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Five-Year Follow-up of the Local Autologous Transplantation of CD133+ Enriched Bone Marrow Cells in Patients with Myocardial Infarction

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Abstract

Background: The implantation of a CD133+ bone marrow cell population into an ischemic myocardium has emerged as a promising therapeutic modality for myocardial regeneration and restoration of ventricular contractility. While previous studies have documented the short-term safety and efficacy of CD133+ cell transplantation in patients with acute myocardial infarction, there are few reports of long-term follow-up results. Here, we present the results of long-term follow-up of our acute myocardial infarction patients who were treated with intramyocardial injection of CD133+ cells after coronary bypass graft.

Methods: After five years, 13 patients in the cell transplantation group and 5 patients in the control group underwent safety and efficacy investigations by New York Heart Association classification and two-dimensional echocardiography (2D echo).

Results: During the five-year study period, no major cardiac adverse events were reported among patients who received CD133+ stem cells. Regarding efficiency, we observed no statistically significant treatment effects for the echocardiographic parameters [left ventricular end-diastolic and end-systolic volumes, and resting ejection fraction] measured during the follow-up period. However, detailed analysis of regional wall motion revealed an improvement in the Wall Motion Score Index from baseline to the six month follow-up, which was maintained during the follow-up period.

Conclusion: Taken together, the long-term results of the present study indicate that transplantation of CD133+ is a safe and feasible procedure; however, we could not show any major benefits in our patients. Thus, this issue needs to be addressed by conducting other studies with more patients.

Keywords: CD133+ cells, follows up, myocardial infarction, transplantation


Introduction

Despite permanent advances in coronary revascularization modalities, acute myocardial infarction (AMI) following coronary artery disease remains a major worldwide medical problem. Currently, interventional revascularization and coronary artery bypass grafting (CABG) constitute the mainstay of treatment for this group of patients. However, in a substantial number of patients the ischemic damage to the heart results in myocardial necrosis and the eventual development of heart failure. While available medical therapies are unable to regenerate dead myocardium, novel treatments are necessary to restore impaired muscle function.

In recent years, implantation of autologous bone marrow stem cells (BMSC) into ischemic myocardium has emerged as a promising therapeutic modality for myocardial regeneration and restoration of ventricular contractility. While a variety of cell populations have been investigated in this regard, the optimal cell type for cardiovascular regeneration in humans remains to be identified. A population of bone marrow cells expressing the CD133 marker has been considered as highly potent cells capable of self-renewal and differentiation into various hematopoietic and mesenchymal cells. While previous studies have documented the short-term safety and efficacy of CD133+ cell transplantation in patients with AMI, data regarding the long-term safety of such therapy are few.

The aim of the present study was to investigate the efficacy and left ventricular (LV) functional improvement after intramyocardial injection of CD133+ in patients with AMI who were candidates for CABG at up to five years of follow-up.

Patients and Methods

In the present cohort study, enrollment of patients began in June 2004. We recruited patients with recent myocardial infarction who were candidates for CABG. The Institutional Review Board of Royan Institute and Tehran Heart Center Hospital, Tehran University of Medical Sciences, Iran approved the study. Informed consent was obtained from all patients.

The inclusion, exclusion and studied methods have been described previously. Briefly, under local anesthesia, bone marrow cells were aspirated from the iliac crest one day prior to surgery and by using AC133/1 monoclonal antibody directly labeled to microbeads (MACS, Miltenyi Biotec GmbH, 172-01, Bergisch...
Gladbach, Germany), CD 133 cells were isolated. The following day during CABG, the purified cells were injected along the border zone of the necrotic area using a 22-gauge needle.

Follow-up evaluations
In order to assess the long-term safety of CD133+ transplantation we monitored patients for evidence of any serious complications, including arrhythmias, neoplasia, myocardial infarction, cerebrovascular events, bleeding and death. In addition, during the follow-up period, patients underwent clinical examinations, were classified subjectively according to the New York Heart Association (NYHA) classification, and had two-dimensional echocardiography (2D echo) performed. Sustained cardiac arrhythmia was detected using 24-hour holter monitoring. We performed 2D echo (Vivide 7 dimension, VingMed, GE) measurements for global and regional contractility studies. LV function was assessed by analysis of LV echocardiography. Another investigator verified all echocardiographic data.

Statistical analysis
All analysis was conducted using SPSS statistical software (version 15; SPSS Inc., Chicago, IL, USA). The data of functional assessments were expressed as median (range). Comparison of baseline characteristics between groups was performed using non-parametric methods with the Mann-Whitney test, when appropriate. A P value of less than 0.05 was statistically significant.

Results
Study group
Beginning from June 2004, 27 patients with AMI (median 75 days, range 18–90 days) who underwent standard CABG were selected to receive either an intramyocardial injection of CD133+ (BMC group, n = 18; mean: 1.77 × 10^6 ± 1.14 × 10^6 CD133+ cells) or cell vehicle media (control group, n = 9) into the ischemic area. Among these patients, 13 in the BMC group (mean age 47.31 years) and 5 in the control group (mean age 55.6 years) underwent long-term safety and efficacy investigations. Regarding vessel involvement, all patients (BMC and control groups) had affected left anterior descending coronary artery. In addition, 13 patients in the BMC group had left circumflex coronary artery involvement and 9 had right coronary artery involvement. In the control group, 5 patients also had left circumflex coronary artery involvement and 2 had right coronary artery involvement.

No significant differences were evident in any of the baseline clinical and echocardiographic parameters between the BMC and control groups. Among the patients excluded from the study (n = 9), 7 (5 in the BMC group and 2 in the control group) refused to participate and 2 patients, both of who belonged to the control group, died during follow-up.

Adverse events
During the five-year study period, no major cardiac adverse events were noted among patients who received CD133+ stem cells. Holter electrocardiogram did not reveal any relevant ventricular arrhythmia at any time point. Atopic tissue formation such as teratogenic tumor or bone were not detected in the myocardium on chest radiographic or echocardiographic scanning and none of the patients required any further coronary revascularization during the follow-up.

While none of the patients in the BMC group had CCU admissions or hospitalizations, three patients in the control group had CCU admissions (two expired). A 67-year-old patient in the control group died following a cerebrovascular event 2.5 years after surgery. Another patient, a 54-year-old man, encountered two CCU admissions and died of a myocardial infarction three years after surgery. No patient had an autopsy performed. The remaining patients in both the control and BMC groups were alive and well at the time of preparation of this paper.
The NYHA indices for classification of physical activity for cardiac patients improved in the BMC group during the follow-up period. As compared with baseline, the NYHA class improved in nine patients in the BMC group of which in three patients the NYHA class improved from class III to class I and in the remaining six improved from class II to class I. These changes have persisted at the five-year follow-up in which only three patients reported NYHA class II. The remaining patients were categorized as NYHA class I.

Data regarding LV end-diastolic and end-systolic volumes and resting ejection fraction, at baseline and long-term follow-up, are presented in Figure 1. Quantitative analysis showed that the median left ventricular ejection fraction (LVEF) measured by echocardiography was significantly higher than the preoperative baseline (35, range 20 – 45) in the targeted area for cell therapy at six months post-surgery (40, range 28 – 48, P < 0.05). Such differences were not evident at subsequent evaluations measured at 36 (median 35, range 25 – 45, P = 0.9) and 60 months (median 32.5, range 25 – 45, P = 0.74) after treatment. However, detailed analysis of regional wall motion revealed an improvement in the Wall Motion Score Index (WMSI) from baseline to six months follow-up which was maintained during the five years of follow-up as follows: baseline: median 2.4, range 1.43 – 3.43; six month follow-up: 1.64, range 0.29 – 2.86; 36 month follow-up: 1.78, range 0.2 – 3.44, and 60 month follow-up: 2, range 1.37 – 2.12, P < 0.01. Also regarding LV diastolic and systolic volumes, no statistically significant treatment effect was observed for these parameters during five years (Figure 1).

Discussion

The results of the present study indicate that this procedure was safe and feasible at midterm and long-term follow-up. Regarding clinical effectiveness, with the exception of the NYHA and WMSI indices, no significant improvements in other cardiac function parameters at long-term follow up were observed.

Formations of atopic tissue in the myocardium along with malignant arrythogenesis are two major concerns associated with stem cell infusion into the ischemic myocardium. Since pluripotent stem cells have the capacity to propagate and differentiate into various tissue cells, there is a possibility that a hamartoma, teratogenic tumor, bone, or other atopic tissue could form in the heart following stem cell transplantation.21 Also, previous experimental studies have demonstrated that transplanted progenitor cells may provide the substrate for electrical instability, leading to malignant arrhythmia.22 However, clinical trials investigating the safety of intramyocardial implantation of CD133+ cells into the ischemic heart have yielded a safe clinical profile for such treatment, and no evidence of intramyocardial tumor development and calcification or ventricular arrhythmia have been revealed in these studies.10,13,16–20 While most of these studies have included short- and mid-term follow-up periods, studies investigating the long-term effects of such modalities are few. The five year follow-up data of the Rostock Stem Cell trial did not reveal any major adverse events (death, myocardial infarction or cardiac reintervention), ventricular arrhythmia or any adverse tissue changes seen with computed tomography.18 The results of the present study are in line with the Rostock trial and confirm the long-term safety of the current treatment strategy, albeit with a limited number of patients to date. However, it is possible that some latent adverse effects related to the cell therapy may not have been detected because of the low numbers of our patients, the scheduled timing of our follow-up examinations, and their limited terms and sensitivities. Therefore, extended clinical trials are required in order to confirm the present results.

Most studies investigating the clinical efficiency of intramyocardial infusion of CD133+ cells have demonstrated a significant increase in LVEF, improvement in tissue perfusion and cardiac function in patients receiving transplanted cells in comparison with a control group.10,13,19,20 However, such studies have investigated the cardiac function of patients during short-term periods and no study to date has yielded the long-term efficacy results of CD133+ cell transplantation. In the present study, while significant improvements were evident in patients during the first 6 months following transplantation, such differences were not evident between the clinical parameters at both 36 and 60 months follow-up in comparison with baseline.

While studies regarding long-term efficacy of CD133+ cell transplantation are lacking, long-term data of other cell populations are available. The three year follow-up results from the ASTAMI study investigating the efficacy of intracoronary injection of autologous mononuclear bone marrow cells did not demonstrate any significant differences between the treatment and control groups in change of global LV systolic function parameters.23 In contrast, data from the BALANCE study exploring the five-year clinical outcome of patients receiving autologous bone marrow cell transplantation revealed significant and longstanding improvements of LV performance in patients after AMI.24 While the exact reason is unclear, possible explanations for these discrepancies include the selection of different patient subgroups, various cell populations, diverse methods of delivery, different treatment timing and the use of inappropriate end points.

In conclusion, the long-term analysis of intramyocardial transplantation of CD133+ bone marrow cells following CABG in patients with AMI indicates the procedure to be safe and not associated with any major side effects. However, the therapy maintained global LV function or clinical outcome improvements but did not increase them during long-term follow up. Since we could not compare the cell and control groups with one another, we could not rule out the possibility that the observed effects were due to the CABG procedure and not CD133+ implantation. Because of the relatively small sample size of the current study and inability to compare the results with the control group, further studies with greater sample sizes and matched control groups are required to confirm the findings of the present study.

Acknowledgments

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