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EMERGENT CAR T-CELL TOXICITIES

How I approach optimization of patients at risk of cardiac and pulmonary complications after CAR T-cell therapy

Cristina Gutierrez,[1] Tomas G. Neilan,[2] and Natalie S. Grover[3]

[1]Department of Critical Care, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA; and [3]Division of Hematology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

Chimeric antigen receptor (CAR) T cells have transformed the care for patients with hematologic malignancies. Patients treated with CAR T cells may experience cardiovascular and pulmonary complications, which primarily occur in the setting of cytokine release syndrome. In addition, many patients considered for CAR T-cell therapy have preexisting cardiac and pulmonary comorbidities. Among patients with good functional status, these conditions should not prevent patients from being offered these lifesaving therapies. In this article, we use a case-based approach to discuss how we evaluate and optimize conditions for patients with cardiac and pulmonary risk factors before CAR T-cell therapy and manage cardiac and pulmonary complications that may arise with treatment.

Introduction

Chimeric antigen receptor (CAR) T cells have transformed the treatment of hematologic malignancies, providing promising new therapies for patients who previously had poor prognoses. There are now several Food and Drug Administration (FDA)-approved CAR T-cell products for hematologic malignancies, and an increasing number of patients, despite their significant comorbidities, are now considered eligible for these treatments. Data suggest that >10% of patients treated with CAR T cells experience cardiovascular or pulmonary adverse events, which primarily occur in the setting of cytokine release syndrome (CRS).[1-6] Most of the early data about cardiac and pulmonary complications from CAR T-cell therapy are derived from patients treated in clinical trials, which typically exclude patients with more severe cardiac and pulmonary disease. Therefore, as more real-world patients with significant cardiac and pulmonary comorbidities are treated with CAR T-cell therapy, the rates of these complications will increase, and questions will arise about how to best evaluate and optimize the conditions of these patients and manage their cardiac and pulmonary complications. In this article, using a case-based discussion, we present our approach to assess and optimize cardiac and pulmonary comorbidities before and during CAR T-cell therapy as well as the management of posttreatment cardiopulmonary complications. Although we will be focusing mostly on approved CAR T-cell products, novel CAR T-cell therapies for various indications are currently being investigated in clinical trials and preclinical settings and may have a different toxicity profile from current ones. Therefore, as new CAR T-cell therapies become more widely available, it is important for physicians providing treatment to review available adverse event data to help risk-stratify patients.

Part 1: preinfusion cardiac and pulmonary evaluation

A 68-year-old man with a history of coronary artery disease (CAD), stable chronic obstructive pulmonary disease (COPD), deep venous thrombosis, and diffuse large B–cell lymphoma was referred for CD19-targeted CAR T-cell therapy. He was previously treated with 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone but relapsed within 6 months of completing treatment. A positron emission tomography–computed tomography scan demonstrated high tumor burden, including bulky mediastinal disease and a moderate pleural effusion. An echocardiogram showed a 40% left ventricular ejection fraction (LVEF) as well as mild pulmonary arterial hypertension (PAH) with preserved right ventricular function. Upon evaluation, he was found to have an Eastern Cooperative Oncology Group score of 1, had no signs of decompensated heart failure or COPD, and had not been hospitalized for these comorbidities in the last 6 months. Since the development of this effusion, he was dyspneic and desaturated on ambulation. He was also being treated with apixaban for his deep venous thrombosis diagnosed 2 months prior to presentation. We questioned what his risks were for cardiac and pulmonary complications and how his condition could best be optimized before treatment with CAR T-cell therapy.

After a patient is deemed an appropriate candidate for CAR T-cell therapy by the oncologist, the main role of the consultant is to optimize the conditions and support patients who are at high risk before CAR T-cell infusion and when toxicities arise (Figure 1). This patient had several cardiac and pulmonary risk

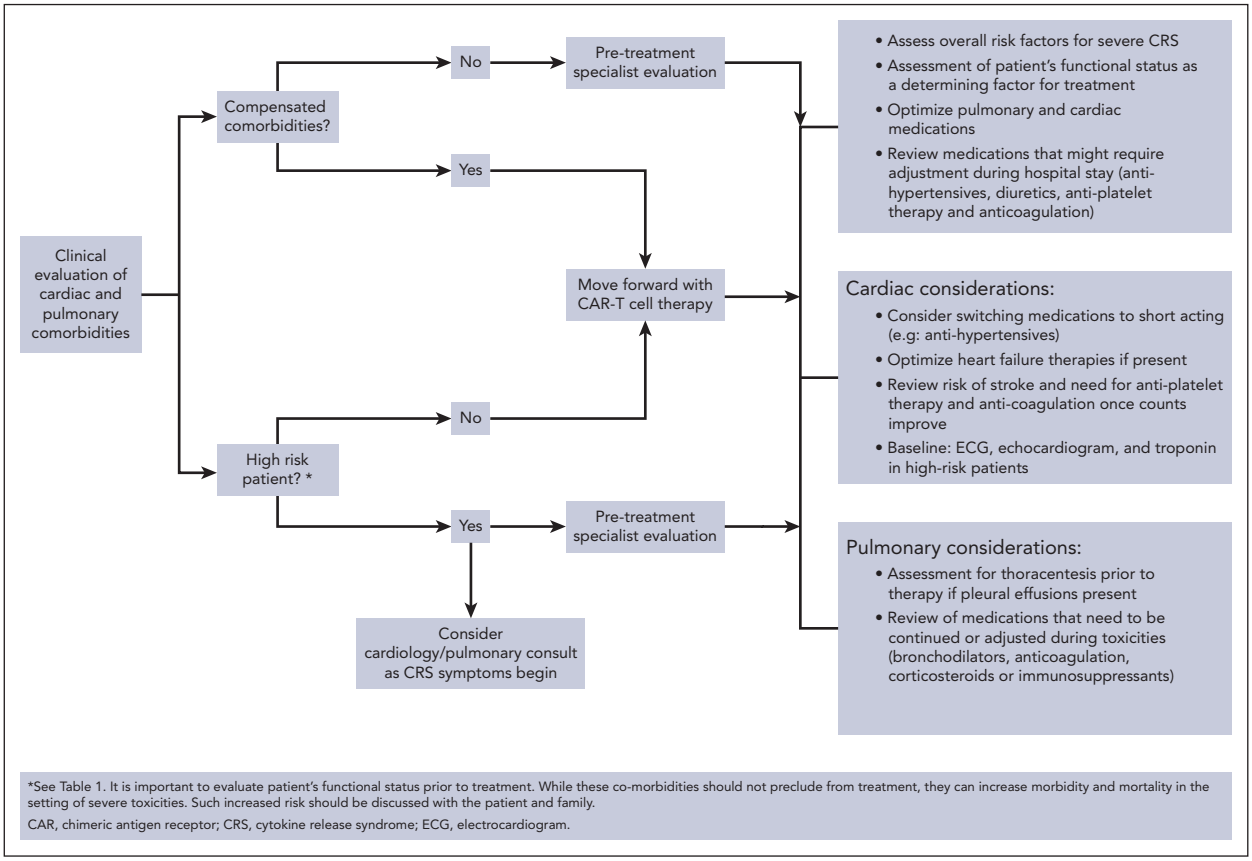

Figure 1. Evaluation and optimization of patients with cardiac and pulmonary comorbidities before CAR T-cell therapy.

factors, including CAD, heart failure, age >65 years, prior anthracycline, COPD, bulky mediastinal mass, PAH, and pleural effusion (Table 1). Although there are limited data assessing how preexisting cardiac and pulmonary comorbidities can affect outcomes, one can assume these patients have lesser reserve volumes and are probably at an increased risk of more life-threatening complications in the setting of CRS. The clinical trials that led to the FDA approval of CAR T cells generally had more stringent exclusion criteria for patients with cardiac and pulmonary comorbidities. For example, Zuma-1 required a LVEF ≥50% and pulse oximetry >92% when breathing room air,[7] whereas the Juliet trial required an LVEF of ≥45% and grade 1 or lower dyspnea as part of its inclusion criteria.[8] Recent studies have revealed that in the real-world setting, many patients referred for CAR T-cell therapy are older and have more comorbidities, including lower LVEF, symptomatic pleural effusions, pulmonary embolisms or deep venous thrombosis, and oxygen supplementation requirements.[9] Although these patients are more ill than those included in the trials, the efficacy, severity of toxicities, rate of intensive care unit (ICU) admission, and mortality are similar to those observed during the trials.[6,9-11] However, a baseline good functional status, described as Eastern Cooperative Oncology Group <2 in these studies, had an important role in these positive outcomes.[9,11] For patients with significant high-risk comorbidities, we recommend a multidisciplinary discussion addressing possible higher morbidity and increased risk of ICU admission during toxicities, taking into account the patient's overall prognosis from their malignancy and other available treatment options.

When evaluating patients before CAR T-cell therapy, we review risk factors for cardiac toxicity from prior treatments, including prior exposure to anthracyclines and history of chest radiation as well as comorbidities, such as hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, CAD, heart failure, and arrhythmias (Table 1).[12-15] We obtain a baseline electrocardiogram and echocardiogram, but we do not use a specific LVEF cut off for patients and instead focus more on a patient's general functional status, New York Heart Association functional status, and heart failure history. We obtain baseline troponin for patients who are at high risk. Some groups consider the additional measurement of natriuretic peptide levels; however, data on the value of these measurement in this setting are limited. We do not obtain assessments for cardiac ischemia because the platelet count may drop dramatically after treatment, and, thus, coronary revascularization is not a viable option. Given that most of the cardiac complications related to CAR T-cell therapy are associated with CRS, we also assess patients for risk factors for severe CRS, including high tumor burden. In addition, we consider differences in products, particularly in the co-stimulatory domain of CD19-directed CAR T cells, with CD28 costimulatory domain (axicabtagene ciloleucel) generally associated with more frequent and higher-grade CRS compared with 4-1BB costimulatory domain (tisagenlecleucel [tisa-cel], lisocabtagene maraleucel [liso-cel]).[16-18] In addition, there may be differences associated with lymphodepletion or conditioning regimen, with small studies suggesting lower rates of CRS as well as hematologic toxicities, including profound thrombocytopenia, with bendamustine than with fludarabine or cyclophosphamide.[19]

Table 1. High-risk cardiopulmonary comorbidities and considerations before CAR T-cell therapy

Cardiac comorbidities/risk factors	Pulmonary comorbidities/risk factors	Malignancy-related considerations
Heart failure, reduced LVEF (<50%), prior or current cardiomyopathy	Moderate-to-severe obstructive or restrictive pulmonary disease	High tumor burden
Prior history of myocardial infarction or coronary revascularization	Moderate-to-severe pulmonary hypertension	Product with higher incidence and grade of CRS
Cardiovascular risk factors (eg, hypertension, diabetes mellitus, obesity, smoking, prior anthracycline, prior chest radiation)	Recurrent pleural effusions requiring frequent thoracentesis	Rapidly progressive disease (giving less time for optimization)
Age >65 y	Large mediastinal masses with concerns of airway involvement	Type of disease (eg, lower rate of toxicity in follicular lymphoma compared with that in diffuse large B–cell lymphoma)
Significant valve disease, moderate or greater regurgitation or stenosis	Home oxygen dependency	Intensity of lymphodepletion/conditioning

These considerations can help guide the choice of CAR T-cell product and monitoring method for these patients when toxicities appear; however, once complications occur, we generally manage cardiopulmonary toxicities similarly regardless of the CAR T-cell product or lymphodepletion regimen received.

We recommend referral of patients having preexisting cardiac conditions including heart failure, reduced LVEF, prior history of cardiomyopathy, known CAD, as well as patients at high risk for cardiac disease because of age and cardiovascular risk factors to cardio-oncology or general cardiology, if cardio-oncology services are not available, before treatment. Regarding cardiac and pulmonary optimization, in most instances, there is limited time because patients need to be treated quickly, often within 1 or 2 months of referral, because of the nature of the disease. However, for some patients with certain disease types, such as indolent lymphomas and multiple myeloma, pursuing alternative therapies or delaying CAR T-cell therapy may be an appropriate option, with careful balancing of the patient's disease status and other treatment options. Occasionally, there may also be limited treatment slots, so patients may have to wait for months before treatment, and, in these rare cases, there may be more time to further optimize their comorbid conditions. In most situations, we do not advocate delaying CAR T-cell therapy specifically for optimization, unless a patient is clearly not a candidate for treatment because of poor functional status and decompensated or end-stage cardiac or pulmonary comorbidities. However, if there is a possibility that some of the comorbidities can be reversed, such as ischemic cardiomyopathy, or improved by increasing diuretics or controlling blood pressure, and the patient either does not require immediate treatment or can pursue less aggressive treatment options, CAR T-cell therapy may be deferred or delayed with future reevaluation.

A cardiologist evaluated our patient and started administration of a beta-blocker and a sodium-glucose cotransporter 2 inhibitor. These treatments alone are not optimal treatment options for his heart failure condition, but in view of the upcoming CAR T-cell therapy and the high potential for hypotension, we did not proceed with other standard heart failure therapies. He was already on a statin, which was continued. The plan was to convert his regimen to a short-acting beta-blocker at the time of treatment. Regarding his anticoagulation condition, at the time of lymphodepletion, because of the concern about thrombocytopenia, we temporarily transitioned his regimen to low molecular weight heparin, with a plan to reduce his dose if there was any evidence of acute kidney injury or if his platelet count dropped $<50 \times 10^3/\mu L$ and to hold anticoagulation if platelet count dropped $<25 \times 10^3/\mu L$.

A few other considerations in the peri-CAR T-cell period for patients with cardiac history include the initiation or transition to short-acting antihypertensives for uncontrolled or preexisting hypertension because of the high risk of hypotension during CRS. The use of statin therapy is balanced against the potential of post-CAR T-cell elevation of liver function tests, so their use may be deferred in the acute peri-CAR T-cell setting. Finally, as with the patient described earlier, among patients with heart failure, we consider optimization of goal-directed therapy (including considering a beta-blocker, angiotensin receptor–neprilysin inhibitor, sodium-glucose cotransporter 2 inhibitor, and mineralocorticoid receptor antagonist, if tolerable). However, similar to the case described earlier, many of these therapies are long acting, and the risk of hypotension has to be weighed. At the time of lymphodepletion, we monitor patients closely for thrombocytopenia and hold anticoagulation for patients who are at high risk for thrombocytopenia (platelets $<50 \times 10^3/\mu L$) or have evidence of impending cytopenias. Before restarting these agents, we monitor patients closely for stability of their platelet counts and coagulopathy (because of CRS, hemophagocytic lymphohistiocytosis-like syndrome, or liver dysfunction). For patients with thrombocytopenia who require anticoagulation for indications such as acute thrombosis, we consider resuming anticoagulation first with either unfractionated heparin drip or split-dose low molecular weight heparin, especially if there is a high risk of them developing delayed cytopenias or coagulopathy. When no complications are observed, and platelets are deemed to be adequate, long-acting anticoagulants can be considered. Although we usually use a cutoff for platelet counts $>50 \times 10^3/\mu L$, close monitoring for signs of bleeding and renal and liver dysfunction is important, and a discussion with the hematology team might be useful to guide the therapy and choice of anticoagulant.[20,21]

Our patient had an established diagnosis of COPD and mild PAH as observed with an echocardiogram, and given his good functional status, healthy right ventricular function, and controlled symptoms, we did not pursue further immediate pulmonary work up. We continued his COPD medications, and given that the patient had a symptomatic malignant pleural effusion, he underwent thoracentesis and we monitored him for reaccumulation to ensure that he did not need catheter placement.

As part of the pulmonary evaluation before CAR T-cell therapy, we assess for malignancy-related risk factors, such as high pulmonary disease burden, airway involvement, and preexisting effusions that could exacerbate respiratory symptoms during CRS (Table 1). It is important to note that pulmonary and pleural involvement could lead to increased CAR T-cell trafficking to the lungs and, therefore, increase respiratory complications.[22] We do not routinely obtain baseline pulmonary function tests or high-resolution pulmonary computed tomography imaging in these patients. Currently, not enough data are available to correlate the outcomes of patients who undergo CAR T-cell therapy with the severity of pulmonary disease and to specify whether a subgroup of patients would benefit from pretreatment workup, such as pulmonary function tests. As with patients with cardiac risk factors, the decision to treat is based more on the patient's functional status, especially if their pulmonary disease is well controlled. Patients who have a history of obstructive or restrictive pulmonary disease with significant recurrence of symptoms or exacerbations should be referred to a pulmonologist to assess compliance, optimization of therapy, and need to restage disease severity. For patients with incidental findings of mild-to-moderate PAH upon echocardiogram testing, workup for pulmonary hypertension should not delay CAR T-cell therapy, especially for those with aggressive disease. If a patient has severe PAH, this could put them at a higher risk of having cardiovascular decompensation during severe CRS, and an evaluation by a pulmonologist can help guide workup or optimization that could be performed in the peri-CAR T-cell therapy period. In this setting, a discussion between the patient and consultants is needed so that they are aware of the increased morbidity and mortality during CRS in comparison with other patients. For patients with known history of pulmonary hypertension, we recommend evaluation by a pulmonologist because some of the medications, such as vasodilators and anticoagulants will need to be continued during treatment. If patients have frequently reaccumulating malignant effusions that lead to dyspnea and hypoxia, we consider intervention before treatment, including drainage or catheter placement. We also work to optimize and continue therapy for patients with underlying comorbidities, such as COPD and asthma in children. Although rare, interstitial lung disease secondary to different causes (postinfectious, connective tissue disease, exposure-related, or idiopathic) could be present during the evaluation of patients. Those patients with stable disease and good functional status, even if they require low-dose corticosteroids and oxygen therapy, could be considered for CAR T-cell therapy on a case-by-case basis. A careful discussion among specialists, regarding what could be a minimal corticosteroid dose the patient might tolerate, is necessary to find an optimal dosage that can hopefully avoid suppression of CAR T proliferation. If corticosteroids and other immunosuppressive therapies are not amenable to weaning because of concerns of respiratory decompensation, then CAR T-cell therapy might not be a good option for treatment. Patients with pulmonary comorbidities may require closer monitoring of their respiratory status with the onset of CRS. We recommend inpatient pulmonary consultation and, sometimes, early ICU admission for patients with known rapidly reaccumulating pleural effusions, patients with moderate-to-severe obstructive or restrictive pulmonary disease or moderate-to-severe pulmonary hypertension, and patients requiring home oxygen supplementation, especially if they have high tumor burden and pleural or pulmonary involvement.[5,23]

Although our patient was determined to be at higher risk for complications with CAR T-cell therapy based on his history and pretreatment assessments, given his high-risk disease and overall good functional status, the decision was made to proceed with treatment using CAR T cells.

Part 2: CRS in the patient with high-risk cardiac or pulmonary disease

Our previously described patient received CD19-directed CAR T cells (liso-cel). On day 3 after treatment, he developed a fever and tachycardia, followed by mild hypotension consistent with grade 2 CRS. He was treated with tocilizumab 8 mg/kg. The following day, his symptoms persisted and worsened, necessitating transfer to the ICU for treatment with vasopressor and oxygen support (high-flow FiO_2 > 60%). A chest radiograph showed diffuse bilateral pulmonary infiltrates with reaccumulation of pleural effusion. A repeat echocardiogram showed a reduced ejection fraction (EF) of 25%, and his troponin level was elevated. An electrocardiogram revealed sinus tachycardia.

It is important to note that there can be many causes of hypotension and hypoxemia in a patient who underwent CAR T-cell therapy (Table 2); therefore, a complete and thorough workup is needed when these clinical signs occur. Although CRS is the most plausible cause for these signs, septic shock, infectious pulmonary complications, and primary cardiovascular events need to be considered and, sometimes, treated concomitantly with CRS. Moreover, the timing of onset, type of CAR, and the patient's comorbidities can help narrow the differential diagnosis. A summary of cardiac and pulmonary considerations during CRS is shown in Figure 2.

Cardiac events associated with CAR T cells are reasonably common, generally short-lived, reversible, and mainly occur in the setting of CRS. For patients who are at higher risk for cardiovascular adverse events and develop CRS, we consider earlier administration of tocilizumab, with the goal of reducing the severity of CRS. Data suggest that the risk of a cardiac events with CRS increased 1.7-fold with each 12-hour delay in tocilizumab administration.[2] We place patients with grade ≥2 CRS on telemetry for the monitoring of arrhythmias. We repeat an echocardiogram in patients with known history of reduced EF, cardiomyopathy, or pulmonary hypertension and those with new symptoms of heart failure or hypotension. If baseline troponin and natriuretic peptide level from patients are available, repeat biomarkers at the time of CRS may help guide the workup and monitoring; a significant change in these should lead to a repeat echocardiogram. For patients with a sudden drop in EF, we generally cannot start goal-directed medical

Table 2. Differential diagnosis and workup of hypotension and hypoxemia in patients treated with CAR T-cell therapy

Sign of CRS	Differential diagnosis	Workup	Considerations
Hypotension	Neutropenic sepsis and septic shock Cardiogenic shock (cardiac tamponade and acute coronary syndrome)* Hemorrhagic	• Obtain cultures, urinalysis, and chest radiograph • ECG, echocardiogram, and cardiac enzyme/natriuretic peptide level • Initiate empiric broad spectrum antibiotics • Resuscitation with IV fluids (3 mL/kg) and vasopressor support, if needed	• Workup should not delay treatment of CRS • Telemetry/ICU admission is recommended • Timing of symptom onset from CAR product infusion can help guide treatment and workup • During resuscitation, evaluation of patients' intravascular status (bedside ultrasound vs noninvasive hemodynamic monitoring) is of importance because of the risk of capillary leakage when associated with CRS • Limited role of cardiac catheterization because of thrombocytopenia and inability to use anticoagulation or antiplatelet therapy
Hypoxemia	Infectious Pleural effusion† Cardiogenic and noncardiogenic pulmonary edema Thrombotic events	• Chest radiograph/CT chest • Sputum cultures, viral swabs, and fungal and viral titers for those at risk • Thoracentesis • Echocardiogram, ECG, and troponin and natriuretic peptide levels if clinical and imaging findings are suggestive of pulmonary edema • Lower extremity ultrasound/CTPA	• Cytology and flow cytometry for CAR T cells in pleural fluid (if available) can help differentiate the cause of effusion • Bronchoscopy can be considered in patients with persistent pulmonary infiltrates despite improvement of CRS symptoms (or low suspicion of CRS to be the cause of hypoxemia) • Workup should not delay the treatment of CRS • Timing of symptom onset from CAR T-cell infusion can help guide treatment and workup

CT, computed tomography; CTPA, computed tomography pulmonary angiography; ECG, electrocardiogram.

*Can also consider on-target off-tumor toxicities, decompensated pulmonary hypertension with right ventricular failure, and severe cardiomyopathy in the setting of CRS.

†Can be present in CRS due to capillary leakage; however, heart failure, progression of malignant effusions, and empyema (in some cases) can also be causative.

therapy because most patients are unable to tolerate agents owing to their low blood pressure. However, this can be reassessed before discharge and when CRS symptoms resolve.

Most of the adult data on cardiac events after treatment with CAR T cells consist of retrospective analyses of the patient population having lymphoma and receiving CD19-directed CAR T cells.[4,24] Most cardiac events occurred in the setting of CRS,[14] with a correlation with higher-grade CRS as well as older age.[24] These events include tachycardia (associated with fever) and hypotension (grade ≥2 CRS), elevated troponin, reduction in LVEF, arrhythmias, and cardiogenic shock. One study evaluated the incidence of major adverse cardiac events, defined as arrhythmias requiring intervention, new or worsening cardiomyopathy or heart failure exacerbation, stroke, myocardial infarction, or cardiac death, after CD19 CAR T-cell infusion. Out of 165 patients with large B–cell lymphoma, 27 (16%) had at least one major adverse cardiac event within 30 days of treatment; two-thirds of these were cardiac arrhythmias.[24] Although there was 1 cardiovascular death, the presence of major adverse cardiac events was not associated with reduced overall survival.[24] Several studies have found no statistically significant association between baseline LVEF and cardiovascular outcomes (major adverse cardiac events or new or worsening cardiomyopathy).[3,24] However, it is important to keep in mind that the overall number of patients with low LVEF is small in these studies, so it is difficult to reach conclusions about outcomes in this population. A baseline elevated troponin was associated with subsequent cardiovascular events, particularly in patients with grade 2 or higher CRS[2]; thus, this may be an aspect to consider in patients with higher baseline biomarkers. In general, cardiac adverse events usually seem to be reversible with low rates of long-term complications.[25]

There are data among pediatric patients treated with CD19-directed CAR T cells for B–cell acute lymphoblastic leukemia, including clinical trials as well as retrospective, real-world data.[1,26-28] This has been reassuring in this population with most instances of left ventricular dysfunction being reversible and with no cardiac-related deaths. Most patients were usually back to their baseline cardiac status by 4 weeks after infusion. This suggests that cardiac toxicity is of minimal concern among patients the pediatric B–cell acute lymphoblastic leukemia being treated with CD19-directed CAR T cells.

Pulmonary complications are less common than cardiovascular events during CRS.[6] They are most frequent among patients with higher-grade CRS, and the most common toxicities reported are hypoxia, pulmonary edema, pleural effusions, and pulmonary embolism.[5,6] Most instances of pulmonary edema are cardiac in nature, but noncardiogenic pulmonary edema due to capillary leakage can also occur.[6] When evaluating patients with pleural effusions, we assess whether these effusions are preexisting and secondary to underlying malignancies or new pleural effusions that develop during CRS and are more likely secondary to an inflammatory process, capillary leakage, or CAR T-cell trafficking.[5,22,23] Pleural effusions that are present at baseline before CAR T-cell therapy frequently persist, often require therapeutic intervention, and seem to be associated with higher rates of toxicity and death. In contrast, new pleural effusions that develop after CAR T-cell therapy and during CRS usually do not require drainage and are less likely to persist.[23]

Although pleural effusions and pulmonary edema are the most common causes of hypoxemia among patients receiving CAR T-cell therapy, a thorough infectious workup is crucial. A bronchoscopy and bronchoalveolar lavage may be useful in some

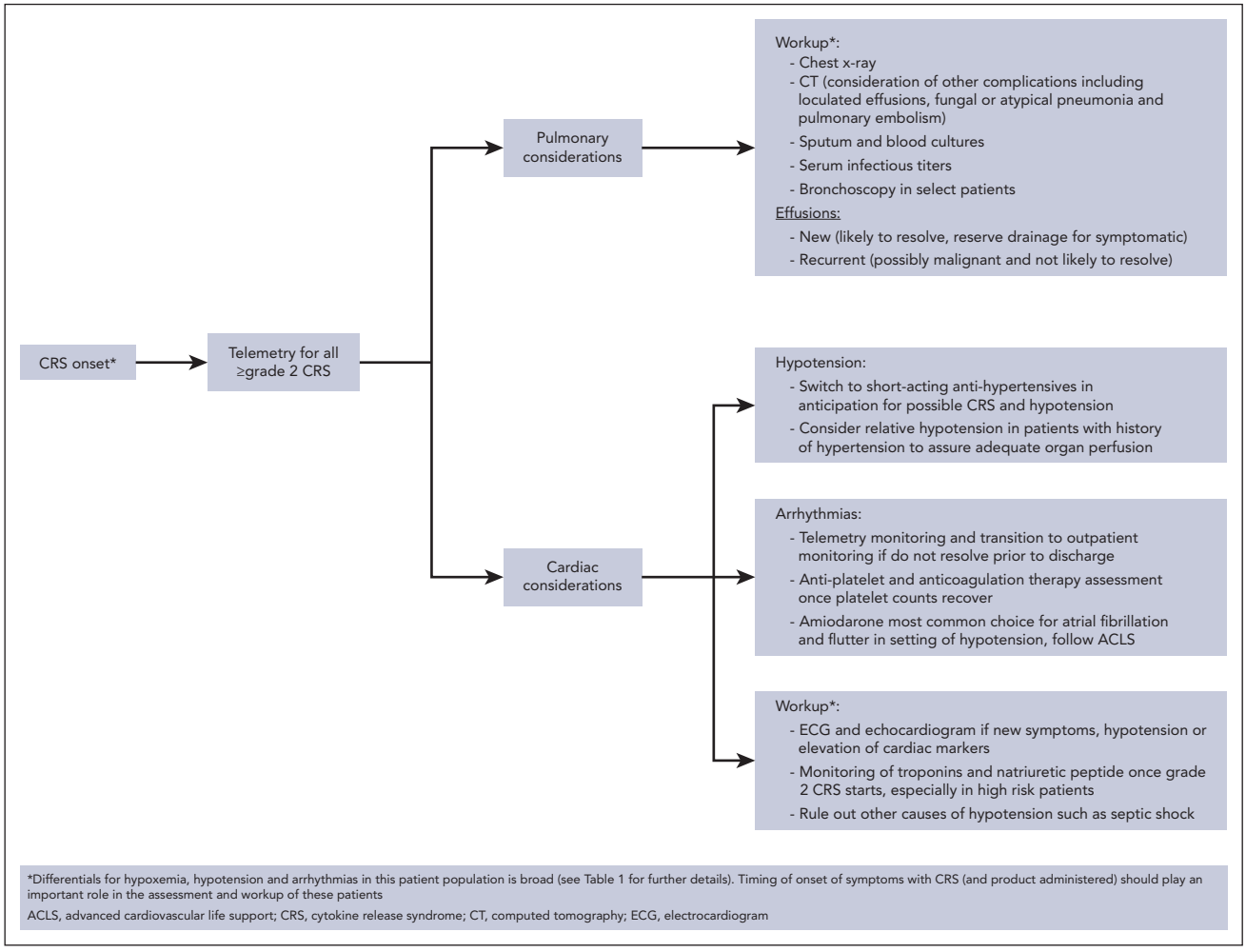

Figure 2. Assessment and considerations of patients with cardiac and pulmonary comorbidities and cardiovascular complications during CRS.

cases, such as in patients with infiltrates that are highly suggestive of infectious etiology or persistent after other signs of CRS have resolved. However, we do not routinely perform bronchoscopies, especially if there is a high suspicion of CRS-driven hypoxemia. Severe hypoxemia related to CRS is rare. Fortunately, with earlier intervention and improved management of CRS, the incidence of requirement of bilevel positive airway pressure or mechanical ventilation is low. However, requiring positive pressure ventilation is associated with higher rates of mortality.[5,6,10,29] Whether this is directly related to CRS or other complications, such as sepsis and multiorgan failure due to disease progression, needs to be evaluated further. We recommend close monitoring of patients with pulmonary comorbidities and hypoxemia who require support via high-flow nasal cannula or bilevel positive airway pressure because deterioration in the health condition of these patients could be rapid.

The pathophysiology of cardiac adverse events in patients after CAR T-cell therapy is multifactorial[12,13] and may include a direct effect of interleukin 6 leading to myocardial dysfunction[30] as well as stress-induced cardiomyopathy. In addition, for cardiac and pulmonary adverse events, there could be direct toxic effects because of CAR T-cell trafficking to sites of disease. In a study of pediatric patients with extramedullary B–cell acute lymphoblastic leukemia treated with CD19-directed CAR T cells, there were reports of patients with pleural based disease developing worsening and new pleural effusions, ground-glass opacities, and new hypoxia with evidence of CAR T-cell trafficking and CAR T cells visualized in pleural fluid.[22] Although we have been mostly focusing on commercial CAR T cells, as new targets become available, it will be important to consider whether there may be direct cardiac and pulmonary effects due to on-target toxicities, as was seen with cardiotoxicity in clinical trials of T cells targeting MAGE-A3.[31] The general treatment for these patients would be supportive care, or, in the future, if a safety switch is available, it may be activated, if toxicities are severe enough.

The patient received another dose of tocilizumab 8 mg/kg and, because of lack of improvement, received corticosteroids and was subsequently weaned off vasopressors. His FiO_2 requirements, pulmonary infiltrates, and pleural effusion improved as his CRS resolved. Two months after treatment, his echocardiogram was repeated, and it showed an improved EF back to a baseline of 40%. Although in this case, the patient's EF returned to baseline and the pleural effusion resolved, in the rare instance that EF remains low or pleural effusion does not resolve after treatment, patients should follow-up with a cardiologist and/or pulmonologist, and goal-directed medical therapy should be started, if they are not on it already.

Part 3: arrhythmias

A 56-year-old female with history of hypertension, CAD, chronic kidney disease, and immunoglobulin Gκ multiple myeloma was admitted for treatment with B-cell maturation antigen–directed CAR T cells (idecabtagene vicleucel). On day 3, she developed fever and tachycardia consistent with grade 1 CRS and was placed on telemetry. She was noted to have new-onset atrial fibrillation. She was hemodynamically stable but off her antihypertensive medications. The patient was treated with 8 mg/kg tocilizumab and corticosteroids but her atrial fibrillation persisted, so she was started on amiodarone and placed on telemetry.

We recommend placing all patients who develop CRS on telemetry for monitoring of arrhythmias, if feasible, especially if patients develop grade 2 CRS. Arrhythmias are common after CAR T-cell therapy and consist of approximately two-thirds of the cardiovascular complications after CAR T-cell therapy.[24] On the basis of data from the FDA adverse event reporting system of CD19 CAR T cells, 74% of reported arrhythmias were atrial fibrillation or flutter and 18% were ventricular tachycardias.[6] In the setting of uncontrolled atrial fibrillation with low blood pressure, we may use amiodarone because CRS-related hypotension may often preclude patients from beta-blockers or calcium channel blockers for rate control. For patients with a preserved blood pressure, beta-blockers are commonly used as first-line therapy. These patients usually cannot receive anticoagulants to prevent atrial fibrillation–related embolism, and, thus, the aggressive use of amiodarone may lead to conversion to sinus rhythm. However, if atrial fibrillation persists beyond 48 hours, we typically stop the amiodarone because the risk of embolism with chemical cardioversion increases. We rarely use digoxin in this case, and digoxin should be reserved for patients in whom amiodarone is contraindicated. Patients with hemodynamic instability should be admitted to the ICU, and cardioversion should be considered. Atrial fibrillation can be paroxysmal and resolve in <24 hours, and we do not use anticoagulation or cardiac medications frequently in that setting. These decisions should be made in consultation with a cardiologist before discharge. For those in whom the atrial fibrillation lasts longer, and stroke risk is high, we first start patients on unfractionated heparin drip when platelet counts are >50 × 10^3/μL and then discharge patients using direct-oral anticoagulants. Most patients who develop atrial fibrillation and atrial flutter during CRS will not likely need long-term anticoagulant. However, the long-term risk of atrial fibrillation recurrence is unknown, and patients will need monitoring. After discharge, we place an ambulatory cardiac monitor to evaluate for arrhythmias. If we do not detect atrial fibrillation at that time, we stop the antiarrhythmic monitoring. For those with persistent atrial fibrillation or flutter, we place an ambulatory cardiac monitor ~4 or 6 months after treatment, and, again, if no further arrhythmias, we stop the direct-oral anticoagulant and do not pursue further treatment.

When patients, who have CRS, are monitored on telemetry, it is not unusual to identify nonsustained ventricular tachycardia. We generally do not treat asymptomatic patients in this setting, unless they have other associated signs or symptoms and just treat the underlying CRS. We also monitor and replete electrolyte abnormalities, including hypokalemia (goal 4.0 mEq/L) and hypomagnesemia (goal 2.0 mg/dL), to reduce contributing factors to arrhythmias.

Over the next 24 hours, her atrial fibrillation, hypotension, and fever resolved and corticosteroids were discontinued. Before discharge, she was taken off of amiodarone. She was not started on an anticoagulant because of the transient nature of her atrial fibrillation.

Conclusions

Patients considered for CAR T-cell therapy often have preexisting cardiac and pulmonary comorbidities as well as risk factors related to prior treatments and exposures. If patients have good functional status and are well compensated, these conditions should not preclude them from being offered these potentially lifesaving therapies. The key factor is that most complications occur in the setting of CRS, so being aware of risk factors for CRS and trying to mitigate them as much as possible in terms of disease status before treatment, product selection, and earlier use of treatments, such as tocilizumab, could help reduce the risk of complications. In general, most cardiopulmonary adverse events occurring after CAR T-cell therapy are reversible, and supportive care and optimization of clinical status with the assistance of cardiac, pulmonary, and ICU colleagues, are important. In addition, larger, prospective studies are needed to further evaluate the effects of CAR T-cell therapies including more subtle, long-term effects, especially among the patients who are at highest risk for complications.

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ORCID profiles: C.G., 0000-0001-6381-6216; N.S.G., 0000-0002-1346-3157.

Correspondence: Natalie S. Grover, Lineberger Comprehensive Cancer Center, University of North Carolina–Chapel Hill, 170 Manning Dr, CB#7305, Chapel Hill, NC 27599; email: natalie_grover@med.unc.edu.

Footnote

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REFERENCES

1. Burstein DS, Maude S, Grupp S, Griffis H, Rossano J, Lin K. Cardiac profile of chimeric antigen receptor T cell therapy in children: a single-institution experience. *Biol Blood Marrow Transplant*. 2018;24(8):1590-1595.
2. Alvi RM, Frigault MJ, Fradley MG, et al. Cardiovascular events among adults treated with chimeric antigen receptor T-cells (CAR-T). *J Am Coll Cardiol*. 2019;74(25):3099-3108.
3. Ganatra S, Redd R, Hayek SS, et al. Chimeric antigen receptor T-cell therapy-associated cardiomyopathy in patients with refractory or relapsed non-Hodgkin lymphoma. *Circulation*. 2020;142(17):1687-1690.
4. Lefebvre B, Kang Y, Smith AM, Frey NV, Carver JR, Scherrer-Crosbie M. Cardiovascular effects of CAR T cell therapy. *JACC CardioOncol*. 2020;2(2):193-203.
5. Wudhikarn K, Pennisi M, Garcia-Recio M, et al. DLBCL patients treated with CD19 CAR T cells experience a high burden of organ toxicities but low nonrelapse mortality. *Blood Adv*. 2020;4(13):3024-3033.
6. Goldman A, Maor E, Bomze D, et al. Adverse cardiovascular and pulmonary events associated with chimeric antigen receptor T-cell therapy. *J Am Coll Cardiol*. 2021;78(18):1800-1813.
7. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544.
8. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380(1):45-56.
9. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. *J Clin Oncol*. 2020;38(27):3119-3128.
10. Gutierrez C, Brown ART, May HP, et al. Critically ill patients treated for chimeric antigen receptor-related toxicity: a multicenter study. *Crit Care Med*. 2022;50(1):81-92.
11. Bastos-Oreiro M, Gutierrez A, Reguera JL, et al. Best treatment option for patients with refractory aggressive B-cell lymphoma in the CAR-T cell era: real-world evidence from GELTAMO/GETH Spanish groups. *Front Immunol*. 2022;13:855730.
12. Ghosh AK, Chen DH, Guha A, Mackenzie S, Walker JM, Roddie C. CAR T cell therapy-related cardiovascular outcomes and management: systemic disease or direct cardiotoxicity? *JACC CardioOncol*. 2020;2(1):97-109.
13. Patel NP, Doukas PG, Gordon LI, Akhter N. Cardiovascular toxicities of CAR T-cell therapy. *Curr Oncol Rep*. 2021;23(7):78.
14. Ganatra S, Carver JR, Hayek SS, et al. Chimeric antigen receptor T-cell therapy for cancer and heart: JACC Council perspectives. *J Am Coll Cardiol*. 2019;74(25):3153-3163.
15. Totzeck M, Michel L, Lin Y, Herrmann J, Rassaf T. Cardiotoxicity from chimeric antigen receptor-T cell therapy for advanced malignancies. *Eur Heart J*. 2022;43(20):1928-1940.
16. Maloney DG, Kuruvilla J, Liu FF, et al. Matching-adjusted indirect treatment comparison of liso-cel versus axi-cel in relapsed or refractory large B cell lymphoma. *J Hematol Oncol*. 2021;14(1):140.
17. Oluwole OO, Chen JMH, Chan K, et al. Matching-adjusted indirect comparison of axi-cel and liso-cel in relapsed or refractory large B-cell lymphoma. *Leuk Lymphoma*. 2022;63(13):3052-3062.
18. Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. *Nat Med*. 2022;28(10):2145-2154.
19. Ghilardi G, Chong EA, Svoboda J, et al. Bendamustine is safe and effective for lymphodepletion before tisagenlecleucel in patients with refractory or relapsed large B-cell lymphomas. *Ann Oncol*. 2022;33(9):916-928.
20. Carney BJ, Wang TF, Ren S, et al. Anticoagulation in cancer-associated thromboembolism with thrombocytopenia: a prospective, multicenter cohort study. *Blood Adv*. 2021;5(24):5546-5553.
21. Samuelson Bannow BT, Lee A, Khorana AA, et al. Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2018;16(6):1246-1249.
22. Holland EM, Yates B, Ling A, et al. Characterization of extramedullary disease in B-ALL and response to CAR T-cell therapy. *Blood Adv*. 2022;6(7):2167-2182.
23. Mirza AS, Kumar A, Hashmi H, et al. Incidence and management of effusions before and after CD19-directed chimeric antigen receptor (CAR) T cell therapy in large B cell lymphoma. *Transplant Cell Ther*. 2021;27(3):242.e1-242.e6.
24. Steiner RE, Banchs J, Koutroumpakis E, et al. Cardiovascular events in patients treated with chimeric antigen receptor T-cell therapy for aggressive B-cell lymphoma. *Haematologica*. 2022;107(7):1555-1566.
25. Cordeiro A, Bezerra ED, Hirayama AV, et al. Late events after treatment with CD19-targeted chimeric antigen receptor modified T cells. *Biol Blood Marrow Transplant*. 2020;26(1):26-33.
26. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):439-448.
27. Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. *Crit Care Med*. 2017;45(2):e124-e131.
28. Shalabi H, Sachdev V, Kulshreshtha A, et al. Impact of cytokine release syndrome on cardiac function following CD19 CAR-T cell therapy in children and young adults with hematological malignancies. *J Immunother Cancer*. 2020;8(2):e001159.
29. Azoulay É, Castro P, Maamar A, et al. Outcomes in patients treated with chimeric antigen receptor T-cell therapy who were admitted to intensive care (CARTTAS): an international, multicentre, observational cohort study. *Lancet Haematol*. 2021;8(5):e355-e364.
30. Pathan N, Hemingway CA, Alizadeh AA, et al. Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. *Lancet (London, England)*. 2004;363(9404):203-209.
31. Linette GP, Stadtmauer EA, Maus MV, et al. Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma. *Blood*. 2013;122(6):863-871.