Clinical Trials: Methods & Design

# Prevention of Chemotherapy-Induced Left Ventricular Dysfunction With Enalapril and Carvedilol: Rationale and Design of the OVERCOME Trial

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**ABSTRACT**

**Background:** The current treatment of hematologic malignancies includes diverse potentially cardiotoxic chemotherapy agents, including high-dose myeloablative regimens used in autologous hematopoietic stem cell transplantation (HSCT). Many of these treatments could induce left ventricular dysfunction (LVD), and limit their efficacy. Angiotensin-converting enzime inhibitors and beta-blockers prevent LVD and prolong survival after infarction, and recent animal and pilot clinical studies suggest that they can prevent the development of chemotherapy-induced cardiac toxicity.

**Methods:** This is a prevention, parallel-assignment, randomized, controlled, clinical efficacy study. Ninety patients recently diagnosed of acute leukemia or undergoing autologous HSCT and with normal LV ejection fraction will be randomized to enalapril and carvedilol or to the control group. Echocardiogram and a cardiac magnetic resonance imaging studies will be performed at baseline and 6−9 months after randomization. The primary efficacy endpoint is the change from baseline in LV ejection fraction. Secondary endpoints include the assessment of LV volumes and diastolic function, and the incidence of death, heart failure, or LVD.

**Conclusions:** The OVERCOME study will be the first clinical trial to test the preventive efficacy on LVD of combined treatment with enalapril and carvedilol administered to patients with hematologic malignancies submitted to current treatment with intensive chemotherapy. (*J Cardiac Fail 2011;17:643−648*)

**Key Words:** Cardiotoxicity, carvedilol, chemotherapy, enalapril, prevention, ventricular dysfunction.

The prognosis of patients with hematologic malignancies has greatly improved in the past several years with the use of new chemotherapeutic drugs and regimens[1,2] at the cost of significant adverse events, such as cardiac toxicity. Even in asymptomatic patients, left ventricular (LV) dysfunction limits the specific treatment of the patients and their long-term survival, because a significant proportion of them will relapse within 5 years after front-line therapy, and will require further salvage treatment, including hematopoietic stem cell transplantation (HSCT) in most instances.[3]

Anthracycline-induced cardiac toxicity may appear acutely, immediately after drug administration, or more frequently, with an early-onset chronic pattern within 1 year after treatment or after several years, finally inducing a form of dilated cardiomyopathy.[2,4,5] The cardiotoxicity of anthracyclines includes the oxidative damage induced by the production of free radicals, with lipid peroxidation of the cell membrane.[2,4,5] These agents also induce a profound depletion of the cardiac stem cell pool by apoptosis,[6] and they impair the vascular development of the heart and reduce

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proliferation and differentiation of the progenitor cells into cells of cardiac lineages, resulting in hearts that are more susceptible to heart failure under stress.[7] Furthermore, several other drugs used in the treatment plan of hematologic malignancies, either as standard dose during front-line therapy or as part of high-dose conditioning regimens of HSCT, may induce cardiac toxicity[2] through a diversity of mechanisms including endothelial toxicity and direct myocyte injury.[2,3,8–11] In this regard, the incidence of subclinical cardiac damage as measured by echocardiography is remarkably high, ~15%–30%, especially in previously treated patients undergoing high-dose regimens.[8–13]

Because of the prognostic impact of any prevention measure on these patients, prospective studies to develop new preventive strategies are warranted. The most successful implemented measures have been the limitation of cumulative anthracycline dose, changes in chemotherapy administration schedule, and close monitoring of cardiac function,[5] whereas the administration of drugs to prevent cardiotoxicity has been disappointing.[14]

Angiotensin-converting enzyme inhibitors (ACEI) have been demonstrated to slow the progression of LV dysfunction and prevent heart failure in asymptomatic high-risk patients[15,16] and to decrease mortality in postinfarction patients with LV dysfunction and in patients with heart failure,[17,18] including patients with anthracycline-induced cardiomyopathy.[19] ACEIs have been shown also to have preventive effects against chemotherapy-induced cardiotoxicity in animal models[20–22] and in patients with early cardiotoxicity,[23] and a preliminary study with valsartan showed prevention of acute cardiotoxic changes in patients receiving doxorubicin.[24] Similar results have been obtained with the administration of beta-blockers in patients with postinfarction LV dysfunction and in patients with heart failure.[25–28] Carvedilol has potent antioxidant and antiapoptotic properties,[29] preventing free radical release, mitochondrial dysfunction, apoptosis, and dilated cardiomyopathy in animals treated with anthracyclines,[30,31] and has shown promising results in preventing chemotherapy-induced LV dysfunction in patients.[32] In addition, the administration of both ACEIs and beta-blockers have been shown to have additive beneficial effects in patients with LV dysfunction after myocardial infarction.[33]

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, a prospective, randomized trial to evaluate the combined effect of enalapril and carvedilol on the prevention of LV dysfunction in patients with malignant hemopathies undergoing intensive chemotherapy.

## Methods

This is a prevention, parallel-assignment, randomized, controlled, clinical efficacy study, and has been registered at w.w.w.ClinicalTrials.gov (registration number NCT01110824).

### Endpoints

The primary outcome measure will be the change from baseline in global left ventricular ejection fraction (LVEF) measured by echocardiography and by cardiac magnetic resonance imaging (CMRI), 6–9 months after randomization.

Secondary outcome measures will include: the incidence of an absolute decrease in LVEF of ≥10% associated with a decline to below its normal limit of 50%; the incidence of death, heart failure, or significant LV systolic dysfunction as defined by LVEF <45%; the incidence of LV dysfunction as assessed by the measurement of the LV strain and of diastolic dysfunction as measured by echo Doppler; right ventricular and LV volumes as measured by CMRI; the incidence of severe adverse events; and a predefined subgroup analysis of the results according to the initial diagnosis (acute leukemia vs other malignant hemopathies).

All outcomes will be assessed by independent investigators blinded to the patients condition and allocated treatment.

### Population of the Study

All consecutive patients with a new diagnosis of acute leukemia and patients with lymphoma or multiple myeloma undergoing autologous HSCT using peripheral blood as stem cell source (PBSCT) in our institution will be considered for the study. Anthracyclines will be administered in a standard short infusion of 15–30 minutes duration, and in the conditioning regimen of autologous PBSCT chemotherapeutic agents will be administered in 60–120 minutes of infusion.

**Inclusion Criteria.** We will include adult patients 18–70 years old, in sinus rhythm and normal LV systolic function (LVEF ≥50%) as asessed by echocardiography, recently diagnosed with acute leukemia (either myeloid or lymphoblastic/precursor lymphoid neoplasm) and to be submitted to immediate intensive chemotherapy, and patients with other malignant hemopathies (relapsed or refractory Hodgkin disease, non-Hodgkin lymphoma, and multiple myeloma) to be submitted to autologous PBSCT. Each of the patients has to accept to be enrolled in the study after signing an informed consent form.

**Exclusion Criteria.** We will exclude patients with congestive heart failure; LVEF <50%; previous myocardial infarction or documented coronary artery disease; significant valvulopathy or myocardiopathy; renal failure defined as an estimated glomerular filtration rate <30 mL $h^{-1}$ $m^{-2}$; hepatocellular insufficiency or grade III–IV increase of liver enzymes not secondary to tumoral liver infiltration; ongoing or expected need to be treated with ACEI, angiotensin II receptor blockers (ARBs), or beta-blockers; previous allergy to ACEI or ARB; systolic blood pressure <90 mm Hg; asthma; atrioventricular (AV) block or sinus bradycardia (heart rate <60 beats per minute); persistent atrial fibrillation; need to be treated with a class I antiarrhythmic drug; pregnancy; or inability or unwillingness to give informed consent.

### Randomization

Patients with all inclusion criteria and without any exclusion criteria that accept to be enrolled in the study after signing an informed consent, will be randomly assigned in a 1:1 ratio to receive (intervention group) or to not receive (control subjects) enalapril and carvedilol. The study is stratified on the type of disease: patients with acute leukemia versus patients with other malignant hemopathies submitted to autologous PBSCT. To ensure balanced allocation of treatment over time, random permuted blocks with