Cancer treatment-related cardiotoxicity: A focus on sacubitril/valsartan

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Abstract

Cardiotoxicity is the most dramatic complications of cancer therapies, leading to halt in potentially life-saving anti-tumor treatment regimens and a poor survival prognosis in a non-negligible percentage of patients. Angiotensin converting enzyme inhibitors (ACEIs) and β-blockers are effective in the treatment of the cancer therapy–related cardiac dysfunction (CTRCD), while their roles in the prevention of cardiotoxicity are unclear. Sacubitril/valsartan was advantageous over ACEI in heart failure patients for further reduction of cardiovascular death or heart failure re-hospitalization. However, there is short of well-established testimony of its efficacy and safety in the prevention and treatment of CTRCD in the cardio-oncology setting. Although some small observational studies found a good performance of sacubitril/valsartan in patients with CTRCD, large-scale prospective clinical studies are required to confirm its excellent results. In this paper, we review the potential benefit of sacubitril/valsartan in human subjects with CTRCD.

Cancer treatment-related cardiotoxicity: A focus on sacubitril/valsartan

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Abstract

Cardiotoxicity is the most dramatic complications of cancer therapies, leading to halt in potentially life-saving anti-tumor treatment regimens and a poor survival prognosis in a non-negligible percentage of patients. Angiotensin converting enzyme inhibitors (ACEIs) and β-blockers are effective in the treatment of the cancer therapy–related cardiac dysfunction (CTRCD), while their roles in the prevention of cardiotoxicity are unclear. Sacubitril/valsartan was advantageous over ACEI in heart failure patients for further reduction of cardiovascular death or heart failure re-hospitalization. However, there is short of well-established testimony of its efficacy and safety in the prevention and treatment of CTRCD in the cardio-oncology setting. Although some small observational studies found a good performance of sacubitril/valsartan in patients with CTRCD, large-scale prospective clinical studies are required to confirm its excellent results. In this paper, we review the potential benefit of sacubitril/valsartan in human subjects with CTRCD.

Keywords: Cardio-oncology; Cancer therapy–related cardiac dysfunction; Cardiotoxicity; Angiotensin receptor-neprilysin inhibitor; Sacubitril/valsartan

Background and epidemiology

Malignant tumors and cardiovascular diseases (CVDs) represent the two main causes of death in the world (1). Both conditions mutually influence each other in pathophysiology (2). Meanwhile, CVDs and tumors hold numerous shared risk factors such as aging, smoking, infections, diet, alcohol, obesity and physical inactivity (1). Therapeutic Advances in cancer has led to an increased prevalence of cancer therapy–related cardiac dysfunction (CTRCD) commonly defined as an absolute reduction in left ventricular ejection fraction (LVEF) of [?]10% or reduction in LVEF to <50% (3).

The SEER database found that cardiovascular event is a major cause of death among cancer survivors (4). Cardiovascular complications of cancer treatment, especially cardiomyopathy and heart failure, lead to the discontinuity of therapeutic regimens and affect the survival prognosis of patients (5). Considering that state of the art in oncology therapeutics and aged tendency of population, establishing a unified framework for the management of CTRCD is required to reduce the risk of cardiac death among cancer survivors (3).

Cardio-oncology aims to address the spectrum of prevention, early diagnosis, monitoring, and timely treatment of CTRCD among cancer survivors (3, 6). However, CTRCD is a heterogeneous condition, with all kinds of clinical presentation from pre-clinic systolic dysfunction to cardiac shock (7). Heart failure secondary to CTRCD is associated with significantly worse outcomes (8).

Cardiotoxicity was further heightened after trastuzumab administered with anthracyclines simultaneously or sequentially. Among 12,500 patients with breast cancer, cumulative rates of CTRCD at the first and five year were 1.2% and 4.3% in patients using anthracycline alone, compared to 6.2% and 20.1% in patients receiving a combination regimens of anthracyclines and trastuzumab (9). A retrospective study from Thailand also found a higher risk profile in CTRCD among breast cancer patients treated with a combination of anthracycline and trastuzumab (10). Cardiac dysfunction induced by anthracyclines was usually irreversible, with significant myocardial ultrastructural abnormalities where oxidative stress damage was considered to be the key mechanism for inducing cardiotoxicity (3). In sufferers progressing anthracycline-induced cardiomyopathy, the recovery of cardiac function was promoted and implemented when CTRCD was diagnosed early and treated timely and promptly (11). One study of anthracycline-induced heart failure showed a 64% response rate when administered within one to two months of discovery of myocardial toxicity, compared to zero response rate when treatment was reinitiated six months later (11).

Monoclonal antibodies including trastuzumab and pertuzumab formed the backbone of therapeutic means in HER2-positive breast cancer. The incidence of severe CTRCD [New York Heart Association (NYHA) class III or IV] was 0-3.9% in the trastuzumab group versus 0-1.3% in the control group in a meta-analysis with five randomized adjuvant trials (12). A retrospective cohort study included 386 breast cancer patients from Taiwan found that trastuzumab therapy increased the risk of major adverse cardiovascular events, especially in heart failure (13). Trastuzumab therapy–induced cardiomyopathy differed from anthracyclines-related cardiotoxicity where it appeared to be reversible in some degree, independent of the cumulative dose, and the second exposure was usually tolerated (12). A meta-analysis of eight randomized controlled trials where the gain of pertuzumab to standard care in HER2-positive cancer patients was to determine the risk of cardiac adverse events (14). Pertuzumab increased the risk profile in symptomatic heart failure, but not silent cardiac insufficiency (14). Besides, immuno-checkpoint inhibitors (ICIs)-induced myocarditis/pericarditis is severe and usually associated with high mortality although rare incidence (15).

Prevention and treatment of CTRCD

Patients who developed CTRCD should have these therapies discontinued while multidisciplinary consultation should be launched to ascertain the cause of heart failure and assess that whether or when cancer treatment needs to be initiated again (7). The comprehensive decision-making to resume, modify, or permanently discontinue therapy should be done in a patient-centered approach (7). Essentials influencing the policymaking included the disease severity of CTRCD and the response to neuroendocrine inhibitor, the offending agent's underlining pathophysiology to myocardial damage, the comorbidity and tumor prognosis (7).

Anthracycline and trastuzumab-induced cardiotoxicity could lead to the interruption or cessation of life-saving cancer therapies. Available data in patients with CTRCD suggest β-blockers and angiotensin converting enzyme inhibitors (ACEIs) were medicative in improving cardiac function (8, 11, 16). In a heterogeneous cohort of 2,625 patients receiving anthracyclines for breast cancer or lymphoma, CTRCD occurred in 9% of patients and was related to anthracycline accumulated dose, of whom 81% had mild cardiac dysfunction (16). Early detection and prompt therapy with β-blockers and ACEI/angiotensin receptor blockers (ARB) critically contributes to recovery of cardiac function (16).

Whether the prophylactic use of β-blockers, spironolactone or ACEI/ARB is protective against CTRCD in patients without established cardiac disease has been investigated in some small clinical trials, with contradictory results (17-24). Of the 473 cancer patients, 114 patients who showed an elevated troponin I greater than 0.07 ng/ml after high-dose chemotherapy were randomly assigned to ACEI or placebo (19). The incidence of CTRCD was obviously higher in control subjects compared to the enalapril group (43% versus 0%) (19). Evident declines of LVEF and increased LV volumes were discovered only in the standard of care arm. Early management with ACEI might prevent the progression of late cardiotoxicity (19). In 468 patients with HER2-positive breast cancer treated with trastuzumab, both lisinopril and carvedilol prevented cardiotoxicity in patients receiving anthracyclines (20). Spironolactone used in female patients diagnosed with breast cancer protected against anthracycline-induced cardiotoxicity (17). A meta-analysis of five randomized trials evaluated the prophylactic effect of β-blockers or ACEIs/ARBs on reducing the incidence of CTRCD in breast cancer patients receiving a trastuzumab regimen (21). Prophylactic treatment with β-blockers or ACEIs/ARBs did not reduce the risk of CTRCD but did reduce the risk of HER2 therapy interruptions and reduced LVEF (21).

Other researches have presented comparable results, but the scale of change in LVEF between groups was usual minor (<5%) and short of clinical implication (18). Furthermore, not all researches have replicated such results (22, 23). A prospective, randomized, double-blind, placebo-controlled study found that carvedilol had no impact on the incidence of early onset of LVEF reduction (22). However, the use of carvedilol resulted in a significant reduction in troponin levels and diastolic dysfunction (22). Although perindopril and bisoprolol protected against trastuzumab-mediated declines in LVEF in patients with HER2-positive early breast cancer, left ventricular remodeling was not prevented by these pharmacotherapies (24). No studies have evaluated whether prophylactic use of neuroendocrine inhibitors in subjects at risk for CTRCD

improved clinical outcomes, such as mortality or hospitalization for heart failure (7).

Sacubitril/valsartan

The introduction of angiotensin receptor-neprilysin inhibitor (ARNI) had a revolutionary therapeutic effect in patients with heart failure and reduced ejection fraction (HFrEF). Sacubitril/valsartan has a distinct dual neuroendocrine regulation mechanism. Sacubitril enhanced natriuretic peptides' levels through inhibiting neprilysin by its metabolite LBQ657, while valsartan inhibits the renin-angiotensin-aldosterone system (RAAS) through blocking angiotensin II type 1 (AT1) receptors (25). Sacubitril/valsartan was advantageous over ACEI in heart failure patients for further reduction of cardiovascular death or heart failure hospitalization (26). In the PIONEER-HF trial, among stabilized patients with HFrEF who were hospitalized for acute decompensated heart failure, the initiation of sacubitril/valsartan therapy was well tolerated and led to a greater decline in the level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) compared to ACEI did (27). Switching treatment from ACEI to sacubitril/valsartan at 8 weeks resulted in a 37% reduction in NT-proBNP concentration during an open-label extension phase of the PIONEER-HF trial (28). Patients who began taking sacubitril/valsartan in hospital had a lower risk profile for heart failure re-hospitalization and cardiovascular death than patients with a delayed initiation of sacubitril/valsartan (8 weeks later) (28).

LV remodelling was crucial in progression to HFrEF (29). The extent of improvement in LV volumes, dimensions, and LVEF after therapy strongly correlated with clinical outcomes, including survival (30). LV remodelling was realized after administration of with sacubitril/valsartan in clinical scenarios (31). A smaller LV capacity was relevant to preferable LV reverse remodelling (31). Therefore, sacubitril/valsartan is the optimal recommendation for the the management of chronic HFrEF patients (7).

Sacubitril/valsartan in CTRCD

To my knowledge, data about the efficacy of sacubitril/valsartan on CTRCD are scarce. Although cancer patients were not excluded "a priori" from enrollment in the pivotal PARADIGM-HF trial, which could be enrolled after 12 or more months from cardiac toxicity, but investigators ultimately decided not to enroll (26). Most observational researches showed that sacubitril/valsartan improved the cardiac structure and function as well as NT-proBNP levels in patients with CTRCD (32).

4.1 Animal experimental models

Researches as the performance of sacubitril/valsartan against doxorubicin-induced cardiotoxicity are rare in animal experimental models. Deteriorative heart function, inordinate mitochondrial structure and respiratory function were found after managed with doxorubicin, which could be markedly alleviated by sacubitril/valsartan treatment in mice (33). The protective action of sacubitril/valsartan on doxorubicin-related heart dysfunction was related to the improvement of fission protein dynamin-related protein 1 (Drp1)-mediated mitochondrial dysfunction in some degree (33). Sacubitril/valsartan could attenuate doxorubicin-related heart failure and arrhythmia in a prophylactic treatment mice model by inhibiting oxidant stress damage, inflammatory response and apoptosis (34). Sacubitril/valsartan provided greater protection against doxorubicin-induced cardiac systolic dysfunction and LV remodeling by downregulating matrix metalloproteinase (MMP) activity in rats (35). Furthermore, endoplasmic reticulum stress (ERS) was one of the key pathogenesis of doxorubicin-related heart failure. Sacubitril/valsartan markedly improved doxorubicin-related cardiac dysfunction by downregulating the protein expression associated with ERS and apoptosis in a rat model (36).

4.2 The electrifying performance of sacubitril/valsartan on CTRCD

A retrospective case study described two anthracycline-related cardiomyopathy survivors with HFrEF who were treated with sacubitril/valsartan with success after poor responses to conventional evidence-based drug treatment (37). Both subjects exhibited fair recovery of NYHA functional class and normalization of NT-proBNP concentration as well as no re-hospitalization for heart failure (37) (**Table 1**). Canale *et al.* reported a case series of four patients with CTRCD and severe HFrEF (38). All patients were managed with

sacubitril/valsartan with success while being combatting malignant ventricular arrhythmias by wearing an automatic defibrillator until heart function recovery (38) (**Table 1**).

In a pilot study, twenty-one patients with HFrEF and a history of histologically confirmed cancer received sacubitril/valsartan (39). Sacubitril/valsartan was well tolerated and effective over a median duration of 12 months. Even patients with long-term cardiotoxicity-related HFrEF could be titrated with ANRI to the target dose, giving rise to significant improvement in NYHA cardiac function grading and LVEF as assessed by echocardiography, as well as in their NT-proBNP levels (39) (**Table 1**). A multicenter registry study in six Spanish hospitals with cardio-oncology clinics followed up sixty-seven cancer survivors managed with sacubitril/valsartan (40). After a median duration of 4.6 [1; 11] months, sacubitril/valsartan was well-tolerated and improved cardiac functional and structural characteristics assessed by echocardiography, NT-proBNP concentration, and NYHA functional class in patients with HFrEF regardless of the achieved agent dose (40) (**Table 1**).

Renato *et al.* (41) reported two clinical cases of cardiotoxicity-related HFrEF where therapeutic action of sacubitril/valsartan against anthracycline cardiomyopathy was proven by the improvement of symptoms and echocardiographic parameters (**Table 1**). Ana *et al.* (42) evaluated the therapeutic effect of sacubitril/valsartan on LVEF and LV remodelling assessed by comprehensive multiparametric cardiac magnetic resonance (CMR) in ten consecutive patients with cardiotoxicity-related HFrEF. LV volumes decreased markedly and LVEF improved significantly after administration of sacubitril/valsartan. A corresponding marked decrease in NT-proBNP concentration and improvement in NYHA functional class were also observed (42). LV dysfunction within CTRCD is partly restorable, but this strongly dependeds on timely treatment with sacubitril/valsartan (42) (**Table 1**). Twenty-eight patients with breast cancer and refractory cardiotoxicity-related HFrEF were initiated with sacubitril/valsartan after poor responses to conventional evidence-based drug treatment (43). Twenty months after captopril or valsartan was replaced with ARNI, there was a significant improvement in NYHA cardiac function grade, six-minute walking distance, LVEF, LV diastolic function, LV end-diastolic diameter and mitral regurgitation assessed by echocardiography, as well as NT-proBNP levels, without drug reactions (43) (**Table 1**). Although this research has some defects, such as a limited sample and an inadequate description of past cancer history, it provides new evidence for improving the clinical management of patients with CTRCD.

4.3 Immunotherapy related cardiotoxicity

Screening, prediction and risk stratification of trastuzumab-induced cardiotoxicity should incorporate cardiac imaging assessment, biochemical markers and prior anthracycline use (44). Initiation of effective prophylactic therapy, such as β-blockers and ACEIs/ARBs, appeared to mitigate risk of trastuzumab-induced cardiotoxicity in patients receiving HER2-directed therapy (44). The SAFE-HEaRt trail enrolled evaluable thirty breast cancer subjects with lessened LVEF within 40-49% took over ACEIs and β-blockers treatment, of whom 29 patients finished the designed HER2-targeed treatment (45). ACEIs and β-blockers showed beneficial performance on preventing cardiotoxicity in evaluable 6, 542 women newly diagnosed with breast cancer undergoing trastuzumab/anthracycline treatment (46). However, sometimes the performance of β-blockers and ACEIs were not satisfactory. A patient with HER2-positive breast cancer experienced worsening cardiotoxicity-related HFrEF after suboptimal responses to traditional guideline-recommended medications for heart failure (47). The patient's heart function greatly improved after the initiation of sacubitril/valsartan for four weeks, contributing to subsequent trastuzumab targeted therapy (47) (**Table 1**).

Sacubitril/valsartanl regimen started as first-line treatment in a patient with relapsing leukaemia and HFrEF caused by previously rituximab therapy (48). Primitive sacubitril/valsartanl regimen was well tolerable and created a durable improvement of symptoms, LVEF and NT-proBNP concentration, contributing to undelayed cancer treatment (48) (**Table 1**). With the development of cancer immunotherapy, ICIs-induced cardiotoxicity has gained increasing attention. A patient with urothelial carcinoma experienced ICIs-induced myocarditis after suboptimal responses to hormone therapy. The patient's cardiotoxicity-related HFrEF greatly improved after the initiation of sacubitril/valsartan for eight weeks combined with Tozizumab and gamma globulin therapy (49) (**Table 1**).

Summary and future perspectives

Chemotherapy-induced cardiotoxicity represents a potentially life threatening complication of anti-tumor treatment in cardio-oncology setting. Project proposals have been made to prevent and cure this complication, particularly through management with neuroendocrine inhibitors. Sacubitril/valsartan currently stood currently for an innovator in the clinical setting of therapy for HFrEF. Current evidences suggest that despite derived from small observational studies, sacubitril/valsartan appears to the intriguing role in treatment of cardiotoxicity-related HFrEF. Sacubitril/valsartan improved the clinical symptomatic status, exercise tolerance, LV functional and structural parameters and cardiac biochemical marker in patients with CTRCD (49).

Although the demonstration of a beneficial effect of sacubitril/valsartan on CTRCD is promising, the conclusions of these small observational studies remain only speculative in cancer survivors. Therefore, the performance of sacubitril/valsartan in patients with CTRCD requires further investigation. Further larger cohort studies and randomized clinical trials are needed to determine the performance of ARNI for the prevention and treatment of CTRCD. A randomized, double blind, multi-center, clinical trial has been designed to assess whether sacubitril/valsartan could prevent cardiotoxicity in early breast cancer patients receiving adjuvant or neo-adjuvant treatment regimens containing anthracyclines (50) (**Table 1**).

The landscape of CTRCD is still comparably new and with rapid developments in the cardio-oncology setting. Prevention and treatment of CTRCD is required to admit of a comprehensive all-round tumor treatment. A focus on available sacubitril/valsartan regimen should be implemented to get this goal.

Declarations

Ethical Approval

Not applicable.

Competing interests

Not applicable.

Authors' contributions

Feng Hu and Huajiong Yu: Conceptualization, Writing-Original draft preparation. Weiping Du and Mengjia Chen: Research investigation, Data collection. Jia Su and Xiaomin Chen: Supervision, Writing-Reviewing and Editing. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

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Table 1 Studies which evaluated sacubitril/valsartan in the context of CTRCD.

Studies (references)
Sheppard *et al.* (37)
Canale *et al.* (38)
Frey *et al.* (39)
Martín-Garcia *et al.* (40)
Renato *et al.* (41)
Ana *et al.* (42)
Gregorietti *et al.* (43)
Xi *et al.* (47)
Lupi *et al.* (48)
Wu *et al.* (49)
PRADA II trial (50)

Abbreviations: NYHA, new york heart association; NT-proBNP, N-terminal pro brain natriuretic peptide; IQR, inter quarti