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Cellular Autotransplantation for Ischemic and Idiopathic Dilated Cardiomyopathy. Preliminary Report

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Background. Heart failure is highly prevalent among patients >65 years old. The incidence increases starting at ~45 years of age. Recent therapeutic advances have included stem cell transplantation in the affected areas of the myocardium in order to improve perfusion and myocardial performance.

Methods. Between July 13, 2004 and August 31, 2005, 39 procedures were undertaken in 34 male and 5 female patients, with a mean age of 53.6 ± 9.08 years (range: 35–71 years old), suffering from terminal heart failure and without any other therapeutic alternative. Thirty four cases presented ischemic cardiomyopathy and five presented idiopathic dilated cardiomyopathy. All patients were treated with autologous stem cell transplantation obtained from the peripheral blood supply through hemophoresis and implanted by means of a left anterior thoracotomy via intramyocardial injection. Functional class, ejection fraction and myocardial perfusion were analyzed preoperatively and postoperatively.

Results. Seven patients presented ventricular fibrillation during the procedure, requiring defibrillation. Two patients died due to intractable arrhythmias during the perioperative period; the remaining patients are currently participating in a rehabilitation program with a favorable evolution. A mid-term follow-up has been completed in 27 patients. Preoperatively, the functional class for 26 of these patients was III. Postoperatively, functional classes are II in 5 cases and I in 15 patients at the mid-term evaluation with ejection fraction improvements of 37.7 ± 14.2 to 42.15 ± 5.9.

Conclusions. Cell therapy is a safe and useful procedure in selected patients with ischemic and idiopathic dilated cardiomyopathy.

Key Words: Stem cell, Cell therapy, Heart failure, Cell transplantation, Ischemic cardiomyopathy, Idiopathic dilated cardiomyopathy.

Introduction

Heart failure (HF) is a highly prevalent disease. Almost 10% of all octogenarians are affected, but the incidence of HF cases increases 2-fold for every decade of life after the age of 45 years (1). This situation is relevant to our country where the primary cause of death is heart disease (2). In our hospital within the Department of Heart Failure Services, we have initially observed a mortality rate of 53% after 6 years for patients with dilated cardiomyopathy and of 36% for patients presenting ischemic cardiomyopathy with severe heart damage (3), but now in both ischemic cardiomyopathy and dilated cardiomyopathy, the mortality rate at 12 months is 63% in our patients. Both are the leading causes of HF worldwide.

Due to advances in cell culture, gene therapy and other technological improvements, a recent development has involved research protocols in which stem cells are introduced into the irreversibly injured myocardium in order

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to obtain its recuperation and where the transmission of infectious disease is avoided through the use of autologous transplantation (4).

In terminal HF, cell transplantation may be used solely or in combination with other surgical procedures such as coronary artery bypass graft surgery (5), with the purpose of stimulating cell proliferation and angiogenesis or of increasing the new cell population in the affected myocardium in order to improve heart function (6).

Materials and Methods

A longitudinal, prospective, comparative study approved by Scientific and Ethical Committees was carried out by the authors in order to evaluate the effect of CD34+ cell autotransplantation in hearts of patients affected by dilated or ischemic cardiomyopathy and who were treated in the Heart Failure Service of our hospital.

Inclusion Criteria

Subjects of both genders and who accepted to participate in the protocol and signed an informed consent were included in the study. These patients were between 30 and 70 years of age. They suffered from terminal heart failure due to ischemic or dilated cardiomyopathy that was clinically diagnosed and that corroborated with complementary studies including cardiac catheterization with global or segmental alterations in mobility in echocardiographic or nuclear medicine evaluations, and/or myocardial ischemia demonstrated in nuclear medicine perfusion assays. All patients had received conventional therapy for heart failure.

Exclusion Criteria

Not included in the protocol were patients who declined to participate, those who did not suffer from heart failure, or those cases with intractable arrhythmias. Also not included were patients with valvular heart disease or patients who had undergone any revascularization procedure during the 6 months prior to evaluation.

Patients with systemic diseases such as hypertension, diabetes mellitus, electrolyte imbalances, creatinine levels >2.5 mg/dL, neoplasia or any acute inflammatory disease were not included. Patients for whom cell implantation was not feasible were excluded.

Cell Preparation

The leukocyte population was increased through the use of granulocyte-stimulating factor (GSF) using a dose of 10 μg/kg administered subcutaneously for 4 days in order to obtain a leukocyte count of 15,000/mm^3, and stem cells were obtained from the peripheral blood supply via hemophoresis with a 13.5-Fr Hickman catheter. In addition, blood samples were obtained in order to run basal studies and included complete hematic biometry, glucose, urea and creatinine levels, serum electrolytes, hepatic functional tests, prothrombin time, partial activated thromboplastin time, thrombin time, and creatine kinase. The same studies were conducted again after harvesting stem cells. Subsequently, harvest of peripheral stem cells was carried out with a cell count of $3-5 \times 10^9$/L in a volume of no more than 60 cc. Collected cells were frozen to a temperature of -4 to -7°C until used.

Stem cell implantation was done under general anesthesia and after conventional monitoring for open-heart surgery (electrocardiography surveillance, arterial line, central venous catheter, and vesical catheterization), asepsis and antisepsis procedures were carried out, and the surgical field was isolated with sterile drapes.

Surgical approach was made via a left anterolateral thoracotomy with a longitudinal pericardiotomy, and remaining scars from previous surgical procedures were removed in order to expose the myocardium for the injection of the stem cells.

Cell implantation was made by means of an intramyocardial injection in the selected areas now directly visible. One-cc sterile syringes were used and each implantation consisted of 0.2 mL. A mean of 20 ± 2 implants were planned for the inferior, anterior, and lateral faces of the ventricle wall. The minimal distance between each injection was 5 mm and the maximum distance was 7 mm. Once the procedure was concluded, the chest was closed in the conventional manner after applying two chest drainage tubes.

For postoperative control, all patients were transferred to the Postoperative Intensive Care Unit with a fast track extubation protocol (within a range of 6 h postoperatively).

At the mid-term follow-up, all patients were evaluated for functional class according to the New York Heart Association (NYHA) classification and to the Canadian Cardiovascular Society scale for severity of angina. In addition, 6-min walking tests as well as electrocardiographic, echocardiographic and nuclear medicine tests were carried out in order to compare pre- and postoperative status of the patients and to corroborate the efficacy of the procedure in the improvement of functional class, ejection fraction, myocardial perfusion, and incidence of arrhythmias.

Results

Between July 13, 2004 and August 31, 2005, 39 procedures were carried out in 34 male and 5 female patients, with a mean age of 53.6 ± 9.08 (range: 36–71 years old). Thirty-four cases presented ischemic cardiomyopathy and five presented idiopathic dilated cardiomyopathy.

Characteristics of the first 27 patients for whom the mid-term follow-up of clinical and echocardiographic evaluations