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Research paper

Cardiovascular perspectives on stem cell transplant and Car-T cell therapy: The old and the new for assessment and management

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Cellular therapy occupies an important role in cancer, and intersections with cardiovascular health are increasingly recognized. Initiated as bone marrow transplantation, and used in parallel to chemotherapy and radiation; this therapy has been used since the 1950s but is currently seeing a dramatic revolution with the development of adoptive T cell therapies (Fig. 1).

Bone marrow transplantation, also known as hematopoietic stem cell transplantation (HSCT), is an anticancer therapy method involving the intravenous infusion of hematopoietic stem cells to re-establish the bone marrow function of blood cellular component production. Dr. E. Donnall Thomas pioneered this therapy in the 1950s after he observed that infusion of a bone marrow extract could re-establish bone marrow function in patients whose bone marrow stopped functioning after chemo- and radiation therapy [1]. HSCT became a successful method of therapy for leukemias, lymphomas, myelodysplastic syndrome, and multiple myeloma. More than one million patients have been treated with HSCT between 1957 and 2012 [2]. The importance of transplantation was recognized with a Nobel Prize awarded to E. Donnall Thomas and Joseph E. Murray "for their discoveries concerning organ and cell transplantation in the treatment of human disease" [3].

From a practical application perspective based on the source of stem cells, HSCT is either autologous or allogeneic. An autologous transplant is performed by mobilizing and harvesting the patient's own hematopoietic stem cells, while in an allogeneic transplant, the source is other donors. Ideally, a donor should have a genetic makeup as closely matched as possible to the patient to prevent graft rejection. An autologous transplant does not face the risk of graft rejection or graft versus host disease, but it does not offer the graft versus tumor effect seen in allogeneic transplants.

HSCT has been shown to dramatically improve survival in patients without other treatment options. There are >22,000 HSCT procedures performed in the US every year. Survival is estimated to be >80 % at 15 years, with >240,000 survivors in 2020 and an estimated >500,000 survivors in 2030 [4,5]. However, HSCT survivors continue to have higher mortality ratio than the general population, even at 30 years or more after HSCT (standardized mortality ratio, 5.4; 95 % CI, 4.0–7.1) [5,6]. Cardiovascular mortality (estimated 6 %) and morbidity (>25 %) are significant in this patient population [7]. The risk of cardiomyopathy is dramatically increased not only by cardiotoxic therapy, such as anthracyclines, but also by well-established cardiovascular diseases and risk factors, including diabetes mellitus and hypertension [7].

To improve the health of these patients, a risk stratification system has been proposed. This system aggregates the intensity of chemotherapy (doxorubicin ≥250 mg/m^2), targeted medical therapy and

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRISPR-Cas9, clustered regularly interspaced short palindromic repeats-CRISPR associated protein Cas9; CT, computer tomography; HSCT, hematopoietic stem cell transplantation; ICANS, immune effector cell associated neurotoxicity syndrome; LV, left ventricle; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MRI, magnetic resonance imagiing; TIL, tumor-infiltrating lymphocytes.

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radiotherapy (≥30 Gy) preceding the HSCT, the presence of cardiovascular disease or just traditional cardiovascular risk factors or age (≥60 years), as well as abnormal cardiac blood biomarkers at baseline [8]. A cardio-oncological evaluation is recommended in high-risk patients, and there are special considerations for the use of cardiovascular imaging technology to assess cardiac structure and function (3D echocardiography and LV global longitudinal strain; cardiac MRI), as well as screening for cardiac ischemia (coronary artery calcium scoring; coronary CT angiogram; echocardiographic, nuclear or cardiac MRI stress test) [9–13]. The management of modifiable cardiovascular risk factors and diseases is essential, including an emphasis on exercise and healthy dietary habits [8,14].

1. Adoptive cell transfer

In parallel to the clinical application of HSCT, the concept of using T cells as anticancer therapy – adoptive cell transfer – has evolved in the last few decades. An initial method involved the administration of tumor-infiltrating lymphocytes (TIL). These were harvested from excised tumors, cultured, selected based on tumor recognition, and expanded for re-infusion to patients [15]. More recently, the development of T cells genetically engineered to carry a chimeric antigen receptor (CAR) that couples an extracellular antigen recognition element with an intracellular activation element (first-generation CAR T) has revolutionized the field of autologous adoptive cell therapy. This development represents the first example of personalized, genetically engineered therapy. T cells removed from the patient's peripheral blood are genetically engineered in a laboratory to expressed CAR, then expanded and infused back to the patient as a "living drug" [16]. Results in initial trials have been dramatic, resulting in approval of several CAR T cell platforms since 2017 (Table 1): tisagenlecleucel (tisa-cel), axicabtagene ciloleucel (axi-cel), brexucabtagene autoleucel (brexu-cel), lisocabtagene maraleucel (liso-cel), idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cita-cel). Most CAR T cell therapies approved so far have been directed against CD19, a surface antigen on B cells (malignant and normal), except idecabtagene vicleucel and ciltacabtagene autoleucel, targeted against the B-cell maturation antigen (BCMA) present on plasma cells.

Cytokine release syndrome (CRS) has been defined in the 2019 American Society for Transplantation and Cellular Therapy (ASTCT) Consensus as a "supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused immune effector cells." This syndrome can present early after CAR T cell infusion, with a median of 6 days onset, with fever, hypotension, hypoxia, and end-organ dysfunction. The cytokine release can also lead to neurotoxicity, the immune effector cell associated neurotoxicity syndrome (ICANS) [17]. Modulation of the cytokine storm has been recognized as an important early step in the management of CRS, and the US FDA has approved tocilizumab (an anti-IL6 receptor monoclonal antibody) for this use [18]. A retrospective analysis of case series has provided insight into significant cardiovascular morbidity: 1) >50 % of CAR T cell therapy patients develop CRS, 2) >50 % of patients with CRS grade 2 or higher have increased troponin levels and decreased LVEF, 3) baseline creatinine and CRS grade 3 or 4 are independently associated with MACE, 4) the risk for cardiovascular events increases 1.7 fold every 12 h in delayed administration of tocilizumab, and 5) 50 % of patients with cardiomyopathy onset during CRS have persistent cardiac

Table 1
Food and Drug Administration approved CAR T therapies.

CAR T cell	Brand name	Approval date	Target	Indication (targeted disease)
Tisagenlecleucel (tisa-cel)	Kymriah	08/30/2017	CD19	B-cell acute lymphoblastic leukemia, Diffuse Large B-cell lymphoma
Axicabtagene ciloleucel (axi-cel)	Yescarta	10/18/2017	CD19	Diffuse Large B-cell lymphoma Follicular lymphoma
Brexucabtagene autoleucel (brexu-cel)	Tecartus	07/24/2020	CD19	Mantle Cell Lymphoma
Lisocabtagene maraleucel (liso-cel)	Breyanzi	02/05/2021	CD19	Diffuse Large B-cell lymphoma
Idecabtagene vicleucel (ide-cel)	Abecma	03/26/2021	BCMA	Multiple myeloma
Ciltacabtagene autoleucel (cita-cel)	CARVYKTI	3/30/2022	BCMA	Multiple myeloma

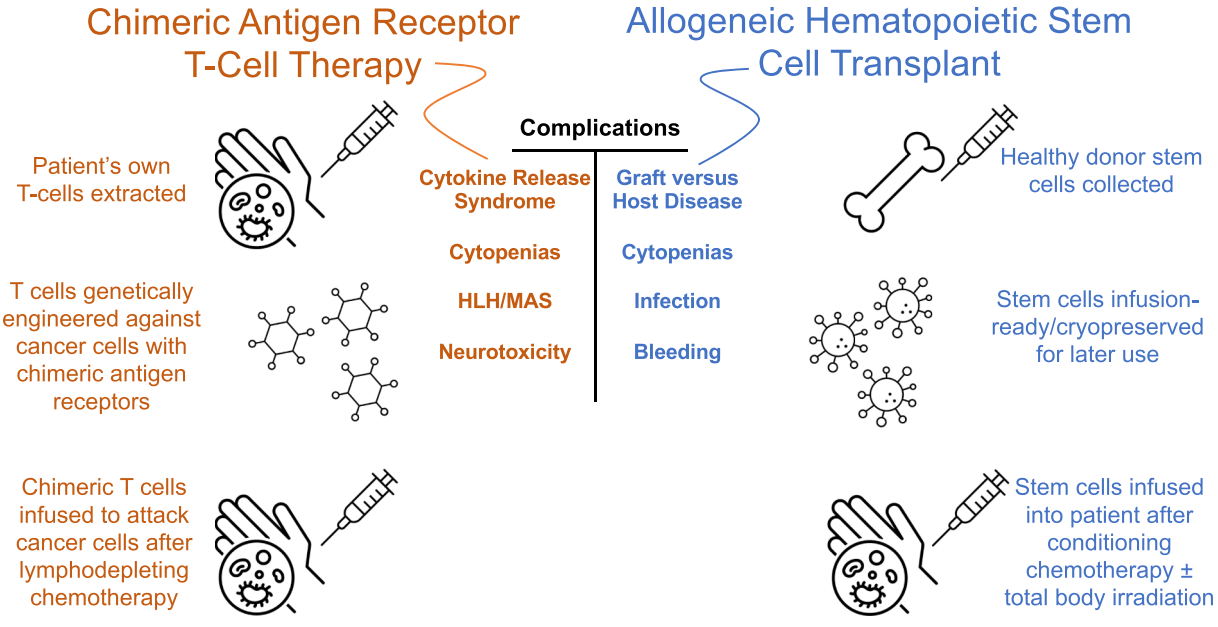

Fig. 1. Adoptive T cell therapies as cellular anticancer therapy. The process and complications of chimeric antigen receptor T cell therapy and hematopoietic stem cell transplant.

dysfunction [19–22]. These observations are motivating a careful preventative cardio-oncological evaluation and close cardiovascular monitoring during and after CAR T cell therapy.

The favorable effect of CAR T cell strategies has already been demonstrated at different stages in autoimmune diseases, post-transplant rejection, and treatment of myocardial interstitial fibrosis [23,24]. Sophisticated genetic engineering of next-generation CAR T cells includes using precision gene editing tools such as CRISPR-CAS9 (clustered regularly interspaced short palindromic repeats-CRISPR-associated protein Cas9) for modulation of T cell expansion, survival, immune recognition (PD-1 immune checkpoint KO) [25], and "off switch" for limited therapy in case of adverse events [26]. Several additional strategies targeting different cytokine signaling processes are under investigation.

Cardiovascular challenges have been recognized, and therefore cardio-oncological risk assessment, stratified monitoring, during treatment and surveillance, after HSCT and adoptive cell transfer, and proactive management represents an essential complement for patient outcomes. Acute cardiovascular complications severity depends on the type of therapy, with a higher degree in patients receiving allogeneic HSCT and CAR T [19,21,22,27]. Potentially life-threatening complications include myocardial dysfunction, cardiac arrhythmias, pericardial complications, resulting in myocardial injury, hemodynamic compromise or cardiac arrest. For patients surviving the first 100 days after HSCT the risk of cardiometabolic complications remains chronically higher than in the general population [28]. Therefore, screening for and management of baseline risk factors, such as hypertension, decreased cardiac function, uncontrolled diabetes, are crucial steps in preparation for cell transfer therapies. Recognition of cardiac dysfunction at any step in the course of cellular therapy requires close cardiovascular management based on current guidelines. International collaborations are needed to address the emerging complex interactions especially with the evolving chimeric antigen receptor therapies and aggregate knowledge from trials and multidisciplinary clinical care (cardio-oncology-transplant medicine).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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