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Xavier Bosch, MD, PhD Montserrat Rovira, MD, PhD Marta Sitges, MD, PhD Ariadna Dom¹ nech, RN Jos° T. Ortiz-P° rez, MD, PhD Teresa M. de Caralt, MD, PhD Manuel Morales-Ruiz, PhD Rosario J. Perea, MD, PhD Mariano MonzÄ, MD, PhD Jordi Esteve, MD, PhD

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Enalapril And Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients with Malignant Hemopathies. The OVERCOME Trial

Brief title: Chemotherapy-Induced Left Ventricular Dysfunction

Xavier Bosch MD, PhD * ¶, Montserrat Rovira MD, PhD † ¶, Marta Sitges MD, PhD * ¶, Ariadna Domènech RN †, José T. Ortiz-Pérez MD, PhD * ¶, Teresa M. de Caralt MD, PhD ‡, Manuel Morales-Ruiz, PhD II ¶ , Rosario J. Perea MD, PhD ‡, Mariano Monzó MD, PhD § ¶, and Jordi Esteve MD, PhD † ¶

***** Cardiology Department, Thorax Institute, Hospital Clinic. Barcelona, Spain
† Hematology Department, Hemato-Oncology Institute, Hospital Clinic. Barcelona, Spain.
‡ Radiology Department. Hospital Clinic. Barcelona, Spain.
§ Human Anatomy Unit, Molecular Oncology and Embryology Laboratory, School of Medicine, Barcelona, Spain.
II Department of Biochemistry and Molecular Genetics, Hospital Clinic. Barcelona, Spain.
¶ Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). University of Barcelona, Spain.

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Address for correspondence:

Xavier Bosch, M.D., Cardiology Department, Thorax Institute

Hospital Clinic , Villarroel 170, 08036 Barcelona, Spain

Phone # 34- 932279305

Fax # 34- 93 2275749

E-mail: xbosch@clinic.ub.es

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ABSTRACT

Objectives: 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 recently diagnosed of 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 receive enalapril and carvedilol (n=45) or to a control group (n=45). Echocardiographic and cardiac magnetic resonance (CMR) imaging studies were performed before and 6 months after randomization. The primary efficacy endpoint was the absolute change from baseline in LVEF.

Results: The mean age of patients was 50±13 yr and 43% were woman. 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 that underwent CMR. The corresponding absolute difference (95% CI) in LVEF was -6.38% (-11.9 to -0.9) in patients with acute leukemia and -1.0% (-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: The 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 future studies.

Clinical Trial ID: The OVERCOME trial. www.clinicaltrials.gov identifier: NCT01110824

Keywords: Prevention; cardiac toxicity; left ventricular dysfunction; chemotherapy; enalapril; carvedilol.

ABBREVIATIONS

ACE-i: Angiotensin-converting enzyme inhibitors
ARB: angiotensin II receptor blockers
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.

INTRODUCTION

The prognosis of patients with hematological malignancies has improved in the last years due to the use of new chemotherapeutic and antineoplastic drugs and more dose intensive regimes(1). Nonetheless, novel therapy has been associated to significant adverse events such as cardiac toxicity(2). In addition to anthracyclines, 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 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 the treatment options of the patients and their long-term survival, since a significant proportion of them will relapse after front-line therapy, and will require further salvage treatment, including HSCT in most instances(3).

Angiotensin-converting enzyme inhibitors (ACE-i) 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 postinfarction patients with LVSD and in patients with heart failure(6), including patients with anthracycline-induced cardiomyopathy(7). ACE-i have also showed 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 postinfarction LVSD or heart failure(6), in animal models of cardiotoxicity(11,12), and in patients treated with anthracyclines(13,14). In addition, the administration of both ACE-i and beta-blockers have been shown to have additive beneficial effects in patients with LVSD(15) and are 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 ethic committee of our Institution that 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 hipotensive effect of the intervention. The study was conducted according to the Helsinki declaration and registered at www.clinicaltrials.gov (identifier: NCT01110824).

Population of the study. Inclusion criteria were adult patients from 18 to 70 year-old, in sinus rhythm and normal echocardiographic LV ejection fraction (LVEF≥50%), recently diagnosed of acute leukemia who were to be submitted to immediate intensive chemotherapy, and patients with relapsed or refractory Hodgkin's and non-Hodgkin's 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 < 30 ml/h/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 ACE-i, angiotensin II receptor blockers (ARB) or beta-blockers; prior allergy to ACE-i or ARB; systolic blood pressure (SBP) lower than 90 mm Hg; Asthma; AV block or sinus bradycardia (heart rate lower than 60 beats per minute); persistent atrial fibrillation; need to be treated with a class I antiarrhythmic drug; pregnancy; inability or unwillingness to give informed consent.

Randomization. Participants were randomly assigned in a 1:1 ratio to receive (intervention group) or not to receive (control group) enalapril and carvedilol. Randomization was centralized, 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 hours before the first cycle of chemotherapy. The initial dose of enalapril was of 2.5 mg twice daily (1.25 mg in patients with SBP between 90 to 100 mm Hg), and was increased gradually every 3 to 6 days under close supervision to 5 and 10 mg twice daily if SBP persistently remain >90 mm Hg and creatinine levels < 2.5 mg/dl (or increase <25% in patients with creatinine levels >1.3 mg/dl). In the case of hypotension, the dose was reduced to the closest level or stopped, and the lowest dose resumed when SBP persistently remained >90 mm Hg. The initial dose of carvedilol was 6.25 mg twice daily and increased gradually every 3 to 6 days to 12.5 and 25 mg twice daily in the absence of clinical signs of congestive heart failure, sinus bradicardia < 60 beats per minute or any degree of AV block. In the case of hypotension or bradicardia, the dose was also reduced to the closest level.

All patients received in-hospital chemotherapy according to the protocols of our institution and HSCT was performed using peripheral blood as stem cell source (PBSCT) (Supplementary Table 1). The admission period was prolonged during all the induction phase in patients with acute leukemia or the whole procedure in patients undergoing autologous PBHSCT, until hematologic recovery, with a mean length of 30 days after inclusion in the trial. After completion of therapy, patients were followed-up in an outpatient clinic where enalapril and carvedilol were directly provided to the patient's, and evaluated at the end of the follow-up period, 6 months after randomization.

Endpoints. The primary outcome measure was the change from baseline in global LVEF measured by echocardiography and by cardiac magnetic resonance imaging (CMR), 6 months after randomization.

Secondary outcome measures included a pre-defined subgroup analysis of the results according to the patient cohort (acute leukemia vs. other malignant hemopathies), and to TnI and BNP levels, the incidence of an absolute decrease in LVEF ≥10 percent units associated with a decline below its normal limit of 50%; the incidence of death, heart failure or significant LVSD as defined by a LVEF<45%; diastolic function measured by echo-Doppler; and the incidence of severe life-threatening adverse events.

Six-month studies were always performed when patients were in stable condition. Otherwise, the study was delayed until patient's recovery. All outcomes were assessed by independent investigators blinded to the patient's condition and allocated treatment. If suspected congestive heart failure occurred in any of the two arms during the study, a complete cardiac evaluation was performed including a clinical echocardiographic study to confirm the diagnosis. If LV dysfunction was confirmed, the patients were considered to have achieved the endpoint of the study and treated with ACEI's and/or beta-blockers according to the treating physician criteria.

Echocardiography. Echocardiographic-Doppler studies were performed with a commercially available system (Vivid 7, General Electric Medical System, Milwaukee, USA). Images were digitally stored for later off-line analysis with specific software (EchoPac, General Electrics; Milwaukee, WI). LVEF was calculated using the Simpson's method. Contrast-enhanced echocardiography was performed when the endocardial border visualization was not optimal. LV diastolic function was assessed in terms of LV inflow diastolic velocities, pulmonary vein flow and lateral mitral annulus motion(17). Early (E) and late (A) peak diastolic velocities of the LV inflow and the deceleration time (DT) of the E

wave were determined by pulsed-wave Doppler, and the E/A ratio was calculated. Pulmonary vein flow peak systolic (S) and diastolic (D) velocities were determined by pulsed-wave Doppler and the S/D ratio was calculated. The early peak diastolic velocity of the mitral annulus (Em) was determined using pulsed-wave Doppler tissue imaging, and the ratio E/Em was calculated as a surrogate of LV filling pressure. Left atrial area was also measured. All echocardiograms were interpreted blindly by a cardiologist unaware of the patient's condition and treatment.

Cardiac Magnetic Resonance Imaging. CMR studies were carried out in a 1.5-T GE Sigma HD-x scanner (Milwaukee, Wisconsin) under electrocardiographic gating and using a cardiac phased-array surface coil. Global LV systolic function was assessed with a standard steady state free precession cine sequence in sequential 10 mm thick short axis slices.

Identifying data was removed from CMR images for analysis. An experienced observer masked to patient treatment allocation and imaging point (baseline or end of the study) performed manual plannimetry of the endocardial border at end-systolic and end-diastolic frames to compute LVEF using commercially available software (Report card, GE, Milwaukee, Wisconsin).

TnI and BNP Measurements. TnI was measured before, daily during each cycle of chemotherapy, and 12 and 24 hours after each cycle. BNP concentration was determined before and 12 hours after each cycle of chemotherapy and following infusion of harvested HSCT. For each patient, only the highest TnI and BNP values were considered. Plasma levels of TnI were measured using a fluorometric enzyme immunoassay analyzer (Tn I-Ultra, ADVIA Centaur CP) with a functional sensitivity of 0.006 ng/ml and a cutoff level of 0.04 ng/ml corresponding to the 99% percentile of control values. BNP was measured using a chemiluminometric immunoassay run on the ADVIA Centaur Immunochemistry analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY).

Sample size and statistical analysis. To detect an intergroup difference of 5 points in LVEF change from baseline to follow up with a statistical power of 90%, a type I error risk of 5%, and with an estimated SD of 6.5%, a total of 72 patients was estimated to be needed on the basis of a 2-sided, 2-sample t test. Assuming a 20% rate of incomplete measurements, a total of 90 patients was needed to be enrolled in the study.

All statistical analyses of the results were performed by the intention to treat method. Comparison of baseline characteristics and of the incidence of clinical events between the intervention and control groups were performed with the unpaired t test, X^2, and the Fischer exact test. BNP data are reported as medians (25, 75 percentile) and compared using the Mann-Whitney U test; the Spearman rank correlation tes was used to correlate peak BNP levels and final LVEF. Differences among the two groups in absolute changes in LVEF from baseline to 6 months after randomization were compared fitting mixed models for repeated measures with the (co)variance type set to unstructured. A sensitivity analysis was also conducted before fitting the model by imputing a conservative value based on the 10^{th} percentile of the overall response to those patients with missing values.

A pre-specified analysis included the assessment of the primary outcome separately for patients with acute leukemia and for patients with lymphoma or multiple myeloma submitted to autologous PBSCT. The level of significance was set at the standard two-sided level of 5%. All analyses were performed using SAS (version 9.1.3) software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients. From May 2008 to June 2010, 114 consecutive patients potentially eligible for the study were assessed, of whom 111 met the inclusion criteria and 21 had some exclusion criteria. Forty-five of the resulting 90 patients were randomized to the intervention group and 45 to the control group (Figure 1). Mean age of patients was 50±13 yr and 43% were woman.

Thirty-six patients had acute leukemia (of myeloid lineage in 30, and lymphoblastic in 6), and 54 had other malignancies undergoing PBSCT (9 with Hodgkin's disease, 23 with non-Hodgkin's lymphoma and 22 with multiple myeloma).

The two groups were well balanced with respect to baseline characteristics and treatment received prior and during the study, including anthracycline dose, except for the smoking habit and prior treatment with radiotherapy that were more frequent in the intervention group (Tables 1 and 2).

Study drugs. In the intervention group the mean dose per patient per day of enalapril and carvedilol was 8.2±5.9 mg and 26.1±18.2 mg respectively at 30 days, and 8.6±5.9 mg and 23.8±17 mg respectively at the end of the study. The maximum administered doses were 10.9±5.9 mg/day for enalapril and 33.4±16 mg/day for carvedilol.

Primary endpoint. Thirteen patients discontinued the study because of death in 11 patients and clinical heart failure in two. In the latter two patients, a final echocardiographic study was obtained resulting in 79 patients (88%) with complete echocardiographic data.

Echocardiographic LVEF was similar in the intervention and control groups at baseline. At 6 months, while no serial changes were observed in the intervention group, patients in the control group had a decrease in their mean LVEF resulting in a global absolute intergroup difference of -3.11 points (p=0.04; Table 3).

Complete CMR studies could be obtained in only 58 patients (64%). Four patients refused to perform the baseline study and 28 did not perform the 6-month evaluation because of death in 11 patients, heart failure in two, and cancer progression and patient's refusal in 17 patients. Mean LVEF did not change in the intervention group but decreased by 3.04 absolute percent points in the control group resulting in a -3.40 absolute percent intergroup difference (p=0.09; Table 3).

When a sensitive analysis was performed imputing the values of the 10% percentile to those patients with missing values, similar results were observed with an estimated -3.61 (95% CI: -6.45 to -0.77) intergroup absolute difference in echocardiographic LVEF (p=0.013), and a -2.96 (95% CI: -6.08 to 0.16) difference in CMR LVEF (p=0.063).

Secondary endpoints

Disease category: Acute leukemia vs. autologous PBSCT. An interaction was observed in the echocardiographic LVEF results according to the disease category (p for interaction = 0.08), with more marked differences in patients treated for acute leukemia than in patients undergoing an autologous PBSCT. The mean intergroup difference in LVEF was of -6.38 (95% CI: -11.88 to -0.87, p=0.025) absolute percent points in patients with acute leukemia (figure 2), and of -1.01 (95% CI: -4.46 to 2.45, p=0.56) in patients with other malignancies undergoing PBSCT.

Left ventricular diastolic function. Baseline parameters of diastolic function were suggestive of normal to mild abnormal relaxation consistent with the mean age of the patients, with no left atrial enlargement, E/A ratio close to 1 and S/D ratio of pulmonary veins over 1. No significant changes in the diastolic parameters were observed in any of the groups at follow-up (Supplementary table 2).

Biomarkers. Eleven patients (10 with acute leukemia and only one patient undergoing PBSCT, p<0.001) experienced TnI elevation during chemotherapy, 7 in the intervention and 4 in the control group (p=0.52). Nine of the 11 patients with positive troponins had TnI elevation at the end or early after a cycle of chemotherapy: 5 during the initial frontline therapy and 4 one month later. Only two patients had troponin elevation both during initial treatment and one month later.The degree of TnI elevation was mild and only 3 patients had TnI elevation over 3 times the upper reference limit. Recurring TnI elevation (≥2 episodes)

occurred in 6 patients, with three patients in each study group. No interaction was found between the effects of enalapril and carvedilol on LVEF and TnI elevation (p=0.59).

BNP elevation over 80 ng/L was common and occurred in 17 (47%) patients with acute leukemia and 24 (44%) patients undergoing HSCT, with no differences between the intervention and the control groups (53% versus 38%, p=0.14). BNP elevation over 200 ng/L occurred in 7 and 2 patients respectively (p=0.16). No correlation was found between peak BNP levels and the change in LVEF (R=-0.11, p=0.34).

Clinical endpoints. During the study period 14 patients withdrew prematurely from the study because of death in 11 patients (cancer-related in 4 and infection-related in 7), heart failure in 2, and cancer progression in one patient. Five out of 7 patients who died from an infectious cause were allocated to the control group. Patients who survived a septic episode during the trial experienced a mean decrease in final LVEF of 4.6 ±9 absolute points, compared to a decrease of 0.6±6 points in patients without sepsis (p=0.04).

Compared to controls, the intervention group had less incidence of premature end of the study (6.7% vs. 24.4%, p=0.02), of death or heart failure (6.7% vs. 22.2%, p=0.036), and of the pre-specified secondary endpoint of death, heart failure or a final LVEF<45% (6.7%% vs. 24.4%, p=0.02; Table 4). Patients treated with enalapril and carvedilol also showed a trend to a lower incidence of heart failure or a >10% decrease in LVEF (9.5% vs. 19%, p=0.22).

Safety. Globally, enalapril and carvedilol were well tolerated although the dose of each drug had to be adjusted frequently according to the global patient status. During the first 30 days, enalapril was stopped in three patients, carvedilol in two and both drugs in one patient, while transient discontinuation was indicated in one, none and two patients respectively. New transient discontinuation frequency for the 1 to 6 month period was indicated in three, two and three patients, respectively.

Nine patients (20%) in the intervention group and 15 (33%) in the control group had severe life-theatening adverse events (p=0.15; Table 4). All of them were related to sepsis and required admission in an intensive care unit. None of the severe adverse effects that occurred in the intervention group were related to the treatment with enalapril and carvedilol.

DISCUSSION

The OVERCOME study has showed that the concomitant treatment with enalapril and carvedilol may prevent LVSD in patients with malignant hemopathies treated with high dose chemotherapy regimens. The results were consistent as measured with 2D-echocardiography or CMR, although the lower number of patients studied with the latter method precluded to obtain a conventional significant statistical difference. In addition, clinical events were less frequent in patients treated with the cardioprotective drugs. These results could have important clinical implications.

Comparison with other studies. Most studies performed on chemotherapy-induced cardiotoxicity have focused on the treatment of patients with heart failure or LVSD(2,7,18). In these patients, the current clinical practice is to stop chemotherapy and to restart it after LV recovery and avoiding further use of anthracyclines. However, even if LVSD improves after treatment, patients with chemotherapy-induced cardiotoxicity are prone to further deterioration in their LV function when fronted with further cycles of chemotherapy or even under stress conditions(19). Hence, in patients with cancer the main objective should be to prevent rather than to treat cardiac toxicity(20).

ACE-i have showed to be effective against chemotherapy-induced cardiotoxicity in animal models(8,9). Although their use to prevent the progression of LVSD was disappointing in a study on pediatric cancer(18), a recent study reported favorable results when administered to adult patients with chemotherapy-induced cardiac toxicity(10). Positive results have been also obtained with the administration of beta-blockers in animal models of

chemotherapy-induced cardiomyopathy(11,12), and in two pilot studies on patients submitted to treatment with anthracyclines(13,14).

The magnitude of the results of our study was mild, with a 3.1% absolute difference in the mean LVEF between the intervention and control groups in the global population. Nevertheless, these results includes very different individual responses, and are in accordance with the results obtained in large clinical trials in which a 20% relative risk reduction is sought(6). Other studies reported a higher effect of cardioprotection strategies. In the study performed by Cardinale et al(10), 43% of the control and none of the enalapril group had a more than 10% drop in LVEF, while heart failure occurred in 24% and 0%, respectively. Differences in the patient population, the intensity and type of chemothepapy and the protocol design of both studies may explain these different results. Thus, the OVERCOME trial included patients with normal LVEF and normal troponin levels, whereas the study of Cardinale et al included only patients who experienced troponin elevation after high-dose chemotherapy, 44% of them with persistent troponin elevation one month after randomization, representing a population with demonstrated chemotherapy-induced cardiotoxicity and at a much higher risk of chemotherapy-induced LVSD. In the study of Kalay et al(13) in which low-dose carvedilol was administered, the patient population was markedly different, with most patients being treated for breast cancer, and all patients received high doses of anthracyclines.

Although, almost half of patients presented elevated peak BNP levels, no intergroup differences were observed, and no correlation existed between LVEF reduction and BNP elevations. Many factors not directly related to cardiac toxicity might account for these findings, such as hyperhydration to prevent renal dysfunction and bladder toxicity during chemotherapy administration, repeated packed red cells and platelet transfusions, severe anemia, hypotension, acute kidney injury, or frequent infection episodes(21).

Effect on patients with acute leukemia. In our study, the effects were more pronounced in patients treated for recently diagnosed acute leukemia than for patients submitted to autologous PBSCT, with a mean 6.4% absolute difference in LVEF in the former. Although this was a subgroup analysis, it were pre-specified in the study protocol and the randomization of the patients was stratified for this condition. In addition, an interaction was found between the effect of the intervention and the cohort of patients. These results are also in agreement with the type of the chemotherapy administered, which included several multiagent chemotherapy courses and repeated doses of anthracyclines in all patients of the acute leukemia group. On the contrary, patients allocated to the PBSCT cohort received only one chemotherapy course, the conditioning regimen, without anthracyclinic agents. Accordingly, the number of patients with troponin elevation during treatment was much higher in the acute leukemia group, reflecting the higher cardiotoxic effect of the chemotherapy administered to these patients.

Diastolic function. Although we found significant changes in LVEF, an accepted measure of global LV systolic function, we did not find differences in LV indices of diastolic function. A recent study on carvedilol has reported similar results(14). The high variability of these measurements and their strong dependence on nonspecific and transient hemodynamic factors is a recognized limitation of these measurements. In addition, ACE-i and beta-blockers have not shown to be efficacious in patients with heart failure and preserved ejection fraction(6).

Effects on clinical events. The patients in the intervention group had a lower incidence of premature discontinuation of the study for any reason, of death or heart failure, and of death, heart failure or significant LVSD. Since two thirds of all deaths were related to infectious complications in the context of post-chemotherapy neutropenia, it is difficult to elucidate whether enalapril and carvedilol could have influenced mortality. Considering that patients who survived septic complications experienced a significant reduction in their LVEF at the

end of the study, when they were in a stable condition, and that LV function is a well known determinant of survival in patients with sepsis(22), it could be speculated that the study intervention might have influenced mortality by impacting on the outcome of severe infectious episodes. Globally, these findings reinforce the importance of the results on LVEF.

Compliance and safety. Although drug dose titration had to be adjusted frequently according to the global patient's satatus, enalapril was stopped in only 3 patients, carvedilol in 2, and both drugs in only one patient. In addition, no differences were observed in the incidence of severe adverse effects between the intervention and control groups. Thus, the trial has proved that the combined administration of these drugs is safe in a setting of intensive therapy for high-risk diseases with a high myelotoxic potential and frequent development of infectious complications and hypotensive episodes.

LIMITATIONS OF THE STUDY

The study was not blinded and placebo was not administered to the control group due to the pilot nature of the trial. However, the analyses of the imaging techniques were blinded; the study was randomized and analyzed by the intention to treat method to minimize any possible bias. Complete CMR studies could only be obtained in 81% of the planned patients. Although statistical inference with missing data and sensitive analysis were applied, the CMR results lack of enough statistical power to refuse a type II error. Also, the number of studied patients limits the value of the interaction found between the effect of the intervention on LVEF and the disease category. Finally, the administered doses of enalapril and of carvedilol were intermediate according to the patient's clinical condition. Larger doses could have obtained stronger effects. However, the doses used were determined by the patient's status and safety, and similar to the doses used in large controlled trials performed in patients with heart failure(6).

CLINICAL IMPLICATIONS

In conclusion, this pilot randomized trial has proved that the combination of enalapril and carvedilol prevented LVEF reduction in patients with diverse hematological malignancies undergoing intensive chemotherapy. The results of the trial could have important clinical implications since each year millions of patients with cancer are treated with chemotherapy worldwide and are surviving the disease in greater numbers. Nonetheless, the clinical relevance of this strategy for prevention of chemotherapy-induced cardiac damage should be confirmed in larger future studies.

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FIGURE LEGENDS

Figure 1. Flow diagram of the OVERCOME study. Eighty-one percent of all eligible patients during a 2-year period were enrolled in the study and randomized to the intervention or control groups.

Figure 2. Change from baseline in LVEF in acute leukemia patients undergoing chemotherapy in the intervention and control groups. While no differences were observed in the intervention group, patients in the control group had a 6.7% absolute decrease in their mean LVEF (p=0.025), with all but 3 patients having some degree of LVEF reduction. Values are mean±SEM.

Table 2. Anticancer treatment received by patients prior and during the study period.

	Intervention (n=45)	Control (n=45)	p
Radiotherapy			
Prior, n (%)	6 (13)	2 (4)	0.27
During study, n (%)	6 (13)	2 (4)	0.27
Total, n (%)	12 (27)	4 (9)	0.05
Chemotherapy			
Prior, n (%)	27 (60)	27 (60)	1.00
No. of lines of therapy	1.4 ±1.6	1.6±1.9	0.47
During study, n	45 (100)	45 (100)	1.00
No. of Cycles	1.73±1.5	1.44±0.8	0.27
Anthracyclines			
Prior, n (%)	19 (42)	17 (38)	0.67
Dose, mg/m^2	151±208	108±150	0.26
During study, n (%)	18 (40)	18 (40)	1.00
Dose, mg/m^2	139±188	133±182	0.87
Total, n (%)	37 (82)	35 (78)	
Dose, mg/m^2	290±189	241±162	0.15
HSCT during study, n (%)	37 (82)	34 (78)	0.76

Table 1. Baseline clinical differences between groups

	Intervention (n=45)	Control (n=45)	p-value
Age, years	49.7±13.9	50.9±13.2	0.67
Women, n (%)	18 (40)	21 (47)	0.52
BSA, m^2	1.86±0.26	1.83±0.21	0.62
Hypertension, n (%)	6 (13)	8 (18)	0.77
Hypercholesterolemia, n (%)	7 (16)	3 (7)	0.32
Statin treatment, n (%)	4 (9)	2 (4)	0.68
Diabetes, n (%)	3 (7)	1 (2)	0.62
Smokers, n (%)	13 (29)	4 (9)	0.03
Patient cohort, n (%)			1.00
Acute leukemia	18 (40)	18 (40)	
Autologous PBSCT	27 (60)	27 (60)	
SBP, mm Hg	118±17	118±16	1.00
DBP, mm Hg	73±12	74±10	0.66
HR, beats per min	75±12	78±13	0.24
eC_{Cr}, mL/min	105±30	100±30	0.30
Hemoglobin, g/L	107.8±17	108±20	0.97
TnI, ng/mL	0.013±0.008	0.013±0.010	0.80
BNP, ng/L	19 (9, 38)	21 (12, 35)	0.88
LVEF, %	62±5.9	63±5.9	0.50

BNP: Brain natriuretic peptide; BSA: Body surface area; DBP: Diastolic blood pressure; eCCr: estimated creatinine clearance rate by the Cockcroft-Gault formula; HR: Heart rate; HSCT: Hematopoietic stem cell transplantation; LVEF: Left ventricular ejection fraction; SBP: Systolic blood pressure; TnI: Troponin I.

Table 4. Clinical endpoints

	Enalapril + Carvedilol	Control	p-value
Premature end of the study, n (%)	3 (6.7)	11 (24.4)	0.02
Total mortality, n (%)	3 (6.7)	8 (17.8)	0.11
Death or heart failure, n (%)	3 (6.7)	10 (22.2)	0.036
Death, heart failure or final LVEF<45%, n (%)	3 (6.7)	11 (24.4)	0.020
≥10% decrease in LVEF with a final LVEF<50%, n (%)	2 (4.8)	2 (5.4)	0.90
Heart failure or ≥10% decrease in LVEF, n (%)	4 (9.5)	7 (19)	0.22
Severe adverse events*, n (%)	9 (20)	15 (33)	0.15

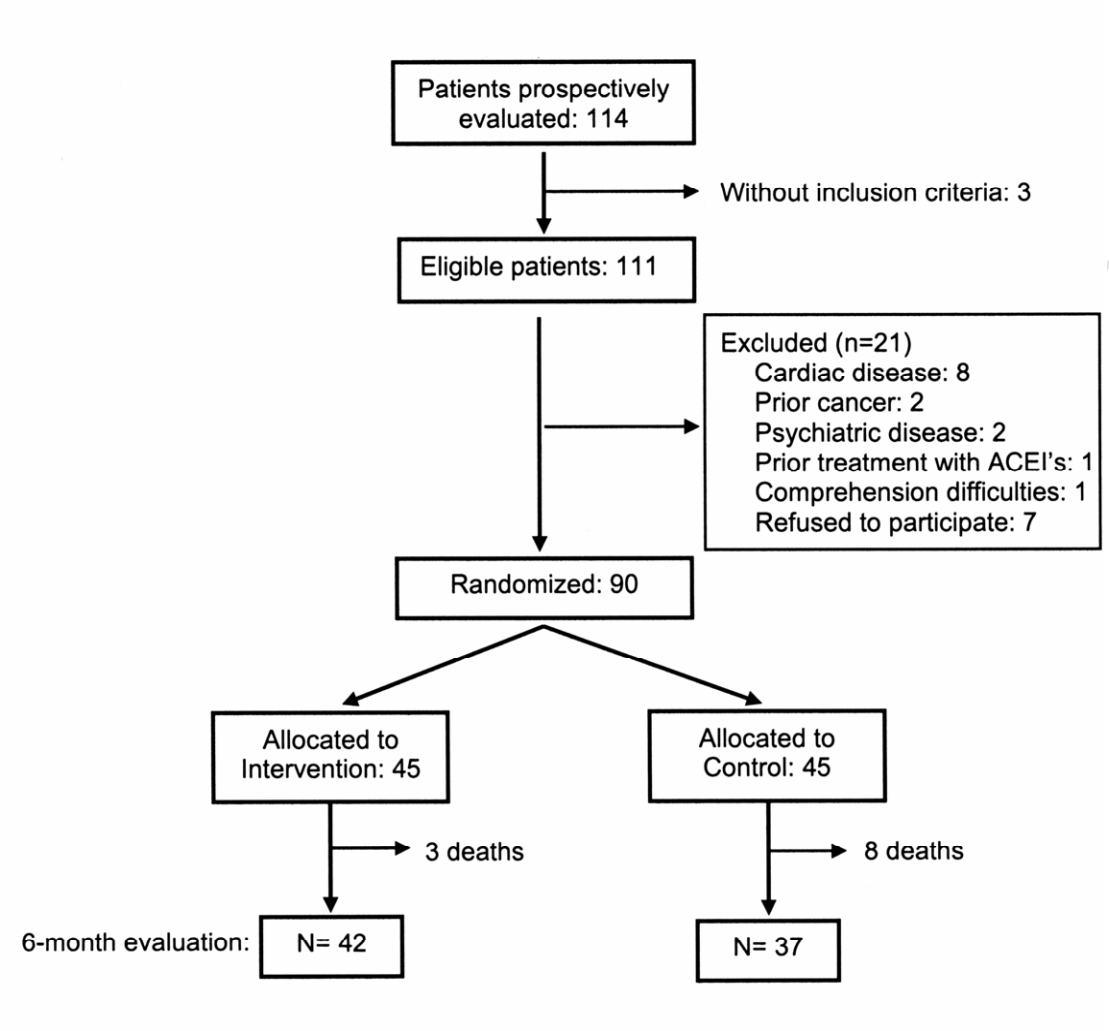
* defined as a serious adverse event that resulted in death or was life-threatening.

Table 3. Differences in the change in LVEF between the intervention and control groups.

	Enalapril + Carvedilol	Control	Intergroup Difference	p-value
Echocardiography				
LVEF, %	N=42	N=37		
Baseline	61.67±5.11	62.59±5.38		
6 months*	-0.17 (-2.24 to 1.90)	-3.28 (-5.49 to -1.07)	-3.11 (-6.10 to -0.11)	0.04
CMR				
LVEF, %	N=31	N=27		
Baseline	56.00±6.00	60.18±7.16		
6 months*	0.36 (-2.41 to 3.13)	-3.04 (-6.01 to -0.07)	-3.40 (-7.43 to 0.63)	0.09

* 6-month change from baseline in absolute LVEF, mean (95% CI).

CMR: Cardiomagnetic resonance imaging; LVEF: left ventricular ejection fraction.


Patients prospectively evaluated: 114
Without inclusion criteria: 3
Eligible patients: 111
Excluded (n=21)
Cardiac disease: 8
Prior cancer: 2
Psychiatric disease: 2
Prior treatment with ACEI's: 1
Comprehension difficulties: 1
Refused to participate: 7
Randomized: 90
Allocated to Intervention: 45
Allocated to Control: 45
3 deaths
8 deaths
6-month evaluation:
N= 42
N= 37