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Rationale and Design of the Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes (SUCCOUR) Trial

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ABSTRACT

OBJECTIVES This study sought to evaluate the hypothesis that global longitudinal strain (GLS) guidance of cardioprotective therapy would improve cardiac function of at-risk patients undergoing potentially cardiotoxic chemotherapy, compared with usual care.

BACKGROUND The conventional criteria for diagnosis of chemotherapy-related cardiac dysfunction (CTRCD) are dependent on the recognition of heart failure symptoms and/or changes in left ventricular ejection fraction. However, the measurement variability of left ventricular ejection fraction necessitates broad diagnostic ranges, with the consequence of low sensitivity for CTRCD. Observational data have shown GLS to be a robust and sensitive marker to predict CTRCD and thereby guide the initiation of cardioprotective therapy, but these data are insufficient to justify changing the diagnostic criteria for CTRCD.

METHODS The SUCCOUR trial is an international multicenter prospective randomized controlled trial. Patients who are taking cardiotoxic chemotherapy (n = 320) with at least 1 risk factor will be randomly allocated into GLS- and ejection fraction–guided strategies. All participants will be followed over 3 years for the primary endpoint (change in 3-dimensional ejection fraction) and other secondary endpoints.

RESULTS Among the first 185 patients (age 54 ± 13 years; 93% women) from 23 international sites, 88% had breast cancer, 9% had lymphoma, and 3% had other cancers. Heart failure risk factors were prevalent: 34% had hypertension and 10% had diabetes mellitus. The most common chemotherapy regimen during this study was the combination of anthracycline and trastuzumab. The baseline 3-dimensional left ventricular ejection fraction was 61 ± 4%, and GLS was 20.3 ± 2.5%. Of 93 patients followed up in the first year of the study, 10 had to withdraw for noncardiac reasons. Of 40 patients randomized to the GLS-guided arm, 15 have been started on cardioprotective therapy, whereas 4 of 46 patients in the ejection fraction–guided arm have been started on therapy.

CONCLUSIONS The SUCCOUR trial will be the first randomized controlled trial of GLS and will provide evidence to inform guidelines regarding the place of GLS for surveillance for CTRCD. (Strain sUrveillance of Chemotherapy for improving Cardiovascular Outcomes [SUCCOUR]; ANZ Clinical Trials ACTRN12614000341628) (J Am Coll Cardiol Img 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

CTRCD = chemotherapy-related cardiac dysfunction

GLS = global longitudinal strain

HF = heart failure

LV = left ventricular

LVEF = left ventricular ejection fraction

SBHF = stage B heart failure

2D = 2-dimensional

3D = 3-dimensional

3DE = 3-dimensional echocardiography

RATIONALE

As cancer therapies and survival have improved, millions of patients treated with cardiotoxic therapy are now cancer survivors (1). Older women with early stage breast cancer are more likely to die from heart disease than cancer (2). The reported incidence of left ventricular (LV) dysfunction varies from 5% to 15% and heart failure (HF) from 0% to 5%, but reports from the Surveillance, Epidemiology, and End Results-Medicare database in the United States showed a cancer cohort treated from 2002 to 2007 to have a 3-year incidence of HF or LV dysfunction of 18% to 42%, depending on the treatment group (3).

Chemotherapy agents with potential cardiotoxicity are widely used in the treatment of hematologic malignancy, sarcoma, and breast cancer (4). The cardiac risks of anthracyclines are dose-related (4,5), but LV dysfunction has been documented with doses under the usual threshold of 450 mg/m^2 doxorubicin (or equivalent) (6). Despite efforts to avoid these drugs, such as replacing them with docetaxel-based protocols in breast cancer (7), they are effective and remain widely used. In addition, several non-anthracycline therapies used in cancer treatment are cardiotoxic (8), principally monoclonal antibodies and tyrosine kinase inhibitors. For example, trastuzumab (Herceptin) is a very effective therapy used in conjunction with anthracyclines in the particularly aggressive cancers overexpressing the growth factor receptor gene HER2 (9,10), but this agent increases the cardiotoxicity risk from anthracyclines. LV dysfunction is noted in 19% to 32% of patients in studies administered trastuzumab after anthracycline-based chemotherapy (11–13) and alone (3). Cardiotoxicity is likely to become an increasing problem because many small molecules and kinase inhibitors have adverse cardiac effects similar to trastuzumab (4,8), and with the increasing age and comorbidity status of the treated population.

Following the initial report of cancer therapy-related cardiac dysfunction (CTRCD) (14), the diagnosis was made on the basis of HF symptoms (15). However, symptoms have limited diagnostic value, because of the overlap of symptoms of HF and cancer, and the adverse outcome of symptomatic HF in this setting, with a 2-year mortality of up to 60% (16). Because late-stage HF has such an adverse prognosis, attention has been directed toward recognition of stage B HF (SBHF) (patients with structural disease but without signs and symptoms of HF) (17,18). SBHF benefits from treatment with beta-blockers and angiotensin-converting enzyme (ACE) inhibitors (19). Although SBHF is readily defined after myocardial infarction, its recognition in patients with global hypokinesis is more challenging, and LV function markers may be of value (20).

Left ventricular ejection fraction (LVEF) has been used as a marker of cardiotoxicity for the past 3 decades (21). In a current definition of cardiotoxicity asymptomatic reductions of >10% to <55% constitute cardiotoxicity (22). However, echocardiographic measurement of 2-dimensional (2D) LVEF presents several challenges related to image quality, assumptions about LV geometry, and expertise (23). The coefficient of variation for repeated 2D echo recording is reported to be 12% (24) with similar reproducibility (>10%) reported more recently (25), so this method fails to detect subtle alterations in LV function. Three-dimensional echocardiography (3DE) has greater reproducibility and accuracy (25), and non-echocardiographic measures, such as cardiac magnetic resonance, would provide better precision; the coefficient of variation for repeated cardiac magnetic resonance measurement of LVEF is approximately 4% (26). However, the cost and availability of cardiac magnetic resonance, especially for repeated testing, mean that this is primarily a reference method. Additionally, LVEF by all methodologies is dependent on hemodynamic conditions, and this parameter is not as sensitive to minor changes as measurements of myocardial deformation (27).

Global longitudinal strain (GLS) from 2D speckle tracking echocardiography is a quantitative technique for the measurement of global long-axis function from gray-scale images (28). Recent work by our (29–31) and other groups (32,33) have shown that changes in tissue deformation, assessed by myocardial strain, identify LV dysfunction earlier than conventional echocardiographic measures in patients receiving cancer therapy. In a retrospective observational analysis, GLS demonstrated a potential to guide the initiation of cardioprotective agents (34). Thus, GLS may help identify early myocardial dysfunction in patients receiving cancer therapy that includes anthracyclines, trastuzumab, or a tyrosine kinase inhibitor, prompting initiation of treatment used in SBHF.

STUDY DESIGN AND OBJECTIVES

DESIGN. This multicenter, randomized controlled trial of GLS uses a prospective randomized open