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Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies

The OVERCOME Trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies)

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Objectives This study sought to evaluate the efficacy of enalapril and carvedilol to prevent chemotherapy-induced left ventricular systolic dysfunction (LVSD) in patients with hematological malignancies.

Background Current chemotherapy may induce LVSD. Angiotensin-converting enzyme inhibitors and beta-blockers prevent LVSD in animal models of anthracycline-induced cardiomyopathy.

Methods In this randomized, controlled study, 90 patients with recently diagnosed acute leukemia (n = 36) or patients with malignant hemopathies undergoing autologous hematopoietic stem cell transplantation (HSCT) (n = 54) and without LVSD were randomly assigned to a group receiving enalapril and carvedilol (n = 45) or to a control group (n = 45). Echocardiographic and cardiac magnetic resonance (CMR) imaging studies were performed before and at 6 months after randomization. The primary efficacy endpoint was the absolute change from baseline in LV ejection fraction (LVEF).

Results The mean age of patients was 50 ± 13 years old, and 43% were women. At 6 months, LVEF did not change in the intervention group but significantly decreased in controls, resulting in a −3.1% absolute difference by echocardiography (p = 0.035) and −3.4% (p = 0.09) in the 59 patients who underwent CMR. The corresponding absolute difference (95% confidence interval [CI]) in LVEF was −6.38% (95% CI: −11.9 to −0.9) in patients with acute leukemia and −1.0% (95% CI: −4.5 to 2.5) in patients undergoing autologous HSCT (p = 0.08 for interaction between treatment effect and disease category). Compared to controls, patients in the intervention group had a lower incidence of the combined event of death or heart failure (6.7% vs. 22%, p = 0.036) and of death, heart failure, or a final LVEF <45% (6.7% vs. 24.4%, p = 0.02).

Conclusions Combined treatment with enalapril and carvedilol may prevent LVSD in patients with malignant hemopathies treated with intensive chemotherapy. The clinical relevance of this strategy should be confirmed in larger studies. (Prevention of Left Ventricular Dysfunction During Chemotherapy [OVERCOME]; NCT01110824) (J Am Coll Cardiol 2013;61:2355–62) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin II receptor blocker

CMR = cardiac magnetic resonance

HSCT = hematopoietic stem-cell transplantation

LVEF = left ventricular ejection fraction

LVSD = left ventricular systolic dysfunction

PBSCT = peripheral blood hematopoietic stem-cell transplantation

SBP = systolic blood pressure

The prognosis of patients with hematological malignancies has improved because of the use of new chemotherapeutic and antineoplastic drugs and more dose-intensive regimens (1). Nonetheless, novel therapy has been associated with significant adverse events such as cardiac toxicity (2). In addition to anthracyclines, several other drugs used in the treatment plans of hematologic malignancies, either at standard doses during front-line therapy or as part of high-dose conditioning regimens for hematopoietic stem-cell transplantation (HSCT), may induce cardiac toxicity (2) through a diversity of mechanisms including endothelial toxicity and direct myocyte injury (3–5). Even in asymptomatic patients, left ventricular systolic dysfunction (LVSD) might limit patients' treatment options and their long-term survival, because a significant proportion of them will relapse after front-line therapy and will require further salvage treatment, including HSCT in most instances (3).

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Angiotensin-converting enzyme inhibitors (ACEI) have been demonstrated to slow the progression of LVSD and to prevent heart failure in asymptomatic high-risk patients (6) and to decrease mortality in post-infarction patients with LVSD and in patients with heart failure (6), including patients with anthracycline-induced cardiomyopathy (7). ACEI therapy has also been shown to have preventive effects against chemotherapy-induced cardiotoxicity in animal models (8,9) and in adult patients with early cardiotoxicity (10). Similar results have been obtained with the administration of beta-blockers in patients with post-infarction LVSD or heart failure (6), in animal models of cardiotoxicity (11,12) and in patients treated with anthracyclines (13,14). In addition, administration of both ACEI and beta-blockers has been shown to have additive beneficial effects in patients with LVSD (15) and is the recommended treatment in current guidelines (6).

Therefore, we designed the OVERCOME (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies) study to evaluate the effect of enalapril and carvedilol on the prevention of LVSD in patients with malignant hemopathies undergoing intensive chemotherapy (16).

Methods

Trial. This was a prevention, randomized, controlled trial performed at the Hospital Clinic of Barcelona, Spain. All patients were informed orally and in writing, and all gave their written consent before inclusion. The protocol was approved by the ethics committee of our institution, which recommended an open-label design of the study, considering the pilot nature of the trial, the severity of the treated diseases, the high incidence of infectious complications, and the potential hypotensive effect of the intervention. The study was conducted according to the Helsinki Declaration and registered with U.S. National Institutes of Health National Clinical Trials (NCT01110824).

Population of the study. Inclusion criteria were adult patients from 18 to 70 years old, in sinus rhythm and with normal echocardiographic LV ejection fraction (LVEF $\geq$50%), recently diagnosed with acute leukemia and referred for immediate intensive chemotherapy, and patients with relapsed or refractory Hodgkin and non-Hodgkin lymphoma and multiple myeloma undergoing autologous HSCT.

Exclusion criteria were the presence of congestive heart failure; LVEF <50%; prior myocardial infarction or documented coronary artery disease; significant valvulopathy or myocardiopathy; renal failure (defined as an estimated glomerular filtration rate of <30 ml/h/m^2); hepatocellular insufficiency or grade III to IV increase of liver enzymes not secondary to tumoral liver infiltration; ongoing or expected need to be treated with ACEI, angiotensin II receptor blockers (ARB), or beta-blockers; prior allergy to ACEI or ARB; systolic blood pressure (SBP) lower than 90 mm Hg; asthma; atrioventricular block or sinus bradycardia (heart rate lower than 60 beats/min); persistent atrial fibrillation; need to be treated with a class I antiarrhythmic drug; pregnancy; and inability or unwillingness to give informed consent.

Randomization. Participants were randomly assigned in a 1:1 ratio to receive (the intervention group) or not to receive (the control group) enalapril and carvedilol. Randomization was centralized and performed by the hospital's Clinical Trials Unit, based on a series of random numbers generated by a computer program in blocks of random size and stratified by the patient cohort: acute leukemia versus other malignant hemopathies undergoing autologous HSCT.

Study treatment. Enalapril and carvedilol was started simultaneously at least 24 h before the first cycle of chemotherapy. The initial dose of enalapril was 2.5 mg twice daily (1.25 mg in patients with SBP between 90 mm Hg and 100 mm Hg) and was increased gradually every 3 to 6 days under close supervision to 5 mg and 10 mg twice daily if SBP persistently remained >90 mm Hg and creatinine levels were <2.5 mg/dl (or increased <25% in patients with creatinine levels of >1.3 mg/dl). In case of hypotension, the dose was reduced to the closest level or stopped, and the lowest dose was resumed when SBP persistently remained >90 mm Hg.