Improved outcome with repeated intracoronary injection of bone marrow-derived cells within a registry: rationale for the randomized outcome trial REPEAT

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Aims	Regenerative therapies have evolved as a promising new option in the treatment of post-infarction heart failure. A major limitation of intracoronary application of autologous bone marrow-derived mononuclear cells (BM-MNCs) is that homing of the applied cells is profoundly reduced in patients with post-infarction heart failure compared with patients with acute myocardial infarction. However, early pilot and also randomized controlled trials have demonstrated significant improvements in overall cardiac function. The aim of the present analysis was to quantify a potential mortality risk reduction and reduced hospitalization in order to provide data for a prospective outcome trial.
Methods and results	The results of an ongoing single-centre registry including 297 post-infarction heart failure patients suggest that repeated intracoronary application of autologous bone marrow-derived cells is associated with a significant better 2-year survival compared with a single BM-MNC application (2-year survival 93.6 vs. 84.0%, $P = 0.03$). Likewise, mortality is significantly lower at 2-year follow-up compared with the mortality estimated by the use of the Seattle Heart Failure Model (SHFM) in patients receiving repeated BM-MNC application (observed mortality 6.4%, predicted mortality 16.2%, $P = 0.02$). Although the trend persisted at 3-year follow-up, the mortality reduction was no longer statistically significant between single and repeated treatment (mortality 21.9 vs. 13.7%, $P = 0.06$).
Conclusion	Repeated intracoronary administration of BM-MNC appears to be associated with improved clinical outcome compared with single treatment at 2 years. This registry provides the rationale for the design of the multicentre randomized, controlled, open-label REPEAT trial, which prospectively compares the effects of single vs. repeated intracoronary application of autologous BM-MNC on total and SHFM-predicted mortality in patients with chronic post-infarction heart failure.
Keywords	Chronic heart failure • Ischaemic cardiomyopathy • Cell therapy • Outcome trial

Introduction

The prevalence of chronic heart failure continues to increase.[1] One major cause for chronic heart failure is coronary artery disease with one or multiple previous myocardial infarctions, which, due to recent advances in therapies, more and more patients survive.[2] However, as a consequence, more patients develop post-

infarction heart failure due to adverse left ventricular remodelling. The presence of chronic post-infarction heart failure is associated with massively reduced life expectancy and quality of life. For example, patients suffering from chronic post-infarction heart failure require frequent hospitalizations due to cardiac decompensation. In fact, from ~15 millions heart failure patients in Europe, 1.5 millions require at least 1 hospitalization for heart failure per

year, which also causes tremendous expenses of 2% of the overall healthcare costs.

Cell therapy offers the attractive option of improving left ventricular function and reducing adverse left ventricular remodelling.[3] Mechanistically, it is currently assumed that the beneficial effects of autologous bone marrow-derived mononuclear cells (BM-MNC) are mediated by the release of paracrine factors from the retained cells which enhance endogenous repair mechanisms and improve the function of the coronary microcirculation (for review see Ref. [4]).

So far, >3000 patients with cardiovascular diseases were treated with adult progenitor cells worldwide, and no serious adverse side effects were reported. In recent meta-analyses, treatment with bone marrow-derived progenitor cells was associated with a significantly reduced mortality in patients with acute myocardial infarction (AMI).[5,6] However, limited data are available about effects of intracoronary infusion of autologous BM-MNC in patients with old, at least 3 months old myocardial infarction and post-infarction heart failure. Our own randomized, cross-over trial showed a significant, albeit modest improvement by absolute 3% in left ventricular ejection fraction (LVEF) at 3 months after intracoronary infusion of bone marrow-derived cells, but no change in the control group.[7] In a smaller, non-randomized Danish trial, 32 patients were treated with two repeated intracoronary infusion of BM-MNC. The symptom status of these patients was significantly improved at 12 months, and there was a tendency towards fewer hospitalizations for heart failure compared with an observational period of 12 months prior to participation in the trial.[8] However, there are no long-term mortality data in large patient populations with post-infarction heart failure, but such studies are required to ultimately assess the value of this treatment modality with a view to it becoming standard clinical practice. For this purpose, we assessed the clinical outcome of 297 consecutive patients receiving intracoronary administration of BM-MNC for chronic post-infarction heart failure between 2002 and 2008 at the Goethe University Frankfurt, with the aim to generate the basis for a randomized trial. Observed mortality was compared with the Seattle Heart Failure Model (SHFM)-predicted mortality, which was shown to be an accurate long-term estimate, including contemporary pharmacological and device therapies.[9]

Methods

Patients

The registry cohort comprises all 297 consecutive patients included into an ongoing registry to assess the effects of intracoronary administration of BM-MNC for treatment of chronic post-ischaemic heart failure due to an at least 3 months old myocardial infarction at a single centre, the Goethe University in Frankfurt, Germany, between January 2002 and December 2008. Patients were eligible for inclusion into the study if they suffered from stable chronic heart failure symptoms NYHA ≥II, had a previous, successfully revascularized myocardial infarction at least 3 months before BM-MNC administration and had a well-demarcated region of left ventricular dysfunction on echocardiography. Exclusion criteria for intracoronary cell treatment were the presence of acutely decompensated heart failure with NYHA class IV, an acute ischaemic event within 3 months prior to inclusion into the registry, a history of severe chronic diseases, documented cancer within the preceding 5 years, or unwillingness to participate.

After establishing the safety of intracoronary BM-MNC administration in 54 patients, from the beginning of 2004, all following patients were invited to receive repeated BM-MNC administration at their clinical follow-up appointment at 3−6 months after the first treatment, in order to assess a potential additive effect of repetitive cell administration. Thus, 111 of the 297 patients received an additional BM-MNC administration at 3−6 months after the initial treatment. The main reason for not repeating BM-MNC therapy was unwillingness to stay in hospital for the second BM-MNC treatment, or long-distance travelling.

The ethics review board of the Goethe University in Frankfurt, Germany, approved the protocol, the study is registered with www.clinicaltrials.gov (NCT00962364), and all patients gave written informed consent to participate in this prospective registry. The study complies with the Declaration of Helsinki.

Preparation and administration of bone marrow-derived mononuclear cells

Bone marrow aspirate (50 mL) was obtained from the iliac crest under local anaesthesia in the morning of the cell administration day (repeated treatment patients received a second bone marrow aspiration and *de novo* cell isolation procedure at the time of the second cell treatment). BM-MNC were then isolated by Ficoll density-gradient centrifugation, as previously reported.[7,10] A mean of $190 \pm 110 \times 10^6$ cells were available for the intracoronary infusion procedure after processing. For cell administration, arterial puncture was followed by the administration of 5000−7500 U of heparin. BM-MNC were infused into the vessel supplying the most dyskinetic left ventricular area by means of the stop-flow technique with an over-the-wire balloon catheter, as previously described.[10] In all but one patient, the target vessel for cell therapy was a native coronary artery.

Follow-up

Clinical data, medication, and laboratory data were prospectively collected by study nurses. Follow-up visits were scheduled at 3 months after each cell application, and then at 12 months after the first cell application, and were performed by physicians, whereas follow-up telephone calls were performed by study nurses at 24, 36, and 48 months.

Mortality and mode of death were adjudicated by means of reviewing medical records by the study physicians. Mode of death was classified as sudden death (unexpected death in a clinically stable patient, typically within 1 h of symptom onset, from documented or presumed cardiac arrhythmia, and without a clear non-cardiovascular cause), pump failure (progressively reduced cardiac output and failure of organ perfusion), noncardiac death or not classifiable. Implantation of left ventricular assist devices or cardiac transplantations ($n = 2$) was categorized as death due to pump failure at the time of surgery. All events were prospectively ascertained and classified by physicians unaware of the patients' SHFM scores.

Calculation of the Seattle Heart Failure Model score

The SHFM is a validated risk prediction model based on routinely collected clinical variables, including age, gender, aetiology of cardiomyopathy (ischaemic origin), heart rate, systolic blood pressure, ejection fraction, medication (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, aldosterone blocker, beta-blocker, statins, as well as diuretic type and daily dose, and allopurinol), and laboratory values (serum sodium, total cholesterol, haemoglobin, percent lymphocytes, uric acid).[9] In addition, the presence of any implantable device [pacemaker, implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy] is included into the calculation of both, the SHFM Score as well as the SHFM-predicted

Table I Baseline characteristics of the study cohort

	Single Tx (n = 186) Median (IQR)	Repeated Tx (n = 111) Median (IQR)	P value (single vs. repeated)
Age (years)	62 (55–68)	65 (57–72)	**0.004**
Sex (male/female; n)	167/19	95/16	0.35
Weight (kg)	81 (72–90)	78 (71–88)	0.13
SHFM score	0.3 (−0.1–0.8)	0.4 (−0.1–1.0)	0.39
NYHA class n (%)	I: 27 (15) II: 84 (45) III: 69 (37) IV: 6 (3)	11 (10) 40 (36) 59 (53) 1 (1)	**0.04**
Heart rate (b.p.m.)	66 (60–75)	68 (61–76)	0.63
Systolic blood pressure (mmHg)	112 (100–130)	112 (100–135)	0.17
Hypertension (%)	69	74	0.43
Hypercholesterolaemia (%)	86	80	0.26
Diabetes (%)	30	32	0.61
Smoking (ever; %)	73	70	0.69
Family history (%)	53	54	0.97
Creatinine (mg/dL)	1.1 (1.0–1.4)	1.1 (0.9–1.4)	0.93
Peripheral artery occlusive disease (%)	12	16	0.39
Coronary artery disease (1/2/3 vessel disease; %)	23/30/47	23/28/49	0.55
Previous bypass operation (%)	38	42	0.46
Time from last AMI (months)	53 (13–122)	72 (18–156)	0.15
Atrial fibrillation on admission (%)	11	12	1.0
ICD (%)	24	23	1.0
CRT (%)	0.5	3.6	**0.05**
CRT-D (%)	5.4	2.7	0.28
Mitral regurgitation (grade)	1.0 (0.5–2.0)	1.0 (0.5–1.5)	0.33
Quantitative LVEF (%)	39 (29–47)[a]	36 (28–44)[b]	0.09
Sodium (mmol/L)	139 (137–141)	140 (138–142)	0.35
Haemoglobin (g/dL)	14 (13–15)	14 (13–15)	0.30
White blood count (/nL)	7 (6–9)	7 (6–9)	0.18
Lymphocyte count (%)	25 (21–27)	25 (21–27)	0.14
Creatinine (mg/dL)	1.1 (1.0–1.3)	1.1 (0.9–1.4)	0.94
Uric acid (mg/dL)	7 (6–8)	7 (5–9)	0.83
Cholesterol (mg/dL)	162 (136–189)	168 (139–194)	0.06
NT-proBNP (pg/mL)	770 (339–2522)[c]	1023 (426–2299)[d]	0.39
Antiplatelet therapy (%)	97	97	1.00
Oral anticoagulant therapy (%)	30	35	0.44
ACEI or ATRB (%)	95	96	0.58
Beta-blocker (%)	95	89	0.11
Diuretic (%)	83	87	0.41
Statin (%)	91	91	1.0
Aldosterone blocker (%)	43	48	0.47

[a] n = 156.
[b] n = 93.
[c] n = 183.
[d] n = 107.

mortality. However, NT-proBNP or BNP values are not included into the model.

Statistical analysis

Continuous variables are presented as median (interquartile range), unless otherwise noted. Analysis-of-variance testing was used for comparison of continuous variables between groups. Categorical variables were compared with the χ^2 test.

For survival analysis within the individual group, Kaplan−Meier analysis was used, including the standard error (SE) with the Greenwood formula. Furthermore, confidence intervals for survival rates were calculated using the log−log transformation. For comparison of

Table 2 **Cell characteristics**

	Single treatment (n = 186) Median (IQR)	Repeated treatment		P value (single vs. first repeated)	P value (first vs. second Tx)
		First Tx (n = 111) Median (IQR)	Second Tx (n = 111) Median (IQR)		
Cell number ($\times 10^6$ mononuclear cells)	168 (109−254)	151 (93−240)	123 (80−200)	0.20	0.07
SDF-1-induced migration capacity	90 (59−146)	97 (61−142)	104 (65−155)	0.72	0.61
Colony-forming unit capacity	23 (16−38)	20 (14−32)	20 (13−28)	0.02	0.29
$CD45^+CD34^+$ cells (%) (assay 1[a], n = 181)	2.1 (1.2−2.9) (n = 114)	1.8 (0.8−2.5) (n = 44)	2.0 (0.9−3.1) (n = 23)	0.34	0.92
$CD45^+CD34^+$ cells (%) (assay 2[a], n = 220)	1.3 (1.1−1.8) (n = 65)	1.3 (1.0−1.8) (n = 67)	1.4 (1.0−2.0) (n = 88)	0.99	0.90

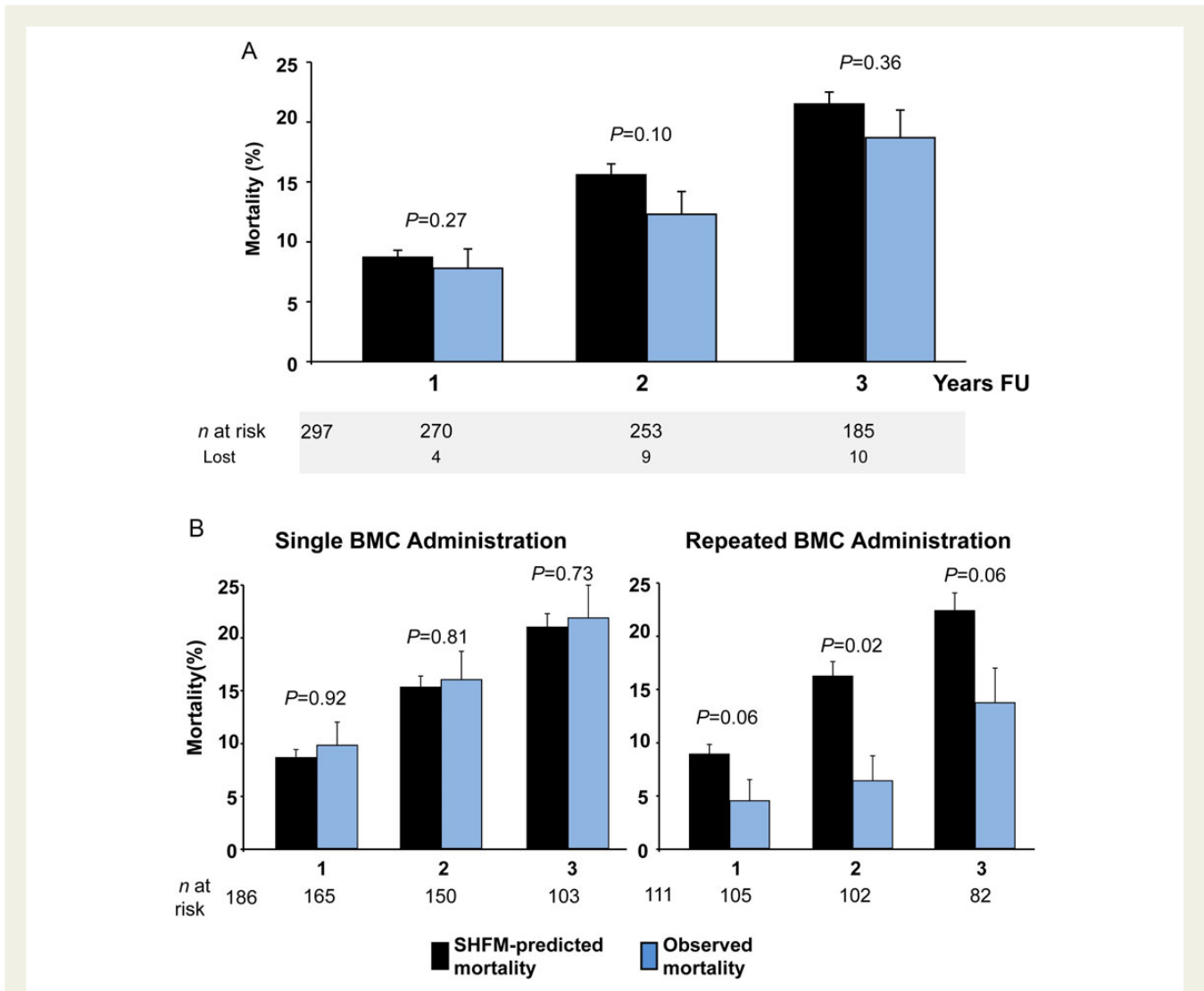[a]The FACS protocol and antibodies were changed during the ongoing registry.

Figure 1 (*A*) Seattle Heart Failure Model-predicted mortality (black) and observed mortality (blue) of the total study cohort. (*B*) Seattle Heart Failure Model-predicted mortality (grey) and observed mortality (black), separated by single and repeated treatment. Standard errors were derived from Kaplan−Meier analysis.
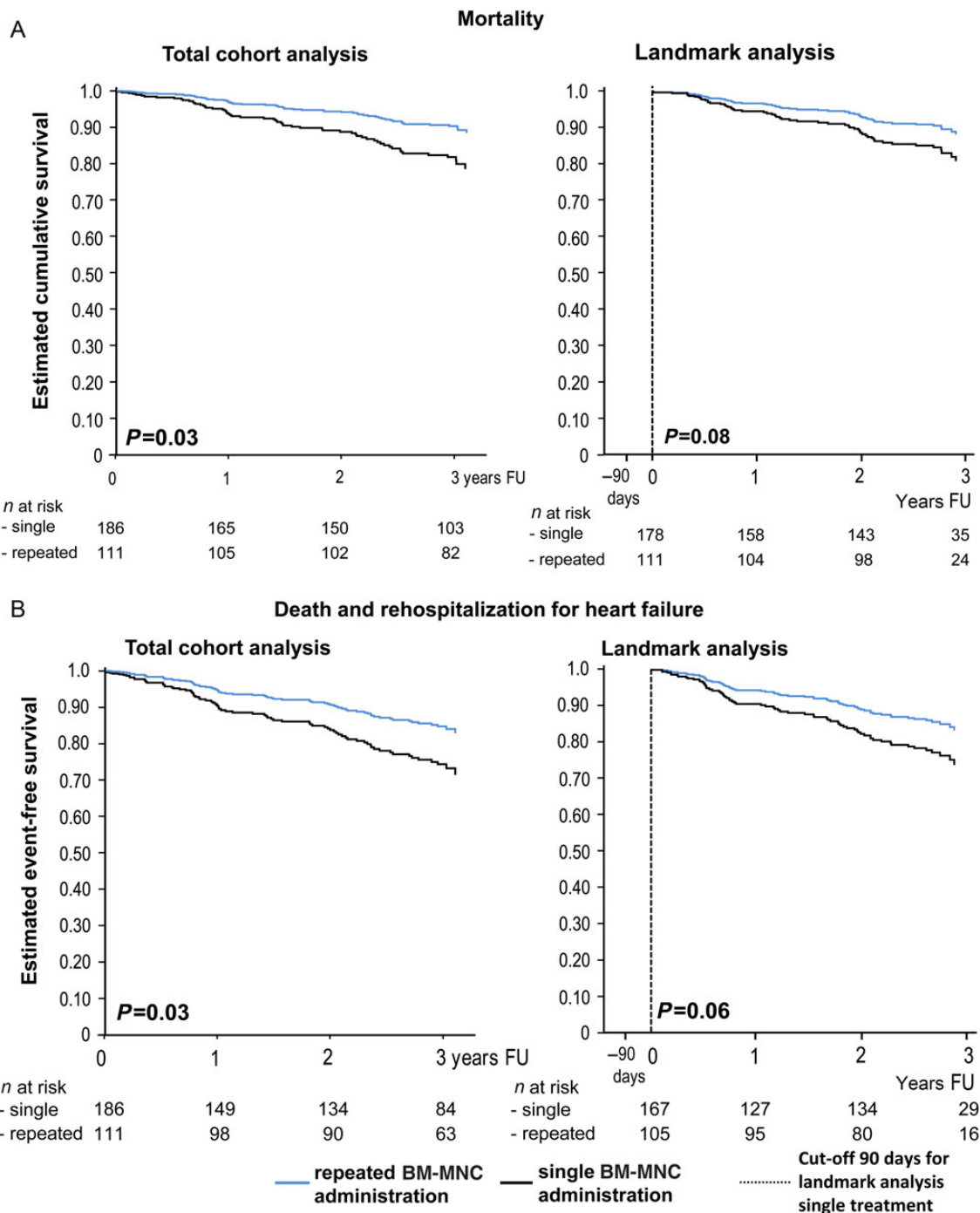
Figure 2 (*A*) Cox regression analysis for total mortality, adjusted for the Seattle Heart Failure Model score, in the entire study cohort (left) and the landmark analysis (right). Note that the reference time (90 days) for the landmark analysis is marked by a vertical line. (*B*) Cox regression analysis for the combined endpoint mortality and rehospitalization for heart failure, adjusted for the Seattle Heart Failure Model score, in the entire study cohort (left) and the landmark analysis (right). The reference time (90 days) for the landmark analysis is marked by a vertical line.

survival rates (*Figure 2*), a multivariable Cox proportional-hazards regression model was used, taking into account the covariates SHFM score, and the number of BM-MNC treatments. 95% confidence intervals for the hazard ratio (HR) were also calculated. Estimated survival curves were computed after fitting the Cox regression model. Landmark analyses were performed with a cut-off of 90 days in the

single treatment group, which was the earliest time for repeated treatment, and with the day of repeated cell treatment in the repeated treatment group.

The calculation of estimated survival by the SHFM score is based on a parametric (exponential) survival model.[9] Therefore, a likelihood ratio test can be defined and calculated for comparison between estimated

mortality according to the SHFM score and the pre-specified parameter in the survival model and observed mortality. Thereby, we compared the pre-specified coefficient of exp(SHFM) with a maximum likelihood estimator for the coefficient of exp(SHFM) from the new data in a comparable exponential model. The maximum likelihood estimator of the coefficient can be calculated as number of cases divided by the sum of observation time t_i multiplied with exp(SHFM) of the ith observed individual patient.

Statistical significance was assumed for *P* values of <0.05. Statistical analyses were performed with SPSS software (version 16.0), SAS software (version 9.4), and the comparison between estimated and observed mortality was performed with R, a language and environment for statistical computing (version 3.0.2).

Results

During 3-year follow-up, 58 patients died and 10 patients were lost to follow-up (3.3%). In detail, four patients were lost at 1-year follow-up and nine patients were lost at 2-year follow-up. The baseline characteristics of the 297 patients are summarized in *Table 1*, according to single or repeated treatment. The most recent myocardial infarction had occurred at a mean time of 88.5 months (median = 60 months) prior to intracoronary BM-MNC administration. All patients received optimal pharmacological treatment. Clinical characteristics did not differ at the time of first or second treatment in the repeated treatment group except for NYHA class, which was significantly improved at the time of repeated treatment (see Supplementary material online, *Table S1*). Characteristics of the applied BM-MNC were also comparable between the two treatment groups (*Table 2*). Total time at risk was 833 patient-years. Of note, baseline characteristics and SHFM score of the 10 patients lost to follow-up at 3 years did not significantly differ from the overall patient cohort.

Overall mortality of the study cohort was 7.8% [SE 1.6, 95% confidence interval (CI): 5.3–11.5%] at 1 year, 12.3% (SE 1.9, 95% CI: 9.4–17.1%) at 2 years, and 18.7% (SE 2.3, 95% CI: 14.7%–23.8%) at 3 years. Of the 58 patients who died up to 3-year follow-up, 30 patients died from progressive pump failure, 3 patients from sudden cardiac death, 2 from myocardial re-infarction, and 1 from pulmonary embolism. Ten patients died of non-cardiac death and cause of death could not be determined in 12 patients. One patient underwent heart transplantation and another received a left ventricular assist device. Both these patients were classified as death due to progressive pump failure. Patients who died during follow-up were significantly older, had increased heart rate, creatinine and NT-proBNP serum levels, and higher functional NYHA class, but lower systolic blood pressure and LVEF at inclusion into the registry (see Supplementary material online, *Table S2*). Moreover, SHFM score was higher in patients who died during the 3-year follow-up time, reflecting more advanced heart failure. This is also evident from more intensive medical therapy and more frequent presence of an ICD. Interestingly, patients who died had undergone repeated cell administration less frequently than survivors (*P* = 0.048).

Observed and model-predicted mortality

As illustrated in *Figure 1A*, observed mortality was consistently lower than model-predicted mortality throughout the 3-year follow-up period. Importantly, the difference between observed and model-predicted mortality was almost entirely driven by a profound mortality risk reduction in patients receiving repeated

administrations of BM-MNC, whereas patients receiving a single BM-MNC administration exhibited mortality rates similar to model-predicted mortality (*Figure 1B*). Most notably, SHFM-predicted mortality did not significantly differ between patients receiving repetitive administration of BM-MNC compared with those receiving only a single treatment. In addition, as summarized in *Table 1*, patients receiving repeated cell administration did not differ from patients receiving single treatment with respect to any of the baseline characteristics, except that repeatedly treated patients were significantly older, and had trends towards more advanced heart failure symptoms and an even lower LVEF compared with patients receiving single treatment. These data reduce the likelihood that selection bias towards less severe heart failure in patients receiving repeated BM-MNC.

Figure 2A illustrates the Cox regression survival curves adjusted for SHFM score, showing a significantly better outcome for patients receiving repeated BM-MNC treatment compared with the single BM-MNC treatment group (HR 0.53, 95% CI: 0.30–0.94, *P* = 0.03). In order to account for a survival selection bias for patients undergoing repeated cell administration, the analysis was repeated on a landmark basis. After censoring all patients who were dead (*n* = 7) or lost to follow-up (*n* = 1) until 3 months after the first cell administration, multivariable Cox regression analysis still suggests that repeated BM-MNC administration may be a predictor for improved survival (HR 0.59, 95% CI: 0.33–1.06, *P* = 0.08). Likewise, cox regression analysis for the combined endpoint death and rehospitalization for heart failure showed a significantly better event-free survival in the total cohort analysis (HR 0.59, 95% CI: 0.36–0.95, *P* = 0.03), and a strong trend towards better outcome for the repeated treatment group in the landmark analysis (HR 0.61, 95% CI: 0.37–1.01, *P* = 0.06; *Figure 2B*).

Discussion

The results of the present registry analysis demonstrate that observed mortality rates compare favourably with predicted mortality according to the SHFM score in patients receiving intracoronary administration of BM-MNC for treatment of chronic post-infarction heart failure. However, the reduction of observed compared with predicted mortality appears to be confined to patients receiving repeated cell administration.

The SHFM score, which uses widely available clinical variables to predict mortality in heart failure[9] and also incorporates the impact of concurrent medical and device therapy,[11,12] has been extensively validated in several patient cohorts including patients with chronic post-infarction heart failure. Given that patients providing informed consent to be included into a study (as also performed in the present registry study) will automatically have a lower risk than an unselected population, it is important to stress that validation of the SHFM has been performed in patients included into randomized trials, the largest of which being the Val-HeFT trial.[13] Importantly, 1-year (90.9%), 2-year (83.9%), and 3-year (77.4%) survival rates in Val-HeFT are essentially identical to those predicted for the study cohort of the present work, with 91% at 1 year, 87% at 2 years, and 80% at 3 years, respectively. Thus, the externally derived SHFM clinical risk predictor model appears to be appropriately suited to detect a potential role for intracoronary BM-MNC administration

to modify mortality in the patients with chronic heart failure of the present study.

The observation of the present study that risk reduction appears to be confined to patients receiving repeated cell administrations does not come as a surprise. Adverse left ventricular remodelling processes operate for years following an AMI, leading to an enlargement of the left ventricle with extensive fibrosis, which constitutes the pathomorphological substrate of post-infarction heart failure.[14] Given the limited plasticity of adult BM-MNC to contribute to contractile recovery of the infarct scar tissue,[15] one cannot expect a single BM-MNC administration to have a sustained effect on cardiac functional recovery. It is currently assumed that potential beneficial effects of autologous BM-MNC are mediated by the release of paracrine factors from the retained cells to enhance endogenous repair mechanisms and improve the function of the coronary microcirculation.[16,17] The data of the present study suggest that repeated intracoronary cell administrations are required to modify the chronic disease process in patients with chronic post-infarction heart failure with a median time lag of 60 months after the most recent AMI. However, we cannot comment whether intramyocardial injection of cells may also require repetitive treatment. The only other study which investigated repeated cell administration in the setting of chronic heart failure, the DanCell study, recently reported 7-year follow-up clinical data of the 32 patients, who received intracoronary infusion of autologous BM-MNC.[18] At 7 years, mortality was 31%, and patients, who received a higher number of CD34+ cells, showed a better survival compared with patients who received low numbers of CD34+ cells, a finding which remained significant in a multivariate analysis. However, the trial comprised only 32 patients compared with our 297 patients, and no comparison was performed to a control group or heart failure score. Of note, in DanCell, although ∼10 times higher cell numbers were intracoronarily injected, there are no cell functional data available, which could also correlate with clinical outcome.[19]

Limitations

Although the present registry analysis is by far the largest cohort of patients with chronic post-infarction heart failure undergoing intracoronary cell therapy with a total time at risk of 821 patient-years, our study has several important limitations. First and most importantly, patients were not randomized to receive single or repeated BM-MNC administration. Thus, although baseline characteristics and SHFM-predicted mortality did not differ between patients receiving single or repeated BM-MNC administration, and even though we performed a landmark analysis in order to exclude a survival selection bias, we cannot fully exclude a potential selection bias, which might not be reflected in model-estimated risk prediction. Secondly, we limited the duration of follow-up to 3 years which might be an issue. However, recent large trials evaluating a potential benefit of both pharmacological and device therapy on prognosis in patients with chronic heart failure are generally designed to cover a 2−3 years observation period.[13,20−22] Thirdly, we did not analyse potential effects of BM-MNC administration on parameters of left ventricular function or quality of life, but rather focused on a single hard endpoint, which was all-cause mortality. Fourthly, the study cohort comprises a consecutive series of all patients treated for post-infarction heart failure by intracoronary BM-MNC administration at a single centre with a highly experienced core lab for cell processing applying rigorous quality standards. Given that the quality of cell processing has a major impact on BM-MNC functionality and efficacy,[23] the observations of the present study may not be extrapolated to clinical trials using different cell types or different cell processing techniques. Finally, although survival and the reduction of the combined endpoint of death and rehospitalization for heart failure were significantly different by Cox regression analysis in favour of the repeated treatment group, the effect lost its significance in the landmark analysis. Although the remaining trend still favoured the repeated treatment group with respect to improved outcome, the limited number of hard clinical events like death and rehospitalization for heart failure is, to our opinion, responsible for the loss of significance.

Thus, taken together, the results of the present registry analysis provide the framework and rationale for a prospective randomized multicentre trial, which will clarify whether intracoronary administration of BM-MNC is capable to reduce mortality in patients with chronic post-infarction heart failure (REPEAT trial). The trial essentials of this currently recruiting study (NCT 01693042) can be found in the Supplementary material online, *Appendix*.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

B.A. and E.H.: performed statistical analysis. A.M.Z.: handled funding and supervision. S.D.R., S.A., and H.B.: acquired the data. B.A., A.M.Z., and S.D.: conceived and designed the research. B.A. and A.M.Z.: drafted the manuscript. S.D., A.M.Z., E.H., H.B., and W.C.L.: made critical revision of the manuscript for key intellectual content.

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