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Review

Cardiotoxicities of Chimeric Antigen Receptor T-Cell Therapy and Bispecific T-Cell Antibodies

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Abstract

Purpose of Review Chimeric antigen receptor T-cells (CAR-T) and bispecific antibodies (BiTE) are novel therapies used to treat hematologic malignancies, lung cancer and melanoma. With the increasing use of these novel therapies, the incidence and prognosis of their cardiovascular side effects needs to be further elucidated.
Recent Findings Randomized trials have highlighted the systemic effects of CAR-T and BiTE therapy including cytokine release syndrome (CRS) and resultant hypotension and respiratory failure. Cohort studies have elucidated the cardiovascular effects associated with CAR-T and BiTE therapy including heart failure, cardiomyopathy, arrythmia, myocardial infarction, stroke and cardiovascular death.
Summary Cardiovascular events after CAR-T and BiTE therapy can occur and are often associated with CRS. CAR-T recipients experiencing severe cardiovascular events may have

worse survival. Further prospective studies are needed to understand the full scope of cardiovascular effects and mitigation strategies for these therapies.

Opinion Statement

The advancement of CAR-T and BiTE therapies for refractory and relapsed leukemia, lymphomas and myelomas has led to improved outcomes for patients. With this advent has come increasing scrutiny regarding cardiovascular risk and tolerability for patients including the occurrence of heart failure, cardiomyopathy, arrythmia, myocardial infarction, stroke and cardiovascular death. Cytokine release syndrome (CRS) is a common adverse event associated with these therapies and can be fatal in some cases. Retrospective studies have suggested an association between high grade CRS and cardiovascular events. Tocilizumab may be an effective therapy for CRS, and its role in mitigating cardiovascular events warrants further investigation. There is also a need to identify which patients should undergo heightened vigilance following CAR-T and BiTE therapy beyond the traditional cardiovascular risk factors based stratification. Additionally, standardization of protocols for cardiovascular monitoring following CAR-T and BiTE therapy with cardiac and inflammatory biomarkers, electrocardiography, telemetry and echocardiography may play a role in early detection among high risk patients. Given the observed association between severe cardiovascular events and worse survival among CAR-T recipients, advances in prevention and treatment of such cardiovascular events may further improve survival for patients.

Introduction

T-cell therapies have greatly improved survival for hematological malignancies. Chimeric antigen receptor T cells (CAR-T) are a novel therapy whereby genetically engineered autologous T-cells are created to target malignant tumor cells. The patient's own T-cells are extracted via leukapheresis, modified with specific chimeric antigen receptors created ex-vivo, and sustained in media and then given back to the patient [1]. The CAR-T cells proliferate and attack tumor antigens and result in the release of tumor antigens which trigger further sustained innate T-cell immune response [2]. Since its first clinical use over a decade ago, CAR-T have resulted in improved durable relapse-free survival. Initial CAR-T therapy focused on the use of CD19 targets in acute lymphoblastic leukemia, and since then further targets have expanded to other hematologic malignancies including lymphoma and multiple myeloma (Table 1). And, CAR-T indications are progressing to earlier lines of therapy. For example, CD19 targeted CAR-T therapies for diffuse large B-cell lymphoma (DLBCL) showed significant improvements in event-free survival compared to standard-of-care autologous stem-cell transplantation, [3] [4] with these results leading to CAR-T therapy being a primary option for second-line therapy in relapsed or refractory cases of DLBCL [5]. High costs and manufacturing times have made widespread use of CAR-T therapy limited to larger academic and tertiary medical centers. Longer production turn-around times, over 30 days in some cases, can result in disease progression while awaiting treatment. The development of more readily

Table 1. FDA approved CAR-T cell therapies*

CAR-T Name	Target Antigen	Targeted Disease
Axicabtagene ciloleucel	CD19	Relapsed/Refractory B-cell NHL [50]
Brexucabtagene autoleucel	CD19	Relapsed/Refractory MCL, B-Cell ALL [51]
Lisocabtegene maraleucel	CD19	Relapsed/Refractory B-Cell NHL [52]
Tisagenlecleucel	CD19	Relapsed/Refractory B-cell ALL and B-cell NHL [53]
Ciltacabtagene autoleucel	BCMA	Relapsed/Refractory MM [54]
Idecabtagene vicleucel	BCMA	Relapsed/Refractory MM [55]

*At the time of this writing

FDA Food and Drug Administration, *ALL* Acute Lymphoblastic Leukemia, *NHL* Non-Hodgkin Lymphoma, *MCL* Mantle Cell Lymphoma, *MM* Multiple Myeloma, *BCMA* B-cell maturation antigen

available, 'off-the-shelf', targeted therapies has led to the creation of bispecific t-cell engaging antibodies (BiTE) targeting two different antigen receptors as opposed to one in CAR-T therapy [6]. One antigen receptor target is usually CD3 resulting in T-cell activation while the other is directed at a specific tumor antigen. Bispecific antibodies are currently Food & Drug Administration (FDA) approved for a variety of malignancies, including lung cancer and melanoma (Table 2). Unlike CAR-T therapy, BiTE therapy has a very short half-life and is given over many cycles, if adverse effects are seen future administrations can be held [7]. Whereas in CAR-T therapy, T-cell proliferation and expansion can occur after the single infusion making it difficult to control or mitigate adverse events once they have begun. The balancing act between immune-targeted treatment and resulting immune-related adverse effects remains one of the biggest challenges in management of patients receiving these T cell-based therapies. This review will focus on cardiovascular events following CAR-T and BiTE therapies.

Table 2. Current FDA approved bispecific T-cell antibodies*

Bispecific Antibody Name	Target Antigens	Targeted Disease
Amivantamab	EGFR, c-MET	Non-small cell lung cancer [56]
Blinatumomab	CD3, CD19	B-cell precursor ALL [57]
Mosunetuzumab	CD3, CD20	Relapsed/Refractory Follicular Lymphoma [58]
Tebentafusp	CD3, gp100	Metastatic/Unresectable Uveal Melanoma [59]
Teclistamab	CD3, BCMA	Relapsed/Refractory MM [60]

*At the time of this writing

FDA Food and Drug Administration, *EGFR* Epidermal growth factor receptor, *ALL* Acute Lymphoblastic Leukemia, *MM* Multiple Myeloma, *BCMA* B-cell maturation antigen

General Considerations for Immune-Related Adverse Effects

Similar to other novel immune-based cancer therapies, the concern for adverse effects looms large with the treatment of CAR-T and BiTE therapy, including immune effector cell-associated neurotoxicity syndrome (ICANS) and cytokine release syndrome (CRS) [2, 8]. Immune effector cell-associated neurotoxicity syndrome (ICANS) is a separate neurotoxic adverse effect originally included in CRS. Now seen as its own separate entity; it can result in anything from confusion to fatal cerebral edema [9••]. ICANS is also graded on a scale from 1 to 4 based on findings such as level of consciousness, motor dysfunction, seizure activity and the presence of cerebral edema [9••]. CRS is a noninfectious flu like syndrome and can progress to life-threatening capillary leakage with hypoxia and hypotension [2, 8]. The American Society for Transplantation and Cellular Therapy consensus grading system for CRS is described in Table 3 [9••, 10]. The first initial studies (ZUMA-1) evaluated the efficacy of CD19 directed CAR-T cells against refractory or relapsed large B-cell Lymphoma. The ZUMA-1 study showed a complete response rate of 54%; however, 95% of patients had a grade 3 or higher adverse event, the most common being fever and neutropenia. With 9% suffering hypotension and 17% needing vasopressors [11]. Similarly, in trials evaluating the efficacy of blinatumomab (BiTE) in refractory or relapsed acute lymphoblastic leukemia, 43% achieved a complete response with the most common adverse events again being fever and neutropenia [12]. In the case of CAR-T, CRS is associated with supraphysiologic levels of cytokines including interleukin-6 (IL6) and interferon-γ [8], and CRS severity is associated with tumor burden[2]. While initial studies suggested that the CAR-T cells themselves were drivers of CRS, recent mice models have shown that the cytokines and factors mediating CRS severity are produced instead by activated macrophages [8, 13, 14]. The lysis of tumor cells likely also contributes to CRS through the induction of

Table 3. Cytokine release syndrome grading*

Fever (≥38 °C **) along with:	
Grade 1	No hypotension or hypoxia
Grade 2	Hypotension not requiring vasopressors, and/or requiring low-flow nasal cannula or blow-by
Grade 3	Requiring vasopressors, and/or requiring high-flow nasal cannula, facemask, non-rebreather mask/Venturi mask
Grade 4	Requiring multiple vasopressors (excluding vasopressin), and/or requiring positive pressure (CPAP, BiPAP, intubation)
Grade 5	Death

CPAP Continuous positive airway pressure, *BiPAP* Bi-level positive airway pressure

*Per 2019 criteria of American Society for Transplantation and Cellular Therapy

**Fever not attributable to any other cause. In patients who receive antipyretic or tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity

pyroptosis in target cells [8], and patients experiencing severe cardiovascular events after CAR-T have over tenfold higher levels of IL6 compared to those without severe cardiovascular events. Attenuation of CRS with the IL6 receptor monoclonal antibody tocilizumab in clinical trials lends credence to the cytokine hypothesis and has led to the FDA approval of its use in severe CRS [15]. Notably tocilizumab has not been shown to diminish efficacy of CAR-T [8, 15]. Glucocorticoids, anakinra and interleukin-1 inhibition can also be effective in the treatment of CRS [8, 16], while anakinra may also have a role in treatment of ICANs after CAR-T therapy [16, 17]. Comparatively, BiTE's may have less severe adverse effects in contrast to CAR-T therapy but limited data exists on head-to-head comparison of both therapies [18, 19••].

Cardiovascular Events After BiTE

BiTE therapy can result in CRS and adverse cardiovascular events. In the seminal TOWER trial evaluating the use of blinatumomab in relapsed or refractory B-cell acute lymphoblastic leukemia, grade ≥ 3 CRS was seen in approximately 5% of patients [20]. And, in a post-marketing surveillance study of the FDA's Adverse Event Reporting System (FAERS),

3,400 BiTE cases were identified involving any of the five current FDA approved BiTEs (Table 2), and 1 in 5 of these BiTE recipients experienced a cardiovascular event, with half of these cardiovascular events occurring within 3 days of BiTE initiation [19••]. The most common cardiovascular event was heart failure (1.5%), followed by tachyarrhythmias (1.2%), myocarditis (0.2%), pericarditis (0.1%), and sudden death (0.03%) [19••]. One in seven cardiovascular events overlapped with CRS, with the overlap highest for those experiencing myocarditis (29%), heart failure (18%), or a fatal cardiovascular event (17%) [19••]. Notably, BiTEs as a class were 20% more likely to be associated with fatal cardiovascular events compared to the rest of FAERS [19••]. Overall, the incidence of CRS and cardiovascular adverse events with BiTE therapy appears to be less than that of CAR-T therapy. This was supported by the results of the ALCANTARA and BLAST trial which evaluated blinatumomab in B-cell acute lymphoblastic leukemia. Neither study showed any cardiovascular adverse event and < 10% experienced severe CRS [21, 22]. Given the short half-life of BiTE therapy and the need for multiple infusion cycles, treatment can often be held without the need for CRS mitigation therapy [23•]. Other strategies include step-up dosing and slower infusion to reduce the incidence of CRS and adverse events. With the increasing number of BiTE therapies in clinical trials, further research is needed to elucidate the true burden of cardiovascular toxicity with these therapies.

Cardiovascular Events and Biomarkers After CAR-T

Studies have reported cardiovascular events among CAR-T recipients, including arrhythmias, heart failure or cardiomyopathy, myocardial infarction, stroke and cardiovascular death [5, 9••, 24, 25••, 26–31], with the time to cardiovascular events following CAR-T infusion reported to range between 4 – 21 days, with most events occurring after CRS initiation [9••, 24]. Table 4 lists the 4–28% observed rate of clinically relevant cardiovascular events following CAR-T infusion, as per retrospective or prospective cohorts, with the wide range likely related to a lack of standardization of a composite cardiovascular events criteria, and the small sample size of prospective studies. Real world data from the FDA Adverse Event Reporting System (FAERS) has shown that cardiovascular and pulmonary adverse events were seen in over one in five CAR-T recipients, with the most common being arrhythmias and cardiomyopathy [27]. Event rates per 1000 patients years have been reported as:

Table 4. Reporting of cardiovascular events after CAR-T infusion*

Study	Year	Type of Cohort	S
Korell et al. [31]	2024	Prospective (n = 137)	37 (27%) CV events[a]
Camilli et al. [30]	2024	Prospective (n = 27)	16 (59%) CV events[b]
Lefebvre et al. [24]	2023	Prospective (n = 44)	2 (5%) CV events[c]
Mahmood et al. [25••]	2023	Retrospective (n = 202)	33 (16%) severe CV events[d]
Lee et al. [26]	2023	Retrospective (n = 78)	11 (14%) CV events[e]
Steiner et al. [5]	2022	Retrospective (n = 165)	27 (16%) CV events[f]
Goldman et al. [27]	2021	Retrospective database (n = 2657)	546 (21%) cardiopulmonary adverse events
Ganatra et al. [28]	2020	Retrospective (n = 187)	12 (6%) cardiomyopathy events
Lefebvre et al. [29]	2020	Retrospective (n = 145)	41 (28%) CV events[g]
Alvi et al. [9••]	2019	Retrospective (n = 137)	17 (12%) CV events[h]

CV Cardiovascular

*All cohorts were CD19 targeting CAR-T, except Lee et al. which was BCMA targeting, and Korell et al. and Alvi et al. which included both CD19 and BCMA targeting CAR-T

CV events were defined as:

[a]Cardiomyopathy (left ventricular ejection fraction [LVEF] drop of ≥ 10% or LVEF drop to ≤ 50%) or heart failure, atrial fibrillation or other EKG changes, or hypotension/hypertension warranting medical intervention

[b]LVEF reduction by ≥ 10% points to an LVEF of 40–49%, or LVEF reduction by < 10% points to an LVEF of 40– 49%, or a decline of global longitudinal strain by ≥ 15% from baseline, or increases in troponin or B-type natriuretic peptide

[c]Symptomatic heart failure, nonfatal acute coronary syndrome, nonfatal ischemic stroke, new-onset cardiac arrhythmia, and cardiac death

[d]Clinical heart failure, cardiogenic shock, and myocardial infarction

[e]Atrial fibrillation, non-sustained ventricular tachycardia, heart failure, cardiovascular death

[f]Arrhythmias requiring an intervention, new or worsening cardiomyopathy, heart failure exacerbation, stroke, myocardial infarction or CV death

[g]CV death, symptomatic heart failure, acute coronary syndrome, ischemic stroke and arrythmia (de novo)

[h]Arrhythmias, heart failure and CV death

6.5 for atrial arrythmias, 5.6 for new onset heart failure, 1.9 for heart failure decompensation and 5.6 for cardiovascular death [9••]. Severe cardiovascular events, defined as a composite of heart failure, cardiogenic shock and myocardial infarction, are associated with a nearly fourfold higher non-relapse mortality and nearly threefold higher overall mortality [25••]. There have also been case reports of myocarditis following CAR-T infusion, with myocardial histology demonstrating lymphocytic infiltration, although the rate of such cardiac inflammation is less common than observed with other immunotherapy such as immune checkpoint inhibitors [32–34]. And, there have also been case reporting of CAR-T associated vasospasm although whether such a presentation is driven by an anaphylaxis reaction rather than direct toxicity is not well understood [35].

While studies showed higher grade CRS was associated with more cardiovascular events, a similar link between ICANS and cardiovascular events has not been observed [5, 9••, 24].Studies have also been varied in reporting observed associations between pre-existing risk factors or conditions and cardiovascular events, with higher event rates observed with advanced age [5], higher creatinine,[29], and preexisting hypertension and heart failure [25••]. Interestingly, exposure to cardiotoxic therapies, such as anthracyclines, or type of malignancy was not associated with elevated risk of cardiovascular events or CRS [36, 9••]. A definitive biomarker profile for those at risk of future cardiovascular event following CAR-T infusion has not been identified, but retrospective data suggests that any troponin elevation above assay is associated with adverse events, especially among those with higher grade CRS [9••, 25••]. In particular, Alvi et al. showed that over half of cardiovascular events were associated with elevated troponins, and four of every five patients with elevated troponins having grade ≥ 2 CRS. Whether the troponin elevation is simply a result of underlying hypotension and hypoxia during CRS, or from endothelial dysfunction related fluid shifts or from direct myocardial damage, as seen from immune-checkpoint inhibitors, has yet to be determined. Patients experiencing cardiovascular events have higher inflammatory biomarker levels including C-reactive protein, ferritin and IL6 although these findings are not as yet clinically applicable given a lack of identified thresholds for elevation [25••].

Mechanism of Cardiovascular Events After CAR-T and BiTE

The mechanism of cardiovascular dysfunction from CAR-T is not well defined and likely reflects the multifactorial process leading to cardiac dysfunction. Proposed framework for CAR-T related cardiotoxicity mechanism includes: 1) on-target, on-tumor, 2) on-target, off-tumor, and 3) off-target, off-tumor (Fig. 1) [37]. On-target, on-tumor effects represents the expected inflammatory CRS response following infusion of millions of genetically modified T-cells that further replicate in the body and engage to kill tumor cells expressing the target antigen. CRS, which manifests similar to vasodilatory shock, is associated with elevation of multiple cytokines including IL6, IL2,

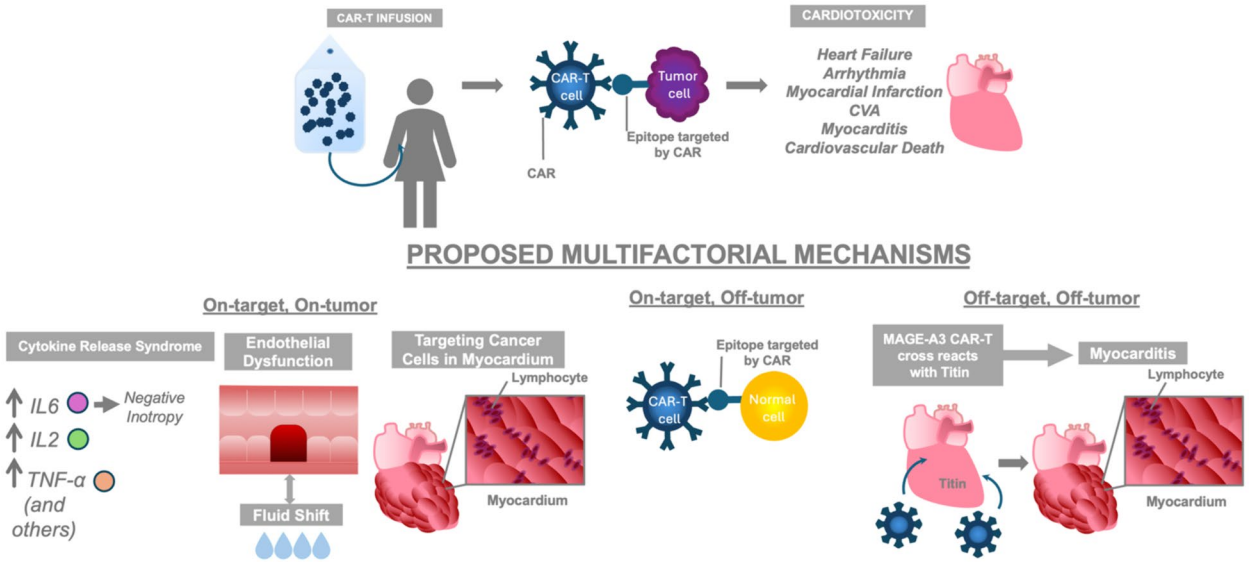

Fig. 1 Proposed mechanisms of CAR-T associated cardiotoxicity. *CAR* chimeric antigen receptor, *CAR-T* CAR T-cell, *CVA* cerebrovascular accident, *IL6* interleukin-6, *IL2* interleukin-2, *TNF-α* tumor necrosis factor-alpha.

interferon-γ and TNF-α. IL6 in particular has been established to have negative inotropic effects, and in mouse models, myocardial dysfunction and cardiotoxic effects have been correlated to IL6 levels [38]. Among CAR-T recipients, those who experienced death or severe cardiovascular events had fivefold or tenfold higher levels of IL6, respectively, [25••] and delay in use of IL6 receptor antagonists have been shown to be associated with nearly twofold higher rate of cardiovascular events [9••]. This inflammatory milieu is further associated with endothelial cell dysfunction and resultant fluid shifts, with markers of endothelial dysfunction portending worse survival, and likely also contributory to exacerbating cardiac dysfunction [39]. And, given the elevated rates of myocardial involvement of leukemias and lymphomas, it is possible that some case reports of myocarditis following CAR-T infusion are related to on-target, on-tumor effects of CAR-T seeking out tumor cells in myocardium [32–34]. On-target, off-tumor effects encompass the theoretical risk of a direct CAR-T attack on normal tissue expressing a shared epitope with the malignancy, although current FDA approved CAR-T constructs were developed with the goal to avoid such cross targeting in healthy versus cancer tissue. Finally, off-tumor, off-target effects may also play a role in the development of cardiovascular complications. Direct CAR-T mediated myocardial injury, through the recognition of a new epitope by engineered T-cells, was the case of MAGE-A3 targeting CAR-T which inadvertently also targeted cardiac-specific titin proteins causing catastrophic cardiogenic shock, myocardial infarction and cardiac arrest [40]. A similar framework for cardiotoxicity likely also applies to BiTE therapy with CRS and fluid shifts related to endothelial dysfunction possibly contributing to cardiovascular event occurrence [37].

Optimization Prior to CAR-T of BiTE Therapy

Optimization of patients for CAR-T or BiTE therapy requires multidisciplinary discussion and coordination. Current guidelines recommend that CAR-T or BiTE candidates undergo baseline testing with ECG, echocardiogram, B-type natriuretic peptide and troponin [41–43]. In our clinic, among patients with symptoms suggestive of ischemia we pursue ischemic testing with the goal to rule out severe coronary artery disease. In the event severe coronary artery disease is diagnosed, we review with our oncology colleagues whether cancer treatment can be deferred for a limited duration to allow for coronary stenting and at least a month of uninterrupted dual antiplatelet therapy, and also add anti-anginal medications. Rarely, we have encountered patients with untreated valvulopathies and via multidisciplinary discussion involving assessment of expected prognosis if cancer therapy is successful, pursued transcatheter valve interventions. As our institutions include in-patient cardio-oncology service, we closely follow patients identified as high risk. For patients with history or risk for heart failure or valvulopathies, we diurese patients to their dry weight, and communicate with the oncology team that patients should get daily standing weights before breakfast and be actively monitored for diuresis to target this dry weight, if clinically appropriate. There have also been case reports of utilizing pulmonary artery pressure monitoring system to facilitate intravascular volume optimization [44]. Among patients with a history of arrythmias, we suggest patients be on telemetry during the first 1–2 weeks following CAR-T infusion. And, for the above described high risk patients, we coordinate with our oncology colleagues that they should have a low-threshold for early use of tocilizumab to treat CRS given the association with higher grade CRS and increased rate of cardiovascular events. Finally, we repeat echocardiography three weeks after CAR-T infusion given the reported rates of post-infusion cardiomyopathy [28, 30].

Further Directions

Further evaluation and mitigation of cardiovascular risk prior to treatment with CAR-T and BiTE therapy is critical in this population. Especially considering over half of patients may have previously received cardiotoxic therapy or radiation further enhancing their risk profile. As more therapies in these classes receive approval, it is critical to learn how these therapies alter and affect the cardiovascular system in the milieu of CAR-T or BiTE infusion. Identifying those deemed to be at highest risk will likely revolve around developing a pre-infusion biomarker based scoring system, or a risk score that incorporates baseline clinical and physiological characteristics. Additionally, the level and frequency of monitoring during and after CAR-T or BiTE therapy will need to be further defined and standardized as cardiac dysfunction can

persist in some patients even after the resolution of CRS [28]. While many of these adverse effects are often in the setting of high grade CRS which may be temporary or reversible, the association of severe cardiovascular events and increased mortality is notable [25••]. Tocilizumab and corticosteroids remain the mainstay of acute treatment for CRS; as of yet, there is no cardiovascular therapy that has been studied or approved to lower the risk of developing cardiovascular events from CAR-T or BiTE therapies. Expanding our understanding of managing cardiovascular adverse events after CAR-T is particularly relevant, as CAR-T is expected to have application in non-cancer patients including improving disease burden in systemic lupus erythematosus [45], and non-alcoholic steatohepatitis [46], multiple sclerosis [47], and even reverse cardiac fibrosis in mice models [48, 49].

Conclusion

The development of CAR-T and BiTE therapies has led improved outcomes in the treatment of relapsed or refractory hematologic malignancies, lung cancer and melanoma that otherwise portend poor prognosis. Balancing their benefit with early identification and management of cardiovascular events may further improve survival in these patients. Further prospective studies are needed to develop a biomarker profile, or risk score, to stratify high risk patients, as well as developed treatment strategies that demonstrate efficacy in managing cardiotoxicity.

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SSM and SZQ wrote the main manuscript text with input from all authors. SSM, EO, GMM, MJG, and AF created figures and tables. All authors reviewed the manuscript.

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

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- •• Of major importance

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Findings from this study provide event rates for cardiovascular events following CAR-T therapy.

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