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STATE OF THE ART REVIEW
Cardio-oncology

Cardiotoxicity from chimeric antigen receptor-T cell therapy for advanced malignancies

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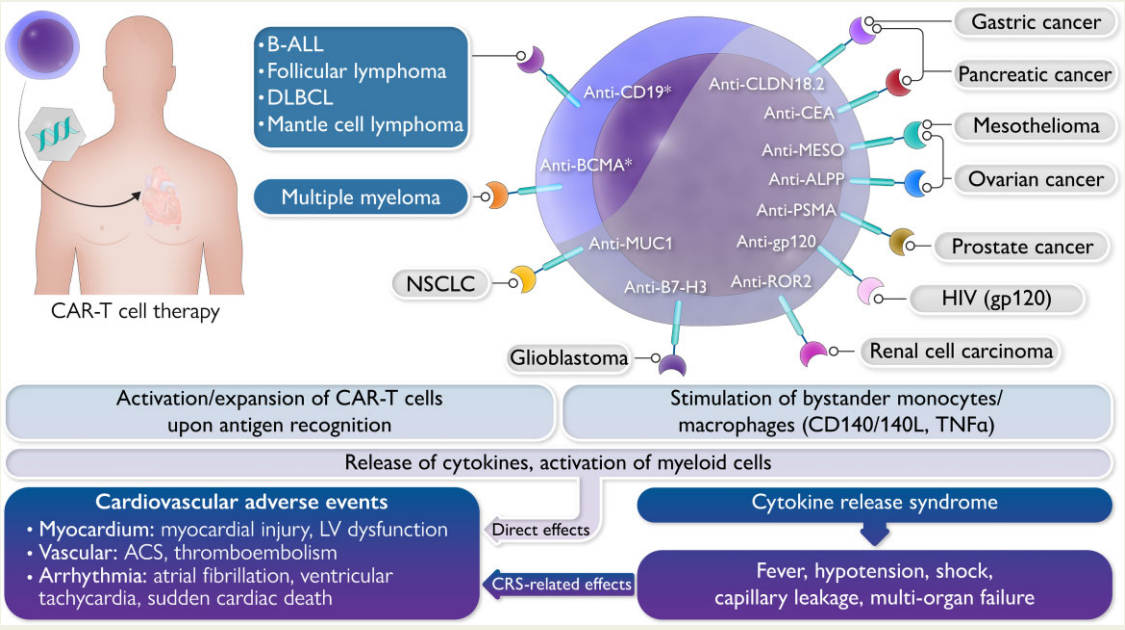

Graphical Abstract Chimeric antigen receptor (CAR)-T cell therapy is achieved by apheresis of T cells followed by transduction with the tumour-specific CAR and reinfusion after *ex vivo* expansion. Approved therapies and their respective molecular target structures are highlighted in light blue (left side), and experimental therapies currently undergoing clinical evaluation in Phase II–III trials are highlighted in grey (right side) as currently listed under www.clinicaltrials.gov (20 December 2021). Activation of CAR-T cells upon antigen recognition and stimulation of the host immune system can induce a broad range of side effects, including cytokine release syndrome (CRS), that can lead to severe direct and indirect cardiovascular complications. *New CAR-T cell therapies with refined anti-CD19 and anti-B-cell maturation antigen CARs are undergoing further clinical evaluation in haematological malignancies. ACS, acute coronary syndrome; ALPP, placental alkaline phosphatase; B-ALL, B-cell acute lymphoblastic leukaemia; B7-H3, B7 homologue 3; CEA, carcinoembryonic antigen; CLDN18.2, Claudin 18.2; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; FDA, Food and Drug Administration; gp120, envelope glycoprotein 120; HIV, human immunodeficiency virus; LV, left ventricular; MESO, mesothelin; MUC1, mucin 1; NSCLC, non-small-cell lung cancer; PSMA, prostate-specific membrane antigen; ROR2, receptor tyrosine kinase-like orphan receptor 2.

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Abstract

Chimeric antigen receptor (CAR)-T cell therapy is the next revolutionary advance in cancer therapy. By using *ex vivo* engineered T cells to specifically target antigens, a targeted immune reaction is induced. Chimeric antigen receptor-T cell therapy is approved for patients suffering from advanced and refractory B cell and plasma cell malignancies and is undergoing testing for various other haematologic and solid malignancies. In the process of triggering an anticancer immune reaction, a systemic inflammatory response can emerge as cytokine release syndrome (CRS). The severity of CRS is highly variable across patients, ranging from mild flu-like symptoms to fulminant hyperinflammatory states with excessive immune activation, associated multiorgan failure and high mortality risk. Cytokine release syndrome is also an important factor for adverse cardiovascular (CV) events. Sinus tachycardia and hypotension are the most common reflections, similar to what is seen with other systemic inflammatory response syndromes. Corrected QT interval prolongation and tachyarrhythmias, including ventricular arrhythmias and atrial fibrillation, also show a close link with CRS. Events of myocardial ischaemia and venous thromboembolism can be provoked during CAR-T cell therapy. Although not as closely related to CRS, changes in cardiac function can be observed to the point of heart failure and cardiogenic shock. This may also be encountered in patients with severe valvular heart disease in the setting of CRS. This review will discuss the pertinent CV risks of the growing field of CAR-T cell therapy for today's cardiologists, including incidence, characteristics, and treatment options, and will conclude with an integrated management algorithm.

Keywords CAR-T cells • Cardio-oncology • Cardiotoxicity • Chimeric antigen receptor • Cytokine release syndrome

Introduction

Adoptive T cell transfer therapy (ATC) describes the infusion of modified autologous or allogeneic T cells to induce an anticancer immune reaction. The first form of ATC was achieved by modification/reinfusion of tumour-infiltrating lymphocytes (TILs) from resected tumour tissue,[1] but the success of the procedure was limited by technical requirements and early relapses.[1] This led to the eventual development of chimeric antigen receptor (CAR)-T cells as a new concept. Chimeric antigen receptor-T cells are genetically engineered autologous T cells that express an artificial CAR. Manufacturing could be performed on leukapheresed or further isolated cells. *Ex vivo* genetic modification occurs by transduction with lentiviral or retroviral vectors containing CAR constructs. The characteristic chimeric structure of the CAR allows for the simultaneous detection of surface antigens and T cell activation without the need for major histocompatibility complex antigen presentation (*Figure 1*).[1–4] Very high response rates are thus achieved.[5] Newer generations of CAR-T cell therapy are tailored to specific tumours by inclusion, exclusion, and modification of domains, and novel target antigens are under preclinical and clinical evaluation (*Table 1*). Modifications to CAR-T cells, such as engineered immune checkpoint blockers or the enhancement of interleukin (IL)-12 production, further boost CAR-T cell efficacy.[1] While the genetic modification is commonly achieved by viral transduction, CRISPR–Cas9 has now been successfully applied for direct T cell receptor gene editing.[1] It is important to recall that patients receive conditioning chemotherapy, mainly fludarabine and cyclophosphamide, before the infusion of CAR-T cells to increase their expansion, function, and persistence by eradicating immunosuppressive cells and homeostatic cytokine sinks.[11]

Chimeric antigen receptor-T cell therapy has demonstrated efficacy for the treatment of advanced haematologic malignancies, particularly B-cell acute lymphoblastic leukaemia (B-ALL), aggressive and indolent B-cell non-Hodgkin lymphoma, and multiple myeloma.[2,12,13] Five CAR-T cell therapeutics are currently approved for clinical application. Tisagenlecleucel is available for the treatment of B-ALL in paediatric patients and young adults, with an overall initial remission rate of 81%.[3] Axicabtagene ciloleucel is approved for aggressive B-cell non-Hodgkin lymphoma in adults, with an objective response rate of 82%, and follicular lymphoma.[2] Lisocabtagene maraleucel (second-generation CAR-T cell therapy) was recently approved for relapsed or refractory aggressive large B-cell lymphoma, including diffuse large B-cell lymphoma. Brexucabtagene autoleucel was approved for mantle cell lymphoma and adults with relapsed, refractory B-ALL.[13–15] In a trial assessing long-term response, 19–28z CAR-T cells led to an increased median overall survival of 18 months compared with alternative strategies.[13] High systemic concentrations of CAR-T cells and a low burden of disease predict a favourable response to therapy. Idecabtagene vicleucel, a CAR-T cell therapy directed against B-cell maturation antigen (BCMA), had a promising response rate of 73% in a Phase II study in patients with multiple myeloma and is the first non-CD19 CAR-T cell therapy approved for multiple myeloma.[16]

Building on this prior experience and promising targets identified in pre-clinical studies, >600 interventional studies on CAR-T cell therapy (with new characteristics or for new cancer entities) are currently listed on www.clinicaltrials.gov (25 December 2021), including 14 Phase III studies. In particular, extending CAR-T cell therapy to solid tumours is the subject of ongoing research efforts (*Figure 2*),[5] as is an extension to non-malignant diseases, including autoimmune diseases and human immunodeficiency virus (HIV).[10,17]

Clinical observations, including those made in Phase I–III trials, indicate that a high percentage of patients undergoing CAR-T cell therapy experience cardiovascular (CV) side effects [including 10–30% with a decline in left ventricular ejection fraction (LVEF) among those assessed] and that these side effects are associated with significant morbidity and mortality. The number of patients eligible for CAR-T cell therapy is expected to rapidly increase, as is the need for the management of side effects. Familiarity with this topic is henceforth important for every cardiologist. This review aims to

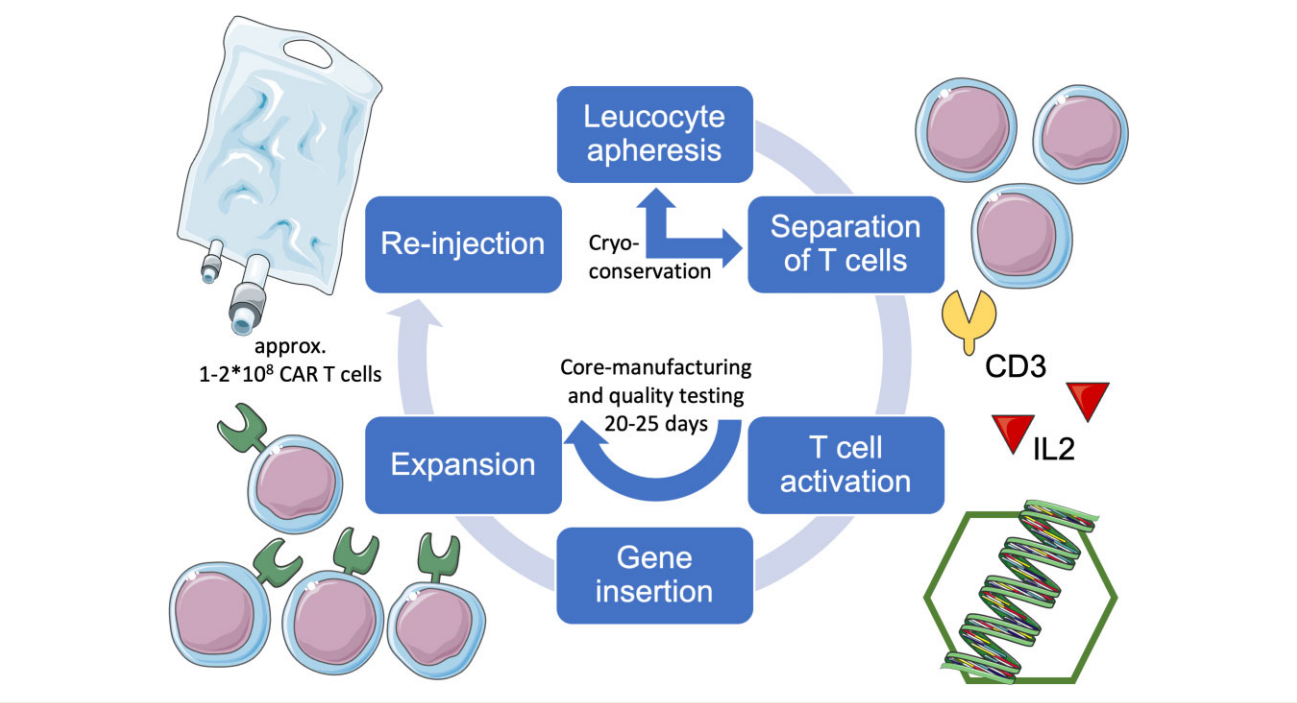

Figure 1 Chimeric antigen receptor-T cell therapy. After apheresis, T cells are separated and cultured. Separated T cells are then transduced with the tumour-specific chimeric antigen receptor and expanded *in vitro*. After quality testing, cells are reinfused into patients who usually receive conditioning chemotherapy. Approx, approximately; CAR, chimeric antigen receptor.

summarize the current knowledge on CAR-T cell therapy-related CV toxicity to provide recommendations on prevention, monitoring and treatment and to discuss future challenges and directions (Graphical Abstract).

Adverse events from CAR-T cell therapy

Chimeric antigen receptor-T cell therapy is associated with a range of general and organ-specific toxicities. Cytokine release syndrome (CRS) is the most common treatment-related adverse event and is described in 85–93% of patients at any grade, with 0–46% experiencing severe or fatal forms.[18,19] Symptoms range from mild flu-like symptoms and fever to life-threatening complications, including capillary leakage, severe hypotension, shock, and multiorgan failure.[2,13] The severity of the inflammatory reaction, and thus the severity of CRS, has commonly been correlated with tumour burden. Further risk factors for severe CRS include severe comorbidities, early-onset (≤3 days following CAR-T cell infusion) CRS, CAR-T cell dose, and the addition of fludarabine to lymphodepletion therapy.[20] Several grading systems have been used over the past years, but the most commonly used is provided by the American Society for Transplantation and Cellular Therapy (ASTCT)[18] and the Common Terminology Criteria for Adverse Events (CTCAE)[19] (*Table 2*). Typically, high-grade CRS is defined as three or higher. Novel grading systems continue to evolve, including the so-called CARTOX system (CAR-T cell therapy-associated TOXicity), and their applicability requires further investigation.[22]

The development of CRS is based on a cascade of proinflammatory effects of CAR-T cells with the tumour microenvironment. Systemic immunity serves as the main trigger for the creation of a loop of hyperinflammation. IL-1 and IL-6 correlate with the severity of CRS and CRS-related mortality.[23] IL-1, IL-1Ra, CC-chemokine ligands 2 and 3 (CCL2 and CCL3), and interferon-gamma (IFN-γ) are also commonly elevated, and IFN-γ is associated with the degree of toxicity together with tumour necrosis factor alpha (TNFα).[24] TNFα is considered a contributing factor upon secretion from cells by triggering the secretion of IL-6, whereas TNFα exhibits direct effects on the tumour.[23] Novel experimental data show that CRS is mediated by the release of cytokines from recipient macrophages upon stimulation by infused CAR-T cells rather than from CAR-T cells themselves.[25] In a mouse model of CRS, transfusion of CAR-T cells led to the secretion of IL-1, IL-6, and nitric oxide (NO) by colocalized recipient myeloid cells. It is expected that the activation of macrophages is mediated by IL-1 and IL-6, both of which are triggered by inducible NO synthase (iNOS). Experimental blockade of both cytokines was associated with lower expression of iNOS in macrophages and led to a reduction in CRS.[25] IL-6 receptor blockade with tocilizumab is the first-line therapy to manage CRS, and tocilizumab is superior to corticosteroids in reducing CRS symptoms.

The management of CRS has evolved in recent years from experience in registration studies and other clinical investigations. With data showing that the use of tocilizumab and corticosteroids to manage CRS does not negatively impact clinical response, providers have moved from conservative, supportive measures to earlier intervention with tocilizumab and steroids with mild, low-grade

Table 1 Current landscape of chimeric antigen receptor-T cell therapies

Substance/trial	Diseases
EMA-/FDA-approved therapies	
Tisagenlecleucel (Kymriah, Novartis)	Paediatric and young adult patients (age 3–25 years) with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL); adult patients with relapsed or refractory (r/r) aggressive B-cell non-Hodgkin lymphoma
Axicabtagene ciloleucel (Yescarta, Kite pharma)	Adult patients with relapsed or refractory indolent and aggressive B-cell non-Hodgkin lymphoma
Lisocabtagene maraleucel (Breyanzi, Juno Therapeutics/Bristol Myers Squibb)	Adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma
Brexucabtagene autoleucel (Tecartus, Kite pharma)	Adult patients with relapsed or refractory mantle cell lymphoma Adults (≥18 years) with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)
Idecabtagene Vicleucel (Abecma, Bristol Myers Squibb)	adult patients with relapsed, refractory multiple myeloma
Therapy in late clinical evaluation (selection of significant substances)	
Ciltacabtagene autoleucel[6] (Janssen)	Relapsed or refractory multiple myeloma
BrainChild-01 (anti-HER2) BrainChild-02 (anti-EGFR) BrainChild-03 (anti-B7-H3)[7]	Children and young adults with relapsed or refractory brain and central nervous system tumours
MB-CART19.1 (anti-CD19) MB-CART20.1 (anti-CD20)[8] MB-CART2019.1 (anti-CD19 and anti-CD20) (Miltenyi Biotec)[8]	Various B-cell malignancies
CTX110 (CRISPR Therapeutics)[8]	Various B-cell malignancies
UniCAR02-T-CD123 (anti-CD123) (Cellex Patient Treatment)	Acute myloid leukaemia
BNT211 (anti-Claudin 6) (BioNTech)[9]	CLDN6-positive relapsed or refractory advanced solid tumours
Anti-CD19 CAR-T cells[10]	Refractory systemic lupus erythematosus (case report)

CRS. This has resulted in a change in the incidence of severe CRS, even with the same CAR-T cell products over time. Optimal monitoring of organ function remains the key to preventing the escalation of CRS.

A range of organ-specific adverse events can be found during CAR-T cell therapy. In most cases, it is expected but unproven whether organ-specific side effects are a symptom of CRS or arise from independent mechanisms. A neurotoxicity is also a common form of the treatment-related adverse event. Chimeric antigen receptor-T cell-related neurotoxicity has been termed immune effector cell-associated neurotoxicity syndrome (ICANS).[18] Signs and symptoms can be broad, including confusion, dysgraphia, language disturbance, seizures, agitation, and somnolence. Cerebral oedema represents the most severe form of neurotoxicity, and although not common, it can be potentially rapidly fatal within days. The underlying pathomechanisms are poorly understood, but cytokine-related vascular dysfunction and disruption of the blood–brain barrier are considered to play major roles. Other CAR-T cell therapy-related complications include haematologic, gastrointestinal, and CV toxicities.[2,13,26]

Cardiovascular adverse events

Cardiovascular toxicity from CAR-T cell therapy has been described in Phase I–III clinical trials and retrospective studies (*Table 3*, Supplementary material online, *Tables S1 and S2*).[2,12,13,27,34] Pharmacovigilance data recently showed relative mortality of 30.9% in patients with CV and pulmonary adverse events (CPAEs) compared with 17.4% in patients with CRS in the setting of CAR-T cell therapy, underscoring the imminent need for the management of these complications.[32] With the transition of CAR-T cell therapy to the standard of care and the increasing number of patients with pre-existing CV diseases, the characterization of CV side effects is of crucial importance. Particularly regarding the cardiocirculatory stress caused by CRS, sufficient cardiac reserve capacity appears to be essential to avoid life-threatening complications.[27] It can be expected that the prevalence of CV side effects will increase with the increasing use of CAR-T cell therapy in the real-life setting, as patients with pre-existing CV disease and high-risk constellations were omitted from clinical trials. Several forms of CV complications, including left ventricular (LV) dysfunction, elevated troponin,

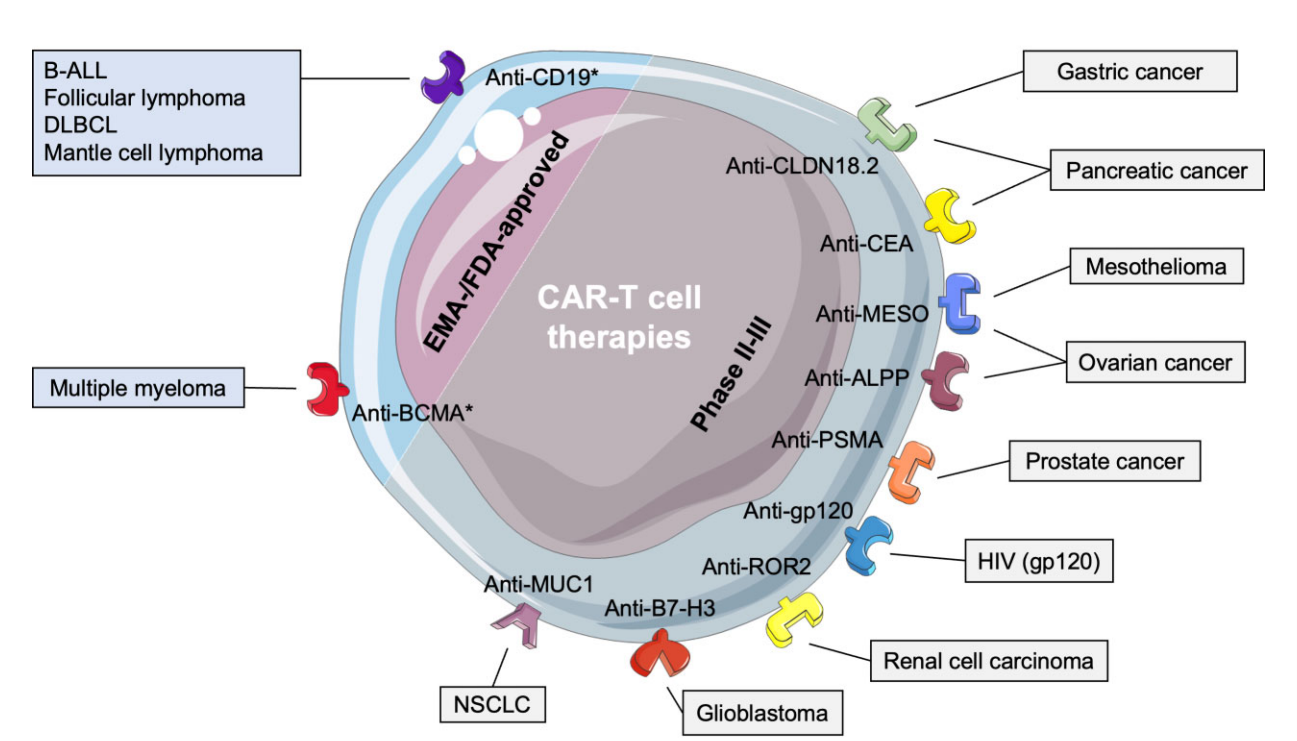

Figure 2 Scientific landscape of chimeric antigen receptor-T cell therapies. Summary of European Medicines Agency-/Food and Drug Administration-approved forms of chimeric antigen receptor-T cell therapy (left, blue text box) and experimental therapies currently undergoing clinical evaluation in Phase II–III trials (right, grey text box) with their respective molecular target antigen as currently listed under www.clinicaltrials.gov (20 December 2021). *New chimeric antigen receptor-T cell therapies with refined anti-CD19 and anti-B-cell maturation antigen chimeric antigen receptors are undergoing further clinical evaluation in haematological malignancies. ALPP, placental alkaline phosphatase; B-ALL, B-cell acute lymphoblastic leukaemia; B7-H3, B7 homologue 3; CEA, carcinoembryonic antigen; CLDN18.2, Claudin 18.2; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; FDA, Food and Drug Administration; gp120, envelope glycoprotein 120; HIV, human immunodeficiency virus; MESO, mesothelin; MUC1, Mucin 1; NSCLC, non-small-cell lung cancer; PSMA, prostate-specific membrane antigen; ROR2, receptor tyrosine kinase-like orphan receptor 2.

arrhythmia, and sudden cardiac death, have been reported following CAR-T cell therapy.[26] While it cannot be ruled out that sinus tachycardia and arterial hypotension develop as separate CV toxicities, they can be perceived mainly as a consequence of CRS. Systemic CRS effects, including tachycardia and low peripheral resistance, stress the CV system and aggravate the manifestation of toxicities. Overt cardiotoxicity is found particularly in patients with apparent or overt pre-existing CV disease or in patients with severe CRS.[27] It should be noted that CV disease, particularly reduced LVEF, served as an exclusion criterion in the majority of trials, therefore, leading to a potential underrepresentation of patients at very high risk for CV complications within the examined collectives.[35]

There is heterogeneity in the adverse event profile of the currently approved CAR-T cell products. As shown in a recent pharmacovigilance database analysis, CRS reporting was more common with axicabtagene ciloleucel than with tisagenlecleucel (12% absolute difference), and of all CV events, arrhythmias and venous thromboembolic events showed a notably lower rate of overreporting with tisagenleleucel.[32] In contrast, hypotension and respiratory, pleural, and pericardial disorders were more commonly reported with tisagenleleucel. While limitations to these pharmacovigilance data need to be acknowledged, these data implicate a more CAR-T cell product-specific view when assessing patients. For instance, tisagenlecleucel could be favoured in patients with a history of tachyarrhythmias and axicabtagene ciloleucel in patients with a history of respiratory, pleural or pericardial disease. Furthermore, some CV adverse events show a stronger association with CRS than others. For instance, concurrent CRS is seen in all patients with reported corrected QT interval (QTc) prolongation/torsades de pointes; in 79% with reported tachyarrhythmia, including atrial fibrillation and ventricular arrhythmias; and in 75% with reported ischaemic heart disease. The lowest level of CRS concurrency was seen for cardiomyopathy (50%). Accordingly, optimal management of CRS is particularly important in patients with a history of ventricular arrhythmias, QTc prolongation/torsades, or atrial fibrillation. Furthermore, it is of significance in patients with a history of ischaemic heart disease.

Pathomechanisms

The underlying pathomechanisms are incompletely understood. Cytokine release syndrome parallels the dynamics in systemic inflammatory response syndrome (SIRS) and subsequent septic cardiomyopathy in many ways.[36] Here, recognition of pathogen-associated

Table 2 Grading of the cytokine release syndrome

	ASTCT consensus criteria[18]	CTCAE 5.0[19]	Lee scale[21]
Grade 1	Temp. ≥38.0° No hypotension No hypoxia	Fever with or without constitutional symptoms	Non-life-threatening symptoms requiring symptomatic treatment (e.g. fever)
Grade 2	Temp. ≥38.0° Hypotension not requiring vasopressors Hypoxia requiring low-flow nasal cannula or blow-by	Hypotension responding to fluids; hypoxia responding to <40% O_2	Symptoms requiring and responding to treatment Oxygen requirement <40%; intravenous fluid or one low-dose vasopressor
Grade 3	Temp. ≥38.0° Hypotension requiring vasopressors with or without vasopressin Hypoxia requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Hypotension managed with one pressor; hypoxia requiring ≥40% O_2	Severe symptoms requiring extensive treatment High-dose vasopressor therapy, multiple vasopressors Severe (CTCAE Grade 3) organ toxicity, CTCAE Grade 4 elevation of transaminases
Grade 4	Temp. ≥38.0° Hypotension requiring multiple vasopressors excluding vasopressin Hypoxia requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)	Life-threatening consequences; urgent intervention indicated	Life-threatening symptoms Mechanical ventilation CTCAE Grade 4 organ toxicity
Grade 5	–	Death	Death

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CTCAE, Common Terminology Criteria for Adverse Events; NIH, National Institutes of Health.

molecular patterns induces immune activation with a subsequent release of proinflammatory cytokines leading to microvascular dysfunction, accompanied by oxidative and nitrosative stress, mitochondrial dysfunction, and altered calcium cycling. This can impair CV integrity, systolic and diastolic LV, and right ventricular function. It may further initiate global myocardial ischaemia and impair the afterload-related cardiac performance, as well as vascular/endothelial performance with a decreased response to catecholamines.[36] Severe CRS with capillary leakage, distributive shock haemodynamics, and multiorgan dysfunction induce CV stress and may induce myocardial injury with subsequent deleterious consequences on cardiac function, mainly as an epiphenomenon (*Figure 3*). This hypothesis is supported by the observation that CV complications are more common in patients with pre-existing CV disease and severe CRS. Secreted inflammatory cytokines are expected to mediate myocardial dysfunction, with a proposed key role of IL-6. An adverse effect of IL-6 on myocardial integrity has already been shown for meningococcal sepsis. Here, IL-6 from affected patients induced cardiotoxicity in an *in vitro* model.[37] Furthermore, severe CRS was associated with profound endothelial dysfunction and the expression of procoagulant factors. In patients with severe CRS, increased expression of von Willebrand factor (vWF) was identified. Patients showed increased concentrations of angiotensin-2 (Ang-2), which promotes capillary leakage, together with decreased Ang-1, leading to an elevated Ang-2:Ang-1 ratio.[20]

As opposed to other forms of cancer immunotherapy, particularly immune checkpoint inhibitors, knowledge on the direct effects of CAR-T cell therapies on the myocardium is sparse, but emerging findings point out the possibility of direct myocardial impairment. Cytokine release syndrome-related elevation of cytokines has the potential to disturb cardiac integrity. Microvascular dysfunction and increased permeability can further augment cardiac stress and trigger a myocardial inflammatory bystander reaction, and procoagulant factors, such as vWF, may induce microvascular obstruction. In addition, excreted cytokines can have a direct effect on cardiac health. TNFα is known to play a role in heart failure and has recently been attributed to immune-related cardiac dysfunction.[38] Hence, TNFα may aggravate cardiac dysfunction during CRS while simultaneously serving as a potential target for a protective therapy, however, with unknown consequences on the anticancer efficacy. Sepsis-induced cardiomyopathy partially resembles the phenotype of CRS, including shared pathomechanisms.

Evidence of direct antimyocardial T cell reactivity was derived from a study with the application of engineered T cells targeting the tumour-associated MAGE-A3 protein in patients with melanoma or multiple myeloma.[4] Three days following T cell infusion, the first patient presented with hypotension and fever, followed by diffuse ST-segment elevations and elevated cardiac troponin. The patient succumbed to fulminant cardiogenic shock. The second patient developed hypotension and hypoxia 3 days after T cell infusion. An echocardiogram revealed a large pericardial effusion. The patient was treated for cardiogenic shock, including an intra-aortic balloon pump but could not be stabilized and died 2 days later.[4] Autopsies showed myocardial necrosis with infiltration of T cells in both patients. In pericardial fluids, high local levels of inflammatory cytokines were determined. *In vitro* testing of the engineered T cells in the presence of cultured induced pluripotent stem cell-derived (iPSC) cardiomyocytes was performed, and T cell activation and killing of iPSC cardiomyocytes were observed. Titin, a protein of the contractile apparatus in cardiomyocytes, was identified as a putative antigen.[4] The results implicate a significant cross-reactivity of CAR-T cells with CV

Table 3 Real-world observational studies on cardiovascular adverse events

Study	Disease	Treatment	CV toxicity
Alvi et al.[27]	Various (registry data)	Tisagenlecleucel, axicabtagene ciloleucel, non-commercial products	Elevated troponin: 55% (29/53 pts) Decreased EF: 28% (8/29 pts)[a] CV death: 4% (6/137 pts) Decompensated HF: 4% (6/137 pts) Arrhythmia: 4% (5/137 pts)[b] CRS Grade ≥2: 40% (55/137 pts) CRS Grade 1: 19% (26/137 pts)
Casadei et al.[28] **(subgroup of Locke et al.**[29] **and Schuster et al.**[30]**)**	Diffuse large B-cell lymphoma	Axicabtagene ciloleucel and Tisagenlecleucel	CRS Grade 3–4: 10% (3/30 pts) CRS Grade 1–2: 77% (23/30 pts)
Ganatra et al.[31]	Non-Hodgkin lymphoma	Various (retrospective study)	Decreased EF: 10% (12/116 pts)[a] CRS Grade 4: 2% (4/187 pts) CRS Grade 3: 3% (6/187 pts) CRS Grade 1–2: 78% (145/187 pts)
Goldman et al.[32b]	Various	Axicabtagene ciloleucel and Tisagenlecleucel (Safety report analysis)	Overall CPAEs: 20.5% (546/2657 safety reports) -Overall fatality of CPAEs: 30.9% Tachyarrhythmia: 2.8% (74/2657 safety reports)[c] -of these: 74% atrial fibrillation Cardiomyopathy 2.6% (69/2657 safety reports) Pericardial disease 0.4% (11/2657 safety reports) VTE: 1.6% (28/2657 pts)
Shalabi et al.[33] **(subgroup of Lee et al.**[12]**)**	ALL, non-Hodgkin lymphoma	KTE-C19, predecessor of tisagenlecleucel	Decreased EF: 12% (6/52 pts)[d] Decreased GLS: 78% (29/37 pts)[e] CRS Grade 4: 6% (3/52 pts) CRS Grade 3: 12% (6/52 pts) CRS Grade 1–2: 54% (28/52 pts)

CPAE, cardiovascular and pulmonary adverse event; CRS, cytokine release syndrome; EF, ejection fraction; GLS, global longitudinal strain, VTE, venous thromboembolism.
[a]Decreased EF was defined as a decrease in left ventricular EF of at least 10% points to <50%.
[b]Arrhythmia was defined as new clinically significant supraventricular tachycardia or new-onset atrial fibrillation/flutter.
[c]Sinus tachycardia was excluded for the definition of arrhythmia.
[d]Decreased EF was defined as a decrease in left ventricular EF of at least 10% points or a decrease in left ventricular EF to <50%.
[e]Decreased GLS was defined as a relative decrease of >15% from baseline or a decrease in GLS to <19%.

structures, which must be closely monitored for new potential targets for CAR-T cell therapy.

The possible spatial proximity between the heart and a mediastinal manifestation of lymphoma offers a further point of attack for direct cardiotoxic effects. Cardiac affection from adjacent hyperinflammation of tumour tissue appears plausible and is supported by a case of sudden cardiac death in a patient with pronounced mediastinal lymphoma that was preceded by a reduced LVEF without high-grade CRS. Post-mortem, arrhythmia was the proposed (yet unproven) cause of death, while autopsy data were not available.[39] Cardiac radiation has already been shown to evoke cardiac inflammatory reactions in a pre-clinical model, but it is currently unknown whether radiotherapy for mediastinal lymphoma that can affect the heart should be considered a further risk factor.

Clinical characteristics

Conclusions about early cardiac involvement can be drawn from the available data on cardiac biomarkers and cardiac function. The largest record of CV adverse events from CAR-T cell therapy was derived from the aforementioned pharmacovigilance database with postmarketing safety reports from 2657 patients receiving axicabtagene ciloleucel or tisagenlecleucel.[32] Here, 20.5% of the safety reports stated CPAEs, including tachyarrhythmia (13.6%), cardiomyopathy (12.6%), venous thromboembolic events (5.1%), and pericardial disease (2.0%). Retrospective observational data report a major CV event rate of 12–28%, particularly shortly after treatment (median time after transfusion of CAR-T cells: 6–21 days), including CV death and decompensated heart failure, each in 35% of affected patients.[27] While elevated troponin was found in 54% of patients undergoing CAR-T cell therapy and biomarker measurement, the frequency of elevated troponin was 94% in patients with severe CV adverse events. Correspondingly, the CV event rate for patients with elevated troponin was 55%, compared to 4% in patients without elevated troponin. In addition, an association between the incidence of troponin elevation and CRS (≥Grade 2) was demonstrated in tested patients (83% vs. 33%), and a reduction in LVEF was found in 28% of patients, all of whom had increased troponin. An important limitation to these data is the lack of routine assessment of cardiac

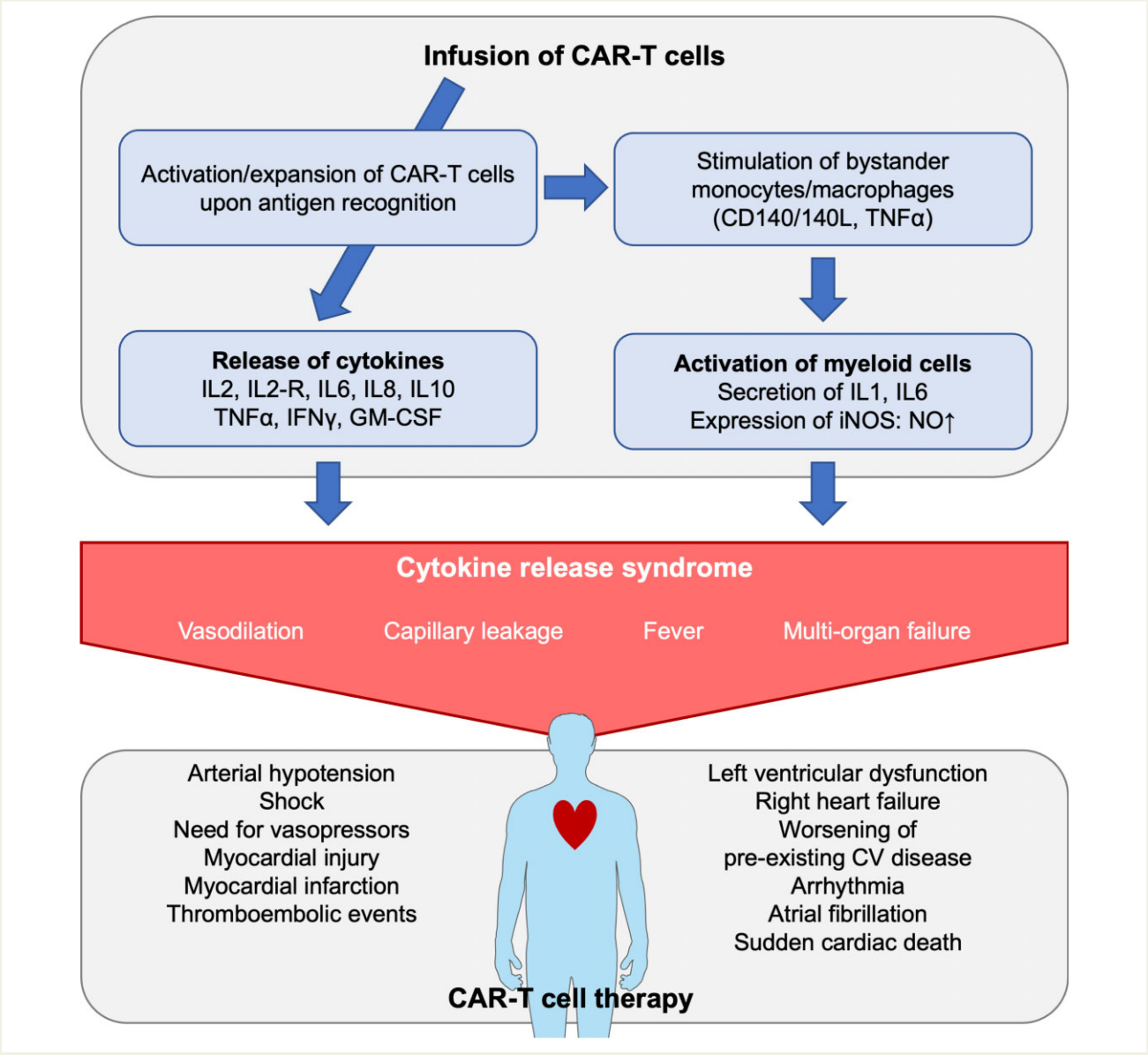

Figure 3 Cytokine release syndrome. The infusion of chimeric antigen receptor-T cells leads to the release of proinflammatory cytokines and activation of host leucocytes, generating a local and systemic inflammatory reaction called cytokine release syndrome. Systemic inflammatory changes can be associated with distinct cardiovascular toxicities. CAR, chimeric antigen receptor; CV, cardiovascular; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; NO, nitric oxide; TNFα, tumour necrosis factor alpha.

troponin levels before and after the start of CAR-T cell therapy, introducing a very important selection bias and overestimation of risk and association. In the study by Alvi *et al.*,[27] patients with elevated troponin were notably older with a higher burden of CV risk factors.

A lower risk of reduced LVEF was found in a recent retrospective study. Here, 10.3% of treated patients showed LV dysfunction (median decrease from 58% to 37%; medium time interval of 12.5 days from CAR-T cell infusion).[31] Age, hyperlipidaemia, and pre-existing coronary artery disease were identified as risk factors for decreased LVEF. Patients with decreased LVEF tended to require more vasopressor support, mechanical ventilation, and administration of tocilizumab for severe CRS.[31] Again, only a fraction of the examined cohort received echocardiography. The presence of decreased LVEF was paralleled in a third retrospective study in 6/37 patients (16%), with 3/6 affected patients showing severely reduced LVEF (<30%). Only limited data on global longitudinal strain (GLS) are available. In a retrospective study, reduced GLS was present in 78% of patients, with unknown progression rates to LVEF reduction.[33] Cardiac troponin was elevated in 67% of patients.[33] No systematic data on angiographic findings in patients with elevated troponin are yet available. Nevertheless, the relevance of LV dysfunction during the acute phase is under debate given its potentially reversible nature. Complete recovery of LV function constituted 50% and partial recovery constituted 25% of patients during follow-up.[26,31]

A significant fraction of CAR-T cell therapy is applied in children and adolescents. Despite the observed age dependency of CV involvement, LV dysfunction has also been observed in paediatric patients. In a cohort of 98 children (mean age: 11.8 years) treated for B-ALL, decreased LV function was observed in 10% of patients with no CV deaths, and LV dysfunction resolved in most patients after 6 months, indicating a lower risk for irreversible CV toxicity than in adults.[40]

A systematic assessment of CV adverse events is currently being conducted in prospective observational trials in the scope of B-cell leukaemia/lymphoma (www.clinicaltrials.gov NCT04026737 and NCT05130489). The latter study will also assess the diagnostic value of cardiac magnetic resonance imaging.

Pre-therapy assessment, monitoring, and treatment

Owing to the high incidence of CRS with subsequent stress on the CV system and potentially life-threatening consequences, algorithms for the cardio-oncology management of patients receiving CAR-T cell therapy have recently been proposed (*Figure 4*).[26,41] Baseline assessment is recommended for all patients before therapy [medical history, clinical examination, and electrocardiogram (ECG)]. Echocardiography and cardiac biomarkers [cardiac troponin and (N-terminal pro-) brain natriuretic peptide (NT-pro) BNP] should be obtained at baseline as references for dynamics during and after therapy and to identify patients with undiagnosed CV disease.[26,27] Echocardiography should include the assessment of GLS, which has been shown to decrease during CAR-T cell therapy.[33] In addition to those with malignant cardiac/pericardial involvement (e.g. pericardial effusion), the following CV disease entities require evaluation, as CAR-T cell therapy may lead to decompensation: (i) patients with heart failure as it may further complicate distributive shock; (ii) patients with coronary artery disease, which increases susceptibility to microvascular dysfunction, inflammation-induced plaque destabilization, and myocardial ischaemia during severe CRS; (iii) patients with moderate to severe valvular heart disease, particularly aortic stenosis or mitral regurgitation, as it may provoke rapid decompensation; (iv) patients with arrhythmias, including atrial fibrillation (such as systemic inflammation and neurogenic drive), can experience an aggravation of arrhythmia burden. These patients and any others with concerns for CV risk should be referred for a cardiology assessment before therapy for potential additional testing (e.g. stress test or Holter ECG), optimization, and outline of a surveillance plan.

Medical therapy for pre-existing CV disease, including heart failure therapy, antihypertensive treatment, and antithrombotic treatment, should be optimized before therapy. Close monitoring for signs of severe CRS or manifest cardiotoxicity, including arrhythmia, hypotension, and symptoms of heart failure, is recommended during the early phase of therapy. While cardiac troponin was proven to predict LV dysfunction during CRS, NT-proBNP may exert a lower diagnostic value given the confounding coadministration of intravenous fluids, hyperdynamic circulation, and renal insufficiency.[27] A standardized cardio-oncology follow-up at Day 7 following CAR-T cell transfusion, including ECG, echocardiography, and biomarkers, may be beneficial to cover the particularly vulnerable early phase. Advanced imaging, including cardiac magnetic resonance imaging, can be considered in individual cases of patients with suspected cardiac involvement, but systematic data are not available. A 3-month follow-up visit is recommended, including cardiac biomarkers, ECG, and echocardiography, in high-risk patients to assess delayed CV toxicity or recovery of manifest CV effects (*Figure 4*).

Interdisciplinary cooperation among oncologists, cardio-oncologists with expertise in critical care, neurologists, pharmacists, and specialized nurses is mandatory for the best possible management of the CV complications of CAR-T cell therapy. The prophylactic use of beta blockers or angiotensin receptor blockers can be considered in patients with elevated baseline risk or when decreased LVEF is observed upon early therapy but requires reconsideration in patients with progressive hypotension and distributive shock.[26] The role of immune-modulating drugs in preventing adverse events in patients at high risk for CV toxicity has not yet been studied. Considering the strong association between elevated troponin and the risk for CAR-T cell therapy-related complications, it is possible that patients with elevated troponin will benefit from early protective therapy with tocilizumab, even in low-grade CRS. Early administration of tocilizumab for the treatment of CRS was associated with a lower risk for troponin elevation in a retrospective analysis.[27] A delay of 12 h from the onset of CRS to the administration of tocilizumab was related to a 1.7-fold increased risk for CV events. In a single-centre, randomized trial, tocilizumab without pre-selecting patients with increased risk reduced the incidence of CRS. Meanwhile, CAR-T cell persistence and subsequent anticancer efficacy were sustained.[42] However, prophylactic use of tocilizumab to reduce severe CRS may increase the rate of severe neurotoxicity; hence, a prophylactic approach cannot be generally recommended, and prospective, randomized evaluations are needed.[29]

The early recognition of CRS is crucial for timely therapeutic intervention. Close monitoring should be initiated, and patients with moderate CRS should receive antipyretics when their body temperature is $\geq$38.0°C. Intravenous fluids should be given when patients develop fever or signs of hypovolemia (e.g. sinus tachycardia, fatigue, dizziness, or moderate hypotension). An assessment of the diameter of the inferior vena cava (IVC) via ultrasound can support the diagnostic assessment. Concomitant systemic infections with comparable clinical presentations should be assessed and treated correspondingly.[43] Tocilizumab use in early CRS is now part of the approved Risk Evaluation and Management System for axicabtagene ciloloeucel, lisocabtagene maraleucel, brexucabtagene autoleucel, and idecaptagene vicleucel.

Severe CRS with arterial hypotension may require early intensive care treatment, including invasive blood pressure monitoring, mechanical ventilation, and mechanical circulatory support. Management may require vasopressor therapy in the event of persisting hypotension, despite intravenous fluid administration, management of coagulopathies, and treatment of multiorgan dysfunction. There is a tendency towards an increased frequency for the use of vasopressors in paediatric patients compared with adults.[40] In the acute phase of severe CRS, liberal red blood cell transfusions aiming to maintain a haemoglobin level $\geq$8 g/dL can be considered. Distributive shock, cardiogenic shock, and mixed forms should be assessed and differentiated by echocardiography, including the assessment of right

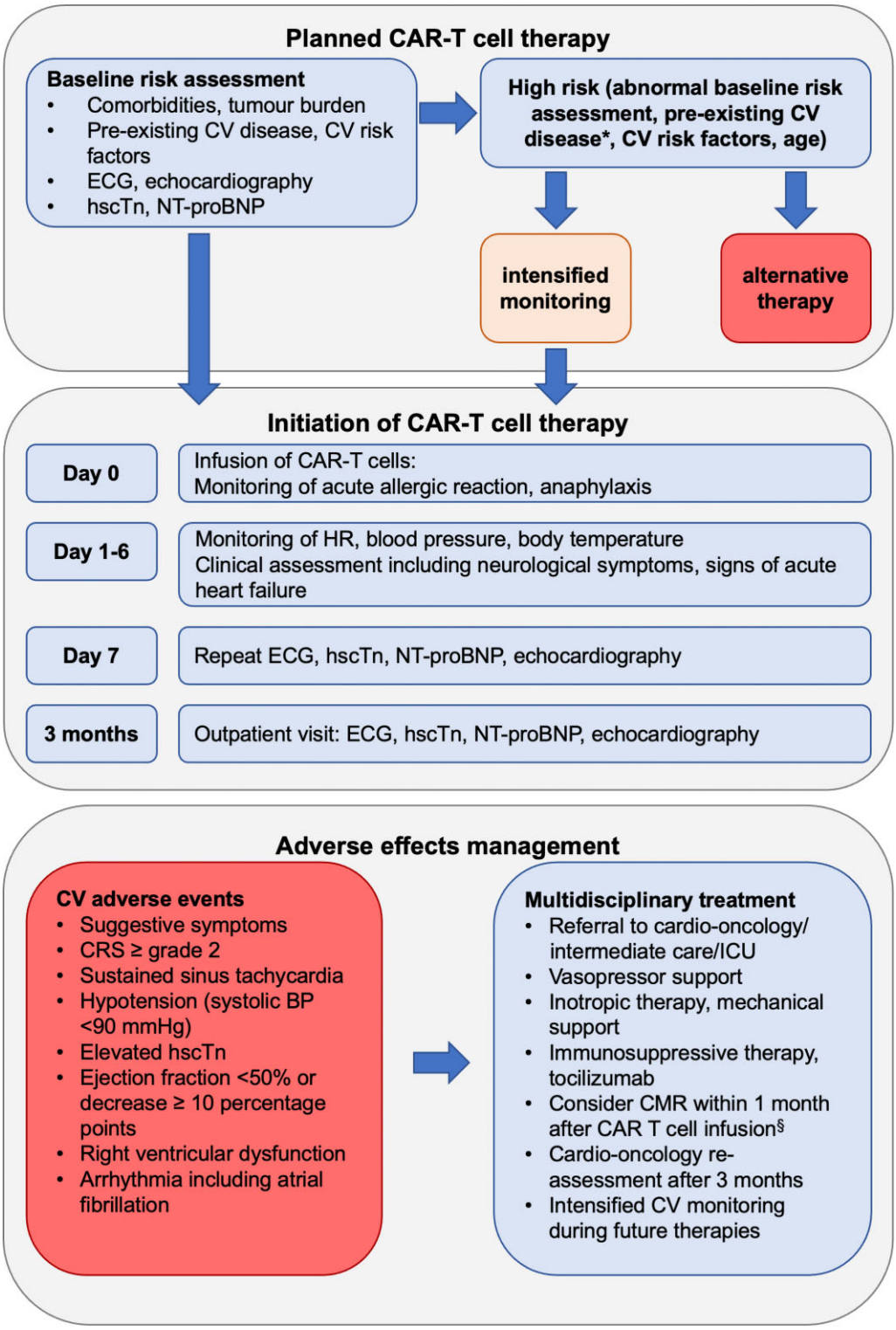

Figure 4 Management of patients undergoing chimeric antigen receptor-T cell therapy. Patients planned for chimeric antigen receptor-T cell therapy should undergo baseline assessment of cardiovascular disease and risk factors, electrocardiogram, echocardiography, and cardiac biomarkers. During therapy, patients are closely monitored for cytokine release syndrome and cardiac complications. Multidisciplinary management is required to manifest cardiovascular side effects. *Pre-existing cardiovascular disease particularly includes valvular heart disease, coronary artery disease, heart failure, arrhythmia (including atrial fibrillation), and thromboembolic disease. §Can be considered in selected patients with persisting signs of cardiac impairment (e.g. left ventricular dysfunction), abnormal biomarkers, and poor echocardiography quality. BP, blood pressure; CMR, cardiac magnetic resonance; hscTn, high-sensitivity cardiac troponin; ICU, intensive care unit; NT-proBNP, N-terminal pro-brain natriuretic peptide.

ventricular filling pressure and stroke volume/cardiac index. A hyperkinetic left ventricle with increasing stroke volume/cardiac index, a small right ventricle, and a collapsing IVC indicate distributive shock, while LV dysfunction, LV dilation, dilated IVC, and right heart stress may indicate cardiac involvement and incipient cardiogenic shock. Invasive assessment with a Swan-Ganz (or similar) catheter represents a valuable tool in patients with undefined haemodynamics.[44,45] Arrhythmias, including atrial fibrillation, are commonly found in severe CRS. [27,34] Treatment should be according to current guidelines, including optimization of serum electrolytes, antiarrhythmic therapy (e.g. amiodarone), and electric cardioversion.

Tocilizumab can be recommended in patients with severe CRS or severe CV adverse events.[41] Corticosteroids serve as a second-line treatment for patients with life-threatening, tocilizumab-refractory toxicity. As neurotoxicity from CAR-T cell therapy (noted in up to 67% of patients) often correlates with CRS, it is important to point out that tocilizumab does not cross the blood–brain barrier and may even worsen neurotoxicity.[46] Hence, patients with neurotoxicity from CAR-T cell therapy require additional corticosteroid therapy. Tocilizumab only temporarily inhibits the proliferation of CAR-T cells with evidence for re-expansion and persisting CAR-T cells.[3] However, the lymphocyte suppressive effects of corticosteroids could last longer, particularly with sustained administration (e.g. for ICANS). Therefore, the application should be limited to immediately life-threatening complications.[26] Siltuximab directly binds IL-6 with high affinity and has been proposed for use in therapy-refractory CRS. It may have beneficial effects, particularly in the setting of severe neurotoxicity. However, siltuximab for CAR-T cell-related toxicity is not officially approved, and its consequences on CV toxicities are currently unknown.[41]

As recent pre-clinical evidence indicates that large quantities of IL-6 are in fact secreted by stimulated recipient macrophages rather than transfused CAR-T cells, it has been proposed that inhibition of IL-1 to prevent macrophage activation may serve to reduce IL-6-mediated detrimental effects without inhibiting CAR-T cell efficacy.[25] In an early case series, the IL-1 receptor antagonist anakinra was successfully applied in patients with severe complications from CAR-T cell therapy who were refractory to tocilizumab and corticosteroid treatment.[47] Remarkably, four of eight patients showed a response to anakinra therapy. While no systemic clinical data on the impact of IL-1 blockade on the efficacy of CAR-T cell therapy are available, pre-clinical evidence and case series indicate sustained therapeutic activity while the severity of CRS is reduced.[25,47] Further experimental protective approaches to mitigate CRS include depletion of granulocyte-macrophage colony-stimulating factor (GM-CSF) signalling, either by genetic depletion of GM-CSF in CAR-T cells or by neutralizing antibodies.[46,48] The anti-GM-CSF antibody lenzilumab has shown promising results in a pre-clinical model where it reduced toxicity while enhancing CAR-T cell efficacy and is currently being tested in a multicentre Phase I/II trial (www.clinicaltrials.gov NCT04314843).[46,48]

Sustained tachycardia with deleterious consequences on cardiac function is a hallmark in patients with SIRS/sepsis, fuelled by a hyperadrenergic state from elevated endogenous and exogenous catecholamine concentrations. In a randomized study, the short-acting beta blocker esmolol improved LV haemodynamics, decreased catecholamine requirements, and was associated with improved 28-day survival in patients with septic shock. Despite the lack of definite evidence, the parallels of sepsis and CRS indicate esmolol as a candidate therapy to mitigate CV adverse effects and potentially CRS-related mortality, requiring future research.[49]

Applying CAR-T cell therapy for cardiovascular disease

As a highly vascularized organ with a dense capillary network, the heart offers an enormous contact area for immune cells and is particularly dependent on immune quiescence to maintain functional integrity at all times. The essential involvement of the immune system in acute and chronic myocardial disease is only just beginning to be understood. For the first time, CAR-T cells have been applied to combat myocardial fibrosis in a mouse model of hypertensive heart failure as a proof of concept.[50] After identifying the upregulation of fibroblast activation protein in patients and mice with myocardial fibrosis, T cells were engineered to target affected fibroblasts, and the results revealed significantly lower levels of myocardial fibrosis in treated mice.[50] Although this is the first experimental model, convincing results show that the application of CAR-T cell therapy in targeted CV medicine is conceivable in the future. The presence of target structures that are absent in healthy tissue is crucial for such a therapeutic approach. In parallel, the toxic effects of cardiac-specific CAR-T cells will be the decisive factor for successful application. Advances in cardioimmunology, including a deeper understanding of CV adaptive immunity and suitable target structures, will clarify whether CAR-T cell therapy will serve to prove the feasibility of the methodology and may pave the way for a new therapeutic paradigm in CV disease.

Conclusion

Chimeric antigen receptor-T cell therapy is a revolutionary form of cancer immunotherapy, and biochemical refinements and expansion to new cancer entities will lead to a rapidly increasing use. The complex nature of CAR-T cell-related adverse effects is just beginning to be understood, and profound effects on the CV system are evident from pre-clinical and clinical data, emphasizing the importance of the best possible cardio-oncological care of this vulnerable collective. As reflected in the entire field of immuno-oncology, the main future challenge for cardio-oncology will be the effective management of CV adverse events while maintaining anticancer efficacy. A better understanding of the characteristics of CV toxicity will lead to improved clinical management and protective treatment.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Corrigendum

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Corrigendum to: Heart failure with preserved ejection fraction in humans and mice: embracing clinical complexity in mouse models

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In the originally published version of this manuscript, there was an error in Prof. Carolyn S. P. Lam's second affiliation.

The incorrect affiliation read:

National University Heart Centre, Singapore and Duke-National University of Singapore

This has now been corrected to:

National Heart Centre, Singapore and Duke-National University of Singapore