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Role of Cardio-Oncology Rehabilitation in Hematopoietic Stem Cell Transplantation and Chimeric Antigen Receptor T-Cell (CAR-T) Therapy

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) and chimeric antigen receptor T-cell (CAR-T) therapy often lead to severe sarcopenia and cachexia during treatment, making it difficult to maintain exercise tolerance. Consequently, "cancer rehabilitation" programs have been implemented to sustain and improve physical activity and motor function. Hematologic malignancies often involve the use of cardiotoxic drugs. Moreover, graft-vs.-host disease associated with allo-HSCT and the cytokine release syndrome in CAR-T therapy elevate the risk of cardiovascular complications. Thus, establishing "cardio-oncology rehabilitation" (CORE) is essential to support cancer patients and survivors. CORE is expected to enhance quality of life, improve cardiopulmonary function, reduce cancer and cardiac events recurrence, and prolong survival. Our institution conducts cardiopulmonary exercise testing before HSCT and CAR-T therapy, with exercise prescriptions based on heart rate at the anaerobic threshold and guidance on resistance exercises. This report discusses current trends in CORE for patients undergoing HSCT and CAR-T therapy, along with future challenges.

Key Words: Cardio-oncology rehabilitation (CORE); Chimeric antigen receptor T-cell (CAR-T); Hematopoietic stem cell transplantation

There have been rapid advancements in diagnosis and treatment of hematologic malignancies such as leukemia, lymphoma, and myeloma , driven by ongoing discoveries from the molecular and genetic aspects. Alongside standard chemotherapy, new treatment modalities, such as targeted therapy, hematopoietic stem cell transplantation (HSCT), and immunotherapy, continue to expand the options for patients. However, because hematologic malignancies require intensive therapy, there is an elevated risk of cancer treatment-related cardiovascular toxicity (CTR-CVD).[1] HSCT presents unique risks for CTR-CVD, including infection-induced septic cardiomyopathy, graft-vs.-host disease (GVHD)-associated cardiovascular complications, and cardiotoxicity from radiation therapy and immunosuppressive agents.[2] Chimeric antigen receptor T-cell (CAR-T) therapy, similarly, has been associated with cardiovascular events, with cytokine release syndrome (CRS) presenting a particular risk factor for cardiotoxicity.[3]

Prolonged hospitalization during hematologic cancer treatment often leads to reduced physical activity and muscle mass, which in turn contributes to frailty. Cancer rehabilitation is therefore recommended to prevent frailty progression during treatment.[4,5] Nevertheless, the intensity of rehabilitation programs varies among institutions because of the lack of clear standards. Recently, cardio-oncology rehabilitation (CORE) has been actively applied for patients with CTR-CVD, or at high cardiovascular risk, a group that frequently exhibits reduced exercise tolerance. CORE utilizes cardiopulmonary exercise testing (CPX) to provide standardized exercise prescriptions based on heart rate, ensuring appropriate rehabilitation intensity for individual cancer patients. Several studies have demonstrated that CORE can be safely implemented during treatment for hematologic malignancies, supporting improvements in exercise tolerance and reducing fatigue.[6,7] Here we discuss the cardiotoxicity associated with HSCT and CAR-T therapy, the current state of CORE, and future perspectives.

Cardiotoxicity in HSCT and CAR-T Therapy

HSCT and CAR-T are effective treatments for hematologic

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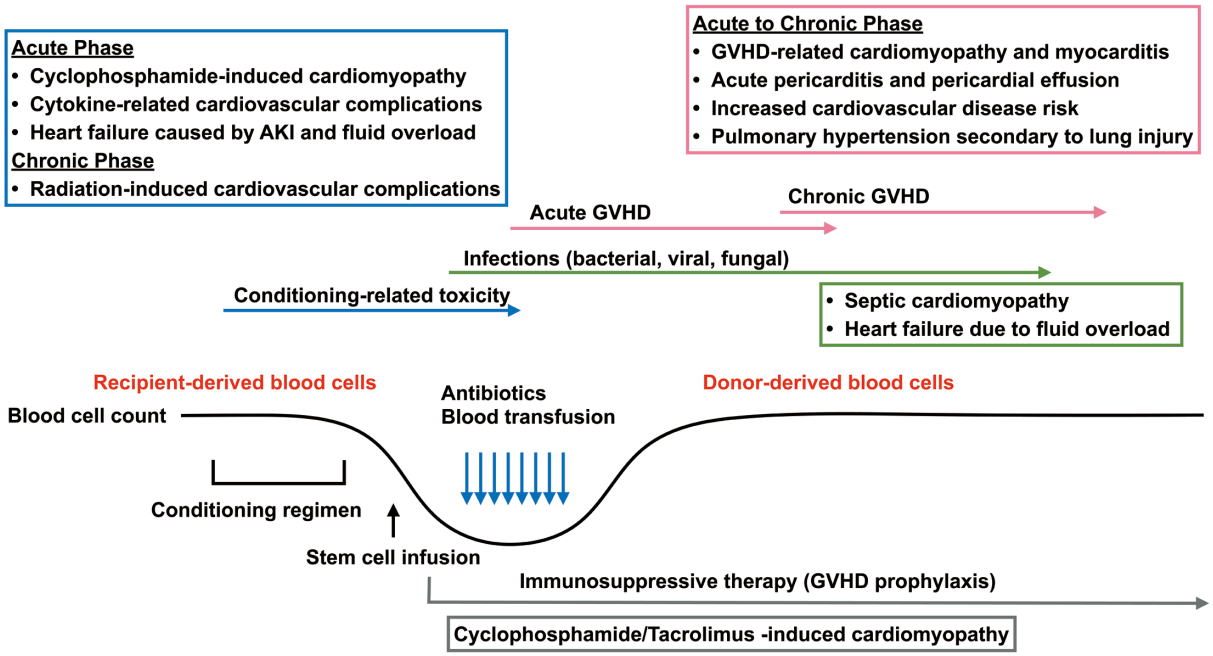

Figure 1. Cardiovascular adverse events associated with HSCT. During HSCT, in addition to direct cardiovascular adverse events caused by conditioning regimens, severe infections due to neutropenia pose a risk of septic cardiomyopathy. GVHD can lead to myocarditis, pericarditis, and pulmonary hypertension, and the immunosuppressive therapies used for GVHD prevention may also contribute to myocardial injury. GVHD, graft-vs.-host disease; HSCT, hematopoietic stem cell transplantation.

malignancies, but they carry significant cardiovascular risks. HSCT survivors face a higher incidence of cardiovascular diseases, such as heart failure and coronary artery disease.[8,9] Approximately 30% of HSCT patients develop heart failure, and 6% experience acute myocarditis.[10] In autologous HSCT, the anthracycline-based induction therapy and conditioning regimens with cyclophosphamide are major causes of CTR-CVD.[9] Additionally, septic cardiomyopathy during the neutropenic phase is a concern.[11] Allo-HSCT replaces malignant bone marrow cells with donor-derived cells, providing antitumor effects via the graft-vs.-tumor mechanism.[12] However, this therapeutic benefit comes with an increased risk of cardiotoxicity associated with GVHD.[13,14] The cardiotoxicity associated with GVHD may involve direct myocardial infiltration by donor T cells, cytokine release, and regulatory T-cell suppression, which are considered to be contributing factors.[15] GVHD patients often show increased cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia, together with an elevated incidence of ischemic heart disease, suggesting accelerated atherosclerosis.[16,17] GVHD prophylaxis with tacrolimus also contributes to cardiotoxicity.[18] In allo-HSCT, total body irradiation may be included in the conditioning regimen, further increasing the risk of long-term cardiovascular complications (**Figure 1**). Left ventricular ejection fraction (LVEF) decreased in 13% of patients within 3 months after allo-HSCT, with a worsened prognosis in those with myocardial dysfunction.[14,19] Consequently, regular cardiovascular evaluations post-transplant are critical for early detection and intervention.

CAR-T therapy involves re-infusing T cells genetically engineered to express chimeric antigen receptors that specifically recognize cancer antigens, enabling direct targeting of cancer cells.[20] Although CAR-T therapy demonstrates significant antitumor efficacy, meta-analyses have indicated that CAR-T recipients experienced an 8.7% incidence of left ventricular dysfunction and a 3.9% incidence of heart failure.[21] The mechanisms underlying CAR-T-associated cardiotoxicity remain unclear. However, cardiovascular events have been shown to correlate with CRS severity, suggesting myocardial injury mediated by cytokines.[3,22] CRS occurs when CAR-T cells activated by tumor cells release cytokines, including interleukin (IL)-6, triggering localized inflammatory responses.[23] Elevated IL-6 levels, also observed in autoimmune myocarditis and sepsis-induced myocarditis, may lead to myocardial inflammation through mechanisms involving microvascular dysfunction, mitochondrial impairment, and intracellular calcium dysregulation by pro-inflammatory cytokines.[24–26] Early administration of tocilizumab (an IL-6 inhibitor) and corticosteroids for CRS has been associated with reduced severity of myocardial injury, suggesting a potential link between IL-6 and CAR-T-related CTR-CVD.[27,28] In addition to CRS, preexisting cardiovascular disease and advanced age are significant risk factors for cardiovascular events associated with CAR-T therapy.[29] Furthermore, a range of CTR-CVD manifestations, including acute pericarditis with cardiac tamponade, takotsubo cardiomyopathy, and supraventricular arrhythmias, has been reported, underscoring the need for vigilance regarding diverse cardiovascular risks post-CAR-T therapy.[21,30,31]

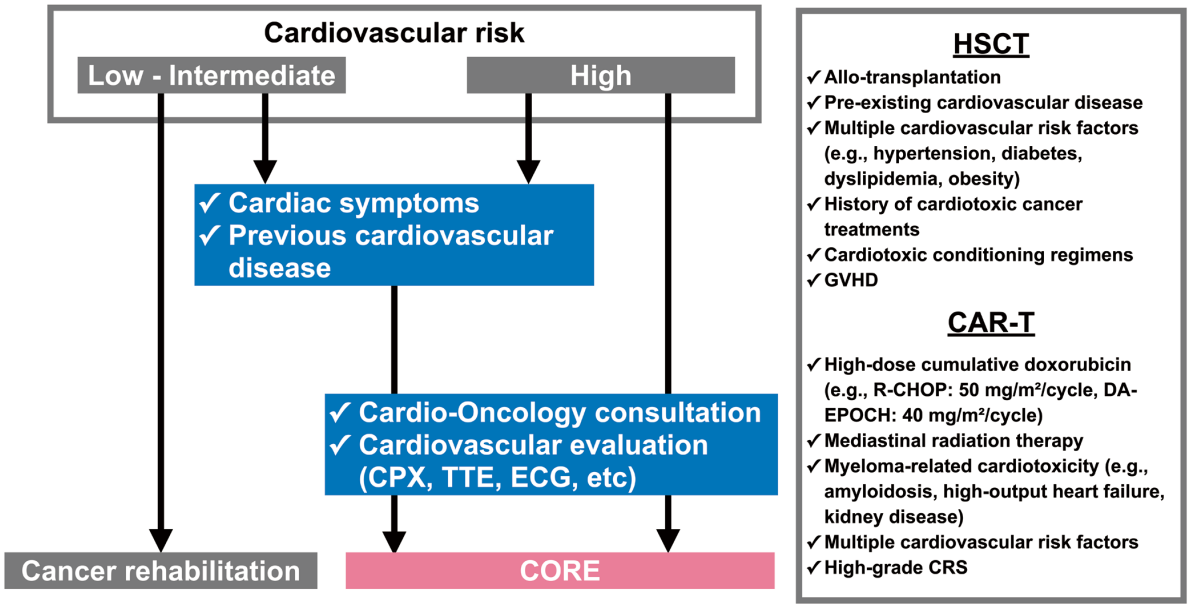

Figure 2. Indications for CORE during HSCT and CAR-T therapies. Patients with cardiovascular symptoms or a history of cardiovascular disease are advised to undergo a cardio-oncology consultation, including cardiovascular assessments with CPX, followed by the implementation of CORE. Additionally, all high-risk patients are recommended to undergo cardiovascular evaluations before HSCT or CAR-T therapy, regardless of symptoms. CAR-T, chimeric antigen receptor T-cell; CORE, Cardio-Oncology Rehabilitation; CPX, cardiopulmonary exercise testing; HSCT, hematopoietic stem cell transplantation.

Effects on Skeletal Muscle and Respiratory Function

In HSCT, high-dose chemotherapy, GVHD, and infections affect physical activity, resulting in reduced motor function, muscle strength, and exercise tolerance.[32,33] In CAR-T therapy, the development of CRS or immune effector cell-associated neurotoxicity syndrome (ICANS) often leads to prolonged bed rest, with reports indicating fatigue in 44–96% of cases.[34–36] Muscle mass maintenance depends on the balance between protein synthesis and protein degradation.[37] Reduced physical activity leads to an early decline in protein synthesis rates, and prolonged bed rest further increases protein degradation, resulting in muscle mass loss.[38] Increased levels of inflammatory cytokines such as tumor necrosis factor-α, IL-6, and IL-1 observed in GVHD and CRS inhibit the skeletal muscle generation process via NF-kappa B, contributing to muscle atrophy.[39]

Additionally, steroid use for managing GVHD and CRS activates the ubiquitin-proteasome pathway and autophagy, accelerating catabolism and leading to increased protein degradation and muscle atrophy in muscle cells.[40,41] Indeed, a correlation has been reported between the dosage of steroids administered during HSCT and decreased muscle strength.[42] Furthermore, treatment-related adverse events such as nausea and pain can induce depression and fatigue, creating a negative cycle of reduced quality of life (QOL), decreased physical activity, prolonged hospitalization, and severe sarcopenia or cachexia.[32,43] Similar to findings in the general population linking frailty with poor prognosis, in post-HSCT cases patients also show a relationship between 6-minute walk distance and treatment-related mortality or non-relapse mortality rates, underscoring the importance of frailty prevention in HSCT and CAR-T patients.[44,45]

HSCT patients also require careful monitoring for lung complications. Neutropenia and immunosuppressive therapies can lead to bacterial, viral, or fungal pneumonia, posing a risk of severe complications.[46] Non-infectious lung injuries caused by GVHD, radiation therapy, or conditioning regimens have also been reported, including cryptogenic organizing pneumonia due to small airway epithelial damage, diffuse alveolar hemorrhage from vascular endothelial injury, and interstitial pneumonia affecting the lung parenchyma.[47] Bronchiolitis obliterans syndrome, characterized by airway inflammation and fibrosis, is another critical pulmonary complication. Interstitial pneumonia has been reported as an immune-related adverse event in CAR-T therapy, indicating that CRS may contribute to respiratory dysfunction.[48] Both HSCT and CAR-T therapy can negatively affect the heart, muscles, and lungs (i.e., the key determinants of exercise tolerance), necessitating targeted interventions for each factor.

Implementing CORE in HSCT and CAR-T Therapy

Cancer rehabilitation during treatment has proven effective in maintaining and improving physical activity and motor function.[49,50] For patients undergoing HSCT, cancer rehabilitation is safe and is recommended to prevent disuse syndrome by preserving lower limb strength and cardiopulmonary function, reducing fatigue, and improving QOL.[4,5,51] Rehabilitation during lymphoma treatment has been reported to mitigate side effects such as peripheral neuropathy and balance disorders, and it is also recom-

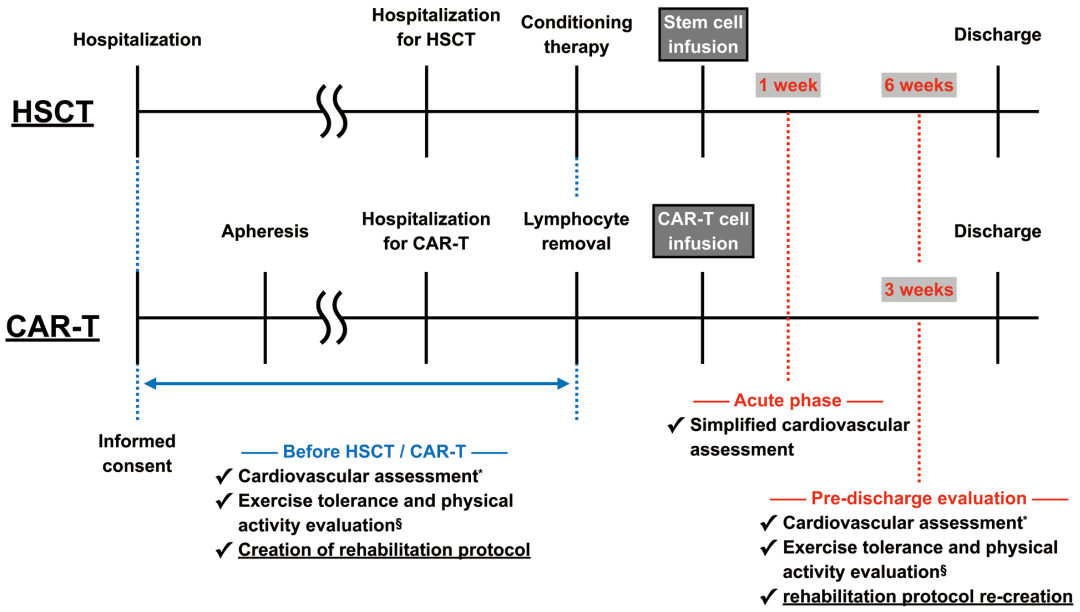

Figure 3. Cardiopulmonary function evaluation and exercise prescription during HSCT and CAR-T therapies. Before conditioning or lymphodepletion for HSCT or CAR-T therapy, cardiac function is evaluated, including ECG, transthoracic echocardiography, and blood tests (troponin, BNP/NTproBNP, cholesterol, HbA1c, etc.). CPX is conducted to assess exercise tolerance and develop a rehabilitation protocol. One week after infusion, ECG and cardiac biomarkers are reassessed, with additional evaluations conducted as needed. Before discharge, cardiac function and CPX are reassessed at 6 weeks post-transplant for HSCT or 3 weeks post-CAR-T therapy. CAR-T, chimeric antigen receptor T-cell; CPX, cardiopulmonary exercise testing; HSCT, hematopoietic stem cell transplantation.

Table 1. CPX Eligibility Criteria for Patients With Hematopoietic Malignancies

Laboratory data
Platelets <30,000/μL
30,000–50,000/μL: Discontinue testing if blood pressure exceeds 180 mmHg
Hemoglobin <7.5 g/dL: Perform based on clinical symptoms
Other clinical conditions
Activity restrictions due to uncontrolled disease progression
Symptomatic bone metastasis
Hemodynamic instability or hypoxia
Severe symptoms such as nausea, vomiting, or diarrhea
Uncontrolled pain
Active bleeding
Fever ≥38°C
Central nervous system impairment, altered consciousness, or increased intracranial pressure

CPX, cardiopulmonary exercise testing.

mended during CAR-T therapy to prevent frailty progression and reduce side effects.[52,53] Studies have also shown that exercise can extend the survival of cancer survivors, underscoring the importance of continuous exercise therapy from the treatment phase through post-treatment.[6,49,50] However, due to the lack of clarity regarding exercise intensity settings in cancer rehabilitation, attention has shifted to CORE, which applies principles of cardiac rehabilitation.

CORE is not only applicable to patients with CTRCD but also to high-risk patients with normal cardiac function (**Figure 2**). In HSCT, cardiovascular risk factors include allo-transplantation, preexisting cardiovascular disease, multiple cardiovascular risk factors, a history of cardiotoxic cancer treatments, cardiotoxic conditioning regimens, and GVHD, all of which define high cardiovascular risk.[1] In diffuse large B-cell lymphoma, a primary indication for CAR-T therapy, high-dose doxorubicin is commonly used as a standard treatment.[54] Multiple myeloma also frequently involves high-output heart failure and treatment-related cardiotoxicity.[55] As such, most patients undergoing HSCT or CAR-T therapy are candidates for CORE.

Across various cancer types, CORE has been shown to significantly improve peak oxygen uptake (peak $\dot{V}O_2$) compared with non-exercising groups.[6,56,57] In lymphoma patients, CORE during chemotherapy has been associated with improvements in both peak $\dot{V}O_2$ and QOL metrics.[7] Similarly, in leukemia patients, CORE during treatment has demonstrated positive effects on peak $\dot{V}O_2$ and muscle strength.[58] Although frailty often persists long-term after HSCT, proactive aerobic exercise has been reported to improve peak $\dot{V}O_2$ and maximum walking distance, reduce heart rate, and alleviate fatigue.[59,60] For patients who are >6 months post-transplant, home-based aerobic programs have also been shown to improve lactate threshold, reduce fatigue, and enhance QOL.[61] However, rehabilitation during transplantation is often limited by myelosuppression. Similarly, in CAR-T therapy, rehabilitation may be challenging during episodes of CRS with associated hypotension or ICANS with altered consciousness. As a result,

Table 2. Rehabilitation Criteria During HSCT and CAR-T Therapies	
Rehabilitation guidelines based on blood counts	
Platelets	
5,000–10,000	Range of motion exercises, indoor walking
10,000–20,000	Sitting or standing exercises, ward-based walking
20,000–50,000	Aerobic exercise at AT level (stationary bike), light resistance training (bodyweight or bands)
≥50,000	Resistance training
Hemoglobin	
≤7.5 g/dL	Exercise based on clinical symptoms
Rehabilitation discontinuation criteria	
Bone findings	Metastatic bone lesions in long bones with >50% cortical involvement, extending to medullary cavity, lesions ≥3 cm in femur
Visceral/organ compression	Compression of hollow organs, blood vessels, spinal cord
Fluid accumulation	Pleural, pericardial, peritoneal, or retroperitoneal effusion with pain, dyspnea, or movement restrictions
CNS impairment	Central nervous system impairment, altered consciousness, increased intracranial pressure
Electrolyte imbalance	Hypo-/hyperkalemia, hyponatremia, hypo-/hypercalcemia
Blood pressure	Orthostatic hypotension, hypertension ≥160/100 mmHg
Heart rate	Tachycardia ≥110 bpm, ventricular arrhythmias

AT, anaerobic threshold; CAR-T, chimeric antigen receptor T-cell; HSCT, hematopoietic stem cell transplantation.

there are limited reports on CORE implementation during HSCT or CAR-T therapy, highlighting the need for further investigation.

CORE Program for HSCT and CAR-T Therapy

For our patients undergoing HSCT or CAR-T therapy, we recommend they undergo CPX prior to conditioning or lymphodepletion therapy. Exercise prescriptions are based on heart rate at the anaerobic threshold (AT) level. In the week after infusion, acute cardiovascular evaluations, including ECG, troponin, and B-type natriuretic peptide (BNP)/NT-proBNP measurements, are performed, with additional echocardiographic assessments conducted as needed. Follow-up CPX is performed at 6 weeks post-stem cell infusion or 3 weeks post-CAR-T cell infusion to reassess exercise tolerance and adjust exercise prescriptions before discharge (**Figure 3**).

When conducting CPX, standard contraindications for exercise stress testing are followed, with additional consideration given to the status of the hematologic malignancy, bone metastases, and myelosuppression[62] (**Table 1**). Due to the risk of bleeding, testing is not performed if the patient's platelet count is <30,000/μL. However, low-intensity exercise has been reported to be safe even in thrombocytopenic conditions.[63] For platelet counts between 30,000 and 50,000/μL, exercise is conducted under medical supervision and is discontinued if blood pressure exceeds 180 mmHg. For patients with anemia, particularly those with hemoglobin levels ≤7.5 g/dL, CPX is performed based on clinical symptoms when feasible.

During HSCT, careful attention must be paid to rehabilitation-related adverse events. However, excessive rest can contribute to frailty progression. For our patients, rehabilitation is suspended on the days of hematopoietic stem cell or CAR-T cell infusion but is otherwise conducted in 20–40-min sessions 5 times per week. Rehabilitation initiation and discontinuation criteria during the acute phase follow general cancer rehabilitation guidelines.[64] While patients are hospitalized in aseptic wards, rehabilitation is possible during the neutropenic phase if there is no uncontrolled infection. Hemoglobin levels <7.5 g/dL are not a barrier to rehabilitation if anemia-related symptoms are absent. Even during thrombocytopenia, low-intensity rehabilitation is feasible, with exercise intensity adjusted based on platelet counts[63] (**Table 2**). For platelet counts ≥20,000/μL, aerobic exercise at the AT level and light resistance training are implemented. By incorporating CORE, we can establish precise exercise prescriptions at the AT level during periods of ambiguity in rehabilitation intensity settings for patients with hematologic malignancies. Accumulating data and ensuring the safety of CORE during the acute phases of HSCT and CAR-T therapy remain critical priorities.

Nutritional Management During HSCT and CAR-T Therapy

Nutritional management is also critical during HSCT and CAR-T therapies. The energy requirements of transplant patients increase due to hypercatabolism, reaching 1.3–1.5 times the estimated basal energy expenditure (30–50 kcal/kg/day).[65] Insufficient energy makes it difficult to maintain body weight and skeletal muscle mass, potentially prolonging hospital stay and increasing costs.[66] Exercise deficiencies, frailty progression, and systemic inflammation further reduce protein synthesis, necessitating high protein intake. Recommended protein intake for cancer patients is 1.0 g/kg/day, but 1.5 g/kg/day is advised for patients with anabolic resistance.[67] Although excessive protein intake should be avoided in patients with kidney impairment, a protein intake of 1.5–2.5 g/kg/day may be necessary in cases of severe malnutrition during HSCT.[65] Although some studies suggest that glutamic acid may reduce transplantation-related adverse events and that branched-chain amino acids could mitigate steroid-induced muscle atrophy, definitive conclusions remain elusive.[40,68] Further research is necessary to clarify the role of nutrition in CORE.

Conclusions

HSCT and CAR-T therapies present high risks for CTR-

CVD. Additionally, pretreatment for the underlying malignancies increases cardiovascular risk, making patients undergoing these therapies strong candidates for CORE. Continuous implementation of CORE from the acute to chronic phases may improve QOL and facilitate social reintegration for patients with hematologic malignancies. Further research is essential to deepen our understanding of CORE for HSCT and CAR-T patients.

Conflict of Interest

None.

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Internal Review Board

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