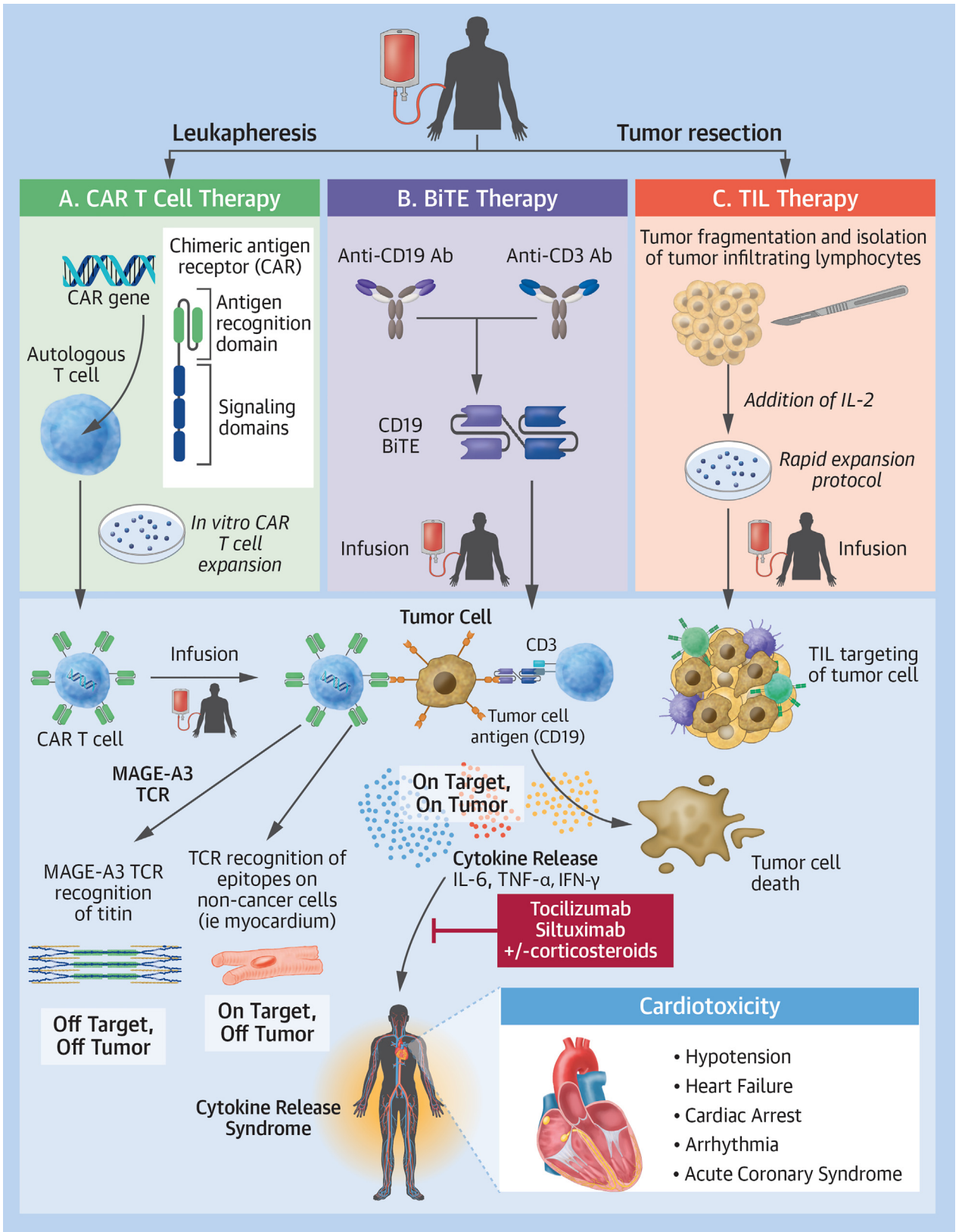
IL = interleukin

LVEF = left ventricular ejection fraction

MACE = major adverse cardiovascular event(s)

TIL = tumor-infiltrating lymphocyte

FIGURE 1 **Mechanisms of T-Cell Therapies and Manifestations of Cardiotoxicity**



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2 cardiac deaths attributed to pulseless electric activity, and a massive pulmonary embolism leading to ST-segment elevation myocardial infarction.[12]

An analysis of CAR T-cell therapy–related individual case safety reports (ICSRs) submitted to VigiBase, the international World Health Organization pharmacovigilance database, noted that 13% of ICSRs were related to cardiotoxicity, including cardiac arrhythmias, pericardial effusion, stress cardiomyopathy, left ventricular dysfunction, and cardiac arrest. Notably, 25% of these cases were fatal. Interestingly, cardiotoxicity-related ICSRs were more frequent with axicabtagene-ciloleucel (57.3%) compared with tisagenlecleucel-T (42.7%).[13]

Various arrhythmias have been reported with CAR T-cell therapy, with an incidence ranging from 5% to 12%. In another pharmacovigilance study leveraging the U.S. Food and Drug Administration Adverse Events Reporting System, the reporting OR was highest for atrial fibrillation, followed by ventricular arrhythmias. In age- and sex-adjusted models, tachyarrhythmias were reported more frequently with axicabtagene-ciloleucel than tisagenlecleucel.[14]

In a retrospective multi-institutional study of 116 patients undergoing CD19-targeted CAR T-cell therapy for relapsed or refractory diffuse large B-cell lymphoma, 10% developed new or worsening cardiomyopathy, with a median decline in left ventricular ejection fraction (LVEF) from 58% to 37% on serial echocardiography performed in the context of high-grade CRS.[10] Although similar rates of cardiomyopathy were seen in a pediatric study of patients treated with CAR T-cell therapy for acute lymphoblastic leukemia,[15] another study of 137 adult patients with CAR T-cell therapy for lymphomas and multiple myeloma reported cardiomyopathy in 5.8% patients, which may be an underestimate given the lack of systematic echocardiographic surveillance in this study.[8]

Evidence regarding the risk for CRS and cardiotoxicity is based largely on CD19-directed CAR T-cell therapy. Available data from one clinical trial suggest that the occurrence of all-grade and high-grade CRS is similar with BCMA-directed CAR T-cell therapy.[16]

BiTE AND TIL. Data regarding the incidence of cardiotoxicity with BiTE and TIL therapies are limited (**Table 1**). In the phase 3 TOWER (Blinatumomab Versus Standard of Care Chemotherapy in Patients With Relapsed or Refractory Acute Lymphoblastic Leukemia) trial of blinatumomab (BiTE therapy), CRS was reported in 14.2% of patients, with grade ≥3 CRS in about 5% of patients.[2] A subsequent real-world study of blinatumomab showed grade 3 or 4 CRS in up to 9% of patients, suggesting that the true incidence of cardiotoxicity may be higher than that observed in clinical trials.[17] Overall, the rates of CRS with BiTE therapy have ranged from 0% to 20%.[18,19] In the TOWER trial, acute coronary syndrome was reported in 0.4% of patients. Additionally, a case of fatal HF was reported after blinatumomab treatment in a child with acute lymphoblastic leukemia.[2]

There are no reports of CRS with TIL therapy. However, several studies have reported hypotension and arrhythmias. In a single-center retrospective study of 43 patients undergoing TIL treatment for melanoma, 14% developed atrial fibrillation, 32% experienced shock requiring vasopressors, and there were no cases of cardiomyopathy or HF.[20]

It is important to note that these data should not be interpreted as evidence of the absence of significant cardiotoxicity with BiTE and TIL therapies; rather, further studies with systematic surveillance for cardiotoxicity are needed in patients undergoing these treatments.

TIMING OF CARDIOTOXICITY

Although CRS can develop at any time and as long as CAR T cells persist in the circulation, it typically occurs early after CAR T-cell infusion with a median time of 2.2 days, with the highest risk for occurrence within the first 2 weeks. Cardiotoxicity similarly occurs early after administration of CAR T-cell administration, usually within the first 2 weeks.[10,21]

RISK FACTORS

High-grade CRS, particularly grade ≥3 CRS, is a risk factor for cardiotoxicity. In a retrospective analysis of 145 patients, grade 3 CRS (HR: 8.42; $P < 0.001$) and

FIGURE 1 Continued

Mechanism of **(A)** chimeric antigen receptor (CAR) T-cell, **(B)** bispecific T-cell engager (BiTE), and **(C)** tumor-infiltrating lymphocyte (TIL) therapy. With these therapies, T-cell activation leads to tumor-cell lysis and initiates a cascade of cytokine release, including interleukin (IL)-1, IL-6, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α. This inflammatory response can trigger cytokine release syndrome (CRS), which has been associated with hypotension, heart failure, arrhythmias, acute coronary syndrome, and cardiac arrest. CRS is most commonly treated with tocilizumab, an anti-IL-6 monoclonal antibody (Ab), and steroids are used in refractory cases. Partly adapted Stein-Merlob AF, Ganatra S, Yan EH. T-cell immunotherapy and cardiovascular disease: chimeric antigen receptor T-cell and bispecific T-cell engager therapies. *Heart Fail Clin.* 2022;18(3):443-454. Created using BioRender.com. MAGE-A3 = melanoma-associated antigen 3; TCR = T-cell receptor.

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TABLE 1 Reported Cardiotoxicity With T-Cell Cell Therapies

First Author/Study (Year)	Indication	Therapeutic Agents	CRS Any Grade, %	CRS Grade ≥3, %
CAR T-cell therapy				
Lee et al (2015)[25]	Pediatrics, ALL, or R/R NHL (n = 21)	Investigational CD19-directed CAR T cells	76	29
ELIANA: Maude et al. (2018)[26]	Pediatrics, young adults R/R B-ALL (n = 75)	Tisagenlecleucel (CD19)	77	46
Burstein et al (2018)[15]	Pediatric ALL (2-27 y) (n = 93)	CD19-directed CAR T cells	–	25.8
ZUMA-1: Locke et al. (2019)[27]	R/R B-ALL (n = 101)	Axicabtagene ciloleucel (CD19)	93	11
JULIET: Schuster et al (2019)[28]	R/R DLBCL (n = 93)	Tisagenlecleucel (CD19)	58	21.5
Alvi et al (2019)[8]	DLBCL, MM, transformed follicular, other (n = 137)	CD19- and BCMA-directed CAR T cells	59	4
Shalabi et al. (2020)[29]	Pediatrics, young adults (R/R B-cell malignancies) (n = 52)	Investigational CD19-directed CAR T cells	71	17
Lefebvre et al (2020)[12]	DLBCL, ALL, CLL (n = 145)	CD19-directed CAR T cells	72	–
Ganatra et al (2020)[10]	R/R NHL (n = 187)	CD19-directed CAR T cells	83	5.3
ZUMA-2: Wang et al (2020)[30]	R/R mantle-cell lymphoma (n = 68)	Brexucabtagene autoleucel (CD19)	91	15
Munshi et al (2021)[16]	Refractory MM (n = 128)	Idecabtagene vicleucel (BCMA)	84	5
TRANSCEND: Abramson et al (2021)[31]	R/R DLBCL (n = 269)	Lisocabtagene maraleucel (CD19)	42	2
Qi et al (2021)[32]	MM, NHL, ALL (n = 126)	CD19-, CD20-, and BCMA-directed CAR T cells	81.7	17.5
Brammer et al (2021)[33]	R/R DLBCL, mantle-cell or follicular lymphoma (n = 90)	CD19-directed CAR T cells	88.9	16.3
BiTE				
Topp et al (2011)[18]	ALL (n = 21)	Blinatumomab	–	–
TOWER: Kantarjian et al (2017)[2]	ALL (n = 271)	Blinatumomab	14.2	4.9
Jung et al (2019)[19]	ALL (n = 50)	Blinatumomab	20	4
GIMEMA: Foà et al (2020)[34]	ALL (n = 58)	Blinatumomab+ dasatinib	–	–
Couturier et al (2020)[35]	ALL (n = 26)	Blinatumomab + ponatinib	11.5	–
Apel et al (2020)[17]	ALL (n = 21)	Blinatumomab	19	9.5
TILs				
Chandran et al (2017)[36]	Melanoma (n = 21)	TILs	–	–
Sarnaik et al (2021)[37]	Melanoma (n = 66)	TILs	–	–
Fradley et al (2021)[20]	Melanoma (n = 43)	TILs	–	–

ALL = acute lymphoblastic lymphoma; B-ALL = B-cell acute lymphoblastic lymphoma; BCMA = B-cell maturation antigen; BiTE = bispecific T-cell engager; CAR = chimeric antigen receptor; CLL = chronic lymphocytic leukemia; CRS = cytokine release syndrome; CV = cardiovascular; DLBCL = diffuse large B-cell lymphoma; ELIANA = Study of Efficacy and Safety of CTL019 in Pediatric ALL Patients; GIMEMA = D-ALBA Frontline Sequential Dasatinib and Blinatumomab in Adult Philadelphia Positive Acute Lymphoblastic Leukemia; HTN = hypertension; JULIET = Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients; MM = multiple myeloma; NHL = non-Hodgkin lymphoma; QTc = corrected QT interval; R/R = relapsing/remitting; TIL = tumor-infiltrating lymphocyte; TOWER = Blinatumomab Versus Standard of Care Chemotherapy in Patients With Relapsed or Refractory Acute Lymphoblastic Leukemia; TRANSCEND = Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma; ZUMA-1 = Study Evaluating the Safety and Efficacy of KTE-C19 in Adult Participants With Refractory Aggressive Non-Hodgkin Lymphoma; ZUMA-2 = Study to Evaluate the Efficacy of Brexucabtagene Autoleucel (KTE-X19) in Participants With Relapsed/Refractory Mantle Cell Lymphoma.

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grade 4 CRS (HR: 29.86; $P < 0.001$) were independent predictors of cardiotoxicity and MACE.[12] Similar findings have been reported in other retrospective studies.[8,10] Although CRS is a common side effect of CAR T-cell therapy, factors that increase in vivo CAR T-cell numbers, such as high disease burden, higher infused CAR T-cell dose, or high-intensity lymphodepletion regimens before CAR T-cell administration, have been associated with an increased risk for high-grade CRS.[21]

Baseline cardiovascular risk factors and disease may also increase the risk for developing CAR T-cell-associated cardiomyopathy. In a retrospective study, patients who developed cardiomyopathy were older, were more likely to be on renin-angiotensin inhibitors and β-blockers at baseline (reflective of underlying risk factors), and had a greater prevalence of hyperlipidemia and coronary artery disease. Prior anthracycline or radiation exposure and a history of stem cell transplantation, commonly associated with the development of cardiomyopathy, were not associated with cardiotoxicity in this study.[10] Baseline renal insufficiency has also been identified as an independent risk factor for MACE.[12] As stated earlier, in studies based on adverse event reporting, cardiotoxicity appears to occur more frequently with axicabtagene-ciloleucel relative to tisagenlecleucel. However, these data should be interpreted with caution, as the true incidence of cardiotoxicity was not captured in these studies.[14]

PRETHERAPY EVALUATION

In the absence of evidence-based guidance, experts recommend a pretherapy cardiovascular examination, electrocardiography, and echocardiography in patients receiving T-cell therapies. Further evaluation for underlying obstructive coronary artery

TABLE 1 Continued

Adverse CV Event, %									
Cardiomyopathy	Heart Failure	Myocardial Infarction	Arrhythmia (All)	Atrial Fibrillation	Hypotension (All)	Shock Requiring Vasopressors	Cardiac Arrest	CV Death	Other
CAR T-cell therapy									
5	–	–	–	–	19.0	–	5	–	QTc (5%), HTN (5%)
–	2.7	–	–	–	–	25	–	4.0	–
10.8	–	–	–	–	–	24	1.1	0	–
–	–	–	–	–	59	17	1.0	1.0	HTN (16%)
–	–	–	–	–	–	26	–	0	–
5.8	4.3	–	5.1	2.2	–	–	2.2	4.3	–
11.5	–	–	–	–	–	17.3	1.9	–	–
–	15.0	1.4	9.0	7.6	–	50.0	0.0	1.4	–
10.3	5.2	–	7.0	–	–	7.0	0	–	–
–	–	–	–	–	51	22	–	–	–
–	–	–	–	–	16	1.0	–	–	–
–	–	–	–	–	22	3	–	0.3	HTN (14%)
–	11.9	7.1	5.6	–	–	–	0	1.6	–
–	1.1	–	12.2	–	87.8	–	–	–	Myocarditis (2.2%)
BiTE									
–	–	–	–	–	–	–	–	–	–
	0.4	0.4	0.8	0.4			0.4	0	HTN (6.4%)
–	–	–	–	–	–	–	–	–	–
–	–	–	1.7	1.7	–	–	–	–	–
–	–	–	–	–	–	–	–	–	–
TILs									
–	–	–	5	–	10	–	–	–	–
–	–	–	–	–	36	11	–	–	–
0	0	2.3	–	14	–	32.6	–	–	–

disease or other structural heart disease may be required in select patients with cardiovascular symptoms, impaired exercise capacity, histories of cardiovascular disease, or multiple cardiovascular risk factors to ensure the ability to withstand the hemodynamic perturbations imposed by high-grade CRS.[9]

Optimization of cardiovascular status and adjustment of medications may be necessary to minimize the risk for serious adverse events. For example, high-grade CRS is associated with hypotension, so antihypertensive medications may need to be down-titrated or discontinued temporarily. Similarly, given the increased risk for thrombocytopenia and bleeding, antiplatelet or antithrombotic medications may need to be adjusted on a case-by-case basis.[9]

DIAGNOSIS

All patients receiving T-cell therapies should undergo blood pressure monitoring. In our view, for patients with grade ≥2 CRS, hemodynamic instability, or any concerning symptoms for cardiotoxicity, electrocardiography, echocardiography, and measurements of cardiac biomarkers, including cardiac troponin and brain natriuretic peptide, should be obtained. Although troponin elevation has been associated with MACE,[8] routine surveillance with troponin may not be helpful in the absence of clinical concern. In contrast, surveillance echocardiography in patients with grade ≥2 CRS should be considered, regardless of symptoms, given that approximately 10% of patients may develop cardiomyopathy with downstream implications.[9] Neurotoxicity is also a common adverse effect of CAR T-cell therapy, and cardiovascular evaluation should be considered in those who develop neurotoxicity.

A thorough work-up should be performed to evaluate for other possible or contributory etiologies of hemodynamic instability, including sepsis, tumor lysis syndrome, pulmonary embolism, or primary cardiac events.

MANAGEMENT

As patients with grade ≥2 CRS are more likely to develop cardiotoxicity,[8,10,12] a generalized approach to the management of CRS is used to mitigate

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cardiotoxicity with additional specific cardiac interventions as needed. In addition to intravenous fluids, vasopressors, and oxygen supplementation as needed, the IL-6 antagonist tocilizumab or siltuximab (not Food and Drug Administration approved for the management of CRS) should be considered for moderate to severe CRS.[8,9] A shorter time to tocilizumab administration from the onset of CRS is associated with a lower risk for MACE.[8] Repeated doses of these agents may be required, and steroids are recommended in cases that are refractory to IL-6 antagonists. Furthermore, patients with grade 3 or 4 CRS should be transferred to intensive care for continuous monitoring, management of arrhythmias and circulatory shock, and provision of noninvasive positive pressure or mechanical ventilation as needed.

Preclinical studies have demonstrated the utility of the IL-1R antagonist anakinra alone and in combination with tocilizumab in the management of CAR T-cell therapy-associated CRS.[22] Case reports have also demonstrated its utility in patients with multiple myeloma receiving anti-BCMA CAR T-cell therapy.[23] These observations suggest that IL-1 inhibition may be a valuable adjunct in the management of CRS following CAR T-cell therapy.

CAR T-cell therapy has been associated with an increased risk for thrombosis and bleeding, in part related to disseminated intravascular coagulation in the context of CRS, and the risk for bleeding is increased in patients with pre-existing thrombocytopenia and neurotoxicity.[24] Therefore, in patients who develop acute coronary syndromes or atrial arrhythmias with CAR T-cell therapy, the risks and benefits of anticoagulation must be considered carefully.

PROGNOSIS

The prognosis of patients who develop T-cell therapy-associated cardiotoxicity is not well studied given patient heterogeneity and small sample sizes. In a retrospective study, among the 10% of patients who developed new or worsening cardiomyopathy, LVEF improved in 75% with supportive care, with only one-half returning to normal LVEFs after about 6 months of follow-up.[10] Additionally, those who developed cardiomyopathy had a higher need for vasopressor support (42% vs 8%; $P = 0.004$) and mechanical ventilation (25% vs 3%; $P = 0.014$) relative to those without cardiomyopathy.[10]

In retrospective cohort studies of adults undergoing CAR T-cell therapy, the incidence of death attributed to cardiotoxicity was 1.4% to 4.3%.[8,11] In addition, in a cross-sectional study leveraging Food and Drug Administration Adverse Events Reporting System data, all-cause mortality was increased in patients with cardiovascular adverse events (30.1% vs 21.1%).[14]

Long-term cardiovascular effects of T-cell therapies are poorly characterized, and prospective studies are needed. It is possible that persistent immune system alteration by circulating cells may pose a higher risk for developing metabolic syndrome, hypertension, vascular disease, and cardiomyopathy after a latent period.

FUTURE DIRECTIONS

There is growing enthusiasm to explore the utility of genetically engineered T cells in the treatment of solid tumors and autoimmune diseases and even to prevent myocardial fibrosis in patients with HF. As the indications and availability of T-cell therapies increase, so do the concerns for potential cardiotoxicity. A multidisciplinary approach to the management of patients on novel immunotherapies is needed to optimize outcomes, and cardio-oncologists play a vital role in the comprehensive care of these patients.

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