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Review Article

Stem cells treatment in chronic ischemic heart disease: a narrative review

Roberto G Carbone[1], Simone Negrini[1], Giuseppe Murdaca[1], Vincenzo Fontana[2], Francesco Puppo[1]

[1]Department of Internal Medicine, University of Genoa, Genoa, Italy; [2]Clinical Epidemiology Unit, IRCCS San Martino Hospital, Genoa, Italy

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Abstract: Chronic ischemic heart disease remains a major cause of morbidity and mortality worldwide. Several trials have been performed to evaluate benefit of stem cells transplantation to restore cardiac function in short- and long-term period after myocardial infarction. This narrative review analyzes 24 clinical trials between 2005 and 2023 comprising 1824 patients with chronic heart disease without heart failure. Percent increase in left ventricular ejection fraction (LVEF) and decrease in New York Heart Association (NYHA) class at 6/12 months after stem cells transplantation are reported. Thirteen trials showed a statistically significant percent LVEF increase between 4% to 19% at 6/12 months after stem cells transplantation (*p* values from 0.05 to 0.0001). No significant differences in LVEF were observed between patients who underwent intracoronary or intramyocardial transplantation. NYHA class decrease from severe to mild/moderate was demonstrated in 10 trials reporting a significant LVEF increase. Patients transplanted with bone marrow and peripheral blood CD133+ stem cells showed a doubling of percentage LVEF increase in comparison to patients transplanted with CD133- cells. This narrative review reports the conflicting results on this topic. Multicenter randomized clinical trials should be performed to define the efficacy of stem cells transplantation in chronic ischemic heart disease.

Keywords: Stem cells, chronic ischemic heart disease, transplantation, left ventricular ejection fraction, New York Heart Association class, clinical trials

Introduction

Chronic ischemic heart disease remains a major cause of morbidity and mortality worldwide and 50% of diagnosed cases die within 5 years [1]. In this context stem cells transplantation has been proposed as a potential therapeutic procedure to reduce ischemic damage and restore cardiac function after acute myocardial infarction [2].

The basis of stem cell therapy is that myocardial endogenous regeneration after an ischemic injury is insufficient to compensate for the damaged myocardial tissue. However, available data in this area are controversial. While stem cell therapy has been shown to be feasible and safe, clinical trials have shown inconsistent benefits regardless of the cell type used [3].

Past research in this field showed that stem cell transplantation may represent a potential therapeutic option for patients with end stage chronic ischemic heart disease who failed previous medical and surgical treatments. However, this treatment modality could have some disadvantages such as complexity of the procedure requiring highly specialized multidisciplinary centers and high cost. Overall, the results of published studies are contradictory and definitive conclusions on long-term efficacy of this treatment have not been consistently confirmed.

The innovation of this narrative review is to focus only on studies that enrolled patients with chronic ischemic heart disease without heart failure making data analysis more homogeneous. Additionally, this study compares the efficacy of the different cell types utilized in transplant procedure.

The principal mechanisms underlying the efficacy of stem cell transplantation include direct

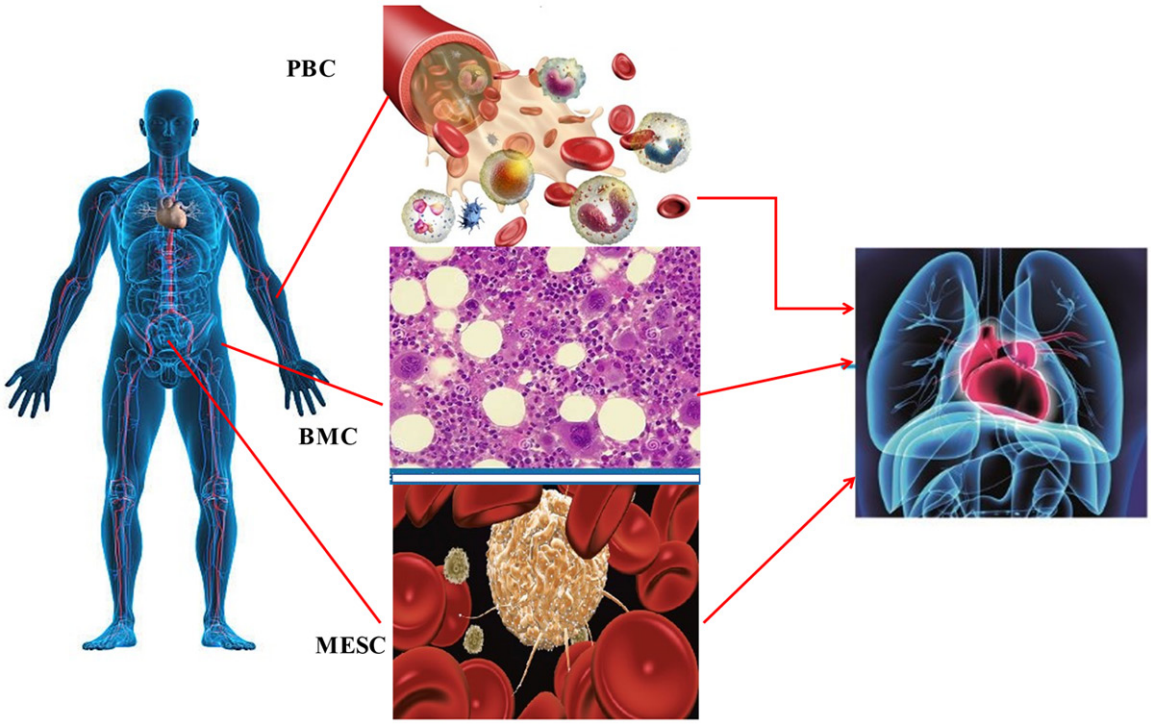

Figure 1. Distinct types of stem cells used for transplantation in chronic ischemic heart disease. PBC: peripheral blood-derived progenitor cells; BMC: bone marrow-derived progenitor cells; MESC: mesenchymal stem cells.

regeneration, immune regulation, microenvironment improvement and endogenous cardiac repair [4]. However, the initially suggested cardio-protective mechanism of neo-myocardiogenesis has not been confirmed. More recent research favors the positive effects exerted by stem cells through paracrine-mediated mechanisms and improvement in microcirculation [4].

Different autologous or allogeneic stem cell types derived from bone marrow, peripheral blood, mesenchymal and cardiac cells have been utilized (**Figure 1**) [2, 4-6]. The efficacy of cell therapies varies significantly from trial to trial due to the different cell types used (bone marrow-derived mononuclear cells, skeletal myoblasts, adipose stem cells, endothelial progenitor cells, cardiac stromal cells, etc.), number of cells injected, patient characteristics, study design, and endpoints [7]. Therefore, conflicting outcome results have been reported and optimal stem cell type and dose as well as transplantation regimen have not been still identified. Finally, little is known about the potential benefits of stem cells transplantation in chronic ischemic heart disease.

The aims of this narrative review are to report: i) the potential benefit of stem cells therapy in chronic ischemic heart disease without heart failure; ii) LFEV percent increase and NYHA class decrease at 6/12 months after stem cells transplantation; iii) the efficacy of different transfused stem cell types on transplant outcome.

Methods

Selection criteria

Clinical trials were selected by applying the search terms “chronic ischemic heart disease”, “bone marrow cells”, “stem cells”, “mesenchymal cells” in www.pubmed.gov and Cochrane library from 2005 to 2023.

Studies were included if they were randomized blinded trials, randomized unblinded trials, and non-randomized trials with a follow up of 6/12 months. Clinical trials including patients suffering from ischemic and non-ischemic heart failure, chronic heart failure, dilated cardiomyopathy and acute and chronic angina were criteria of exclusion as well as clinical trials with incom-

plete outcome data (thus reducing attrition bias).

Outcome parameters

Change in left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) class were identified as the outcome parameters in long term follow-up. LVEF was selected as this value was reported in all studies and represents the main parameter to evaluate myocardial efficiency in patients with chronic ischemic heart disease. LVEF value before and 6/12 months after stem cells transplantation and statistical significance of percent LVEF variation at 6/12 months were recorded as reported in each study. NYHA class at baseline and 6/12 months after stem cells transplantation was also recorded.

Statistical analysis

The absolute mean difference and the relative percent mean difference of LVEF value before and after treatment were calculated utilizing the following formulas: Absolute mean difference (final LVEF - basal LVEF), Relative percent mean difference [100 * (final LVEF - basal LVEF)/basal LVEF].

Results

Trials analysis

Twenty-four clinical trials were selected from 2005 to 2023. Among them 10 were randomized blinded, 10 randomized unblinded, and 4 non-randomized trials, respectively. The total number of patients enrolled was 1824 (929 treated, 779 males, mean age 62 years). Total number of transplanted cells ranged from 5×10^6 to $1,300 \times 10^6$ depending on cell type, cell population purification, and transplantation route (**Table 1**). Mesenchymal stem cells (MESC), bone marrow-derived progenitor cells (BMC), peripheral blood-derived progenitor cells (PBC), and cardiosphere-derived cells (CDC) were transplanted in 9, 8, 5 and 2 trials, respectively. Transplant procedure was intramyocardial in 15 and intracoronary in 9 trials, respectively (**Table 2**).

LVEF variation

Mean LVEF was 34.6% (range 27.1%-44.4%) at baseline. Thirteen trials reported a statistically significant absolute mean percent LVEF increase from 4% to 19% at 6/12 months after stem cells transplantation (*p* values ranging from 0.05 to 0.0001) (**Table 1**). We further analyzed the relative percent mean difference in LVEF value before and after stem cells transplantation. Data analysis confirm a relative percentage LVEF increase from 10.6% to 61.3% in 13 of 24 trials. The absolute mean percent LVEF increase in patients transplanted with either BMC or PBC CD133+ purified stem cells was about double (11.5%) compared to patients transplanted with CD133- cells (5.5%). No significative differences in absolute mean percent LVEF increase were observed between patients who underwent intracoronary or intramyocardial transplantation (8.8% and 8.0%, respectively).

NYHA variation

NYHA class variation was assessed in 19 studies including 10 studies reporting a significant LVEF increase. Among these, NYHA class decreased from IV to II, from III to II, from III to I, and from II to I in 2, 3, 4, and 2 trials, respectively (**Table 1**).

Discussion

Literature data on the efficacy of stem cells transplantation in ischemic heart disease report conflicting results. Jeevanantham et al. [28] published in 2012 a systematic review and meta-analysis reporting 2,635 patients treated with BMC stem cells for ischemic heart disease. Authors concluded that transplantation improved LVEF and that beneficial effects persisted for 6 months reducing mortality and recurrence of myocardial infarction. In 2022, Banovic et al. [4] reviewed clinical trials published in the preceding 20 years. The authors show that 1,326 patients were enrolled in studies in which efficacy of stem cell therapy in chronic ischemic and non-ischemic dilated cardiomyopathy was evaluated and concluded that only small-scale clinical trials have shown promising results. However, the findings were not uniform and the comparison among trials was difficult because patient characteristics, study designs, cell types, transplant procedures, number of injected cells, and endpoints showed marked differences from study to study.

Table 1. Clinical trials evaluating stem cells transplantation in chronic ischemic heart disease

Author [Ref. N.]	Patients				LVEF follow up				*p* value	NYHA class	
	Enrolled	*Treated*	*Age (mean)*	*Male (treated)*	*Baseline*	*6 months*	*12 months*	*% Increase*		*Baseline*	*12 months*
Erbs 2005 [9]	26	13	63	13	43.0 ± 2.0**	58.9 ± 3.2	58.9 ± 3.2	16	< 0.05	-	-
Stamm 2007 [10]	51	42	40	40	39.0 ± 8.7	50.2 ± 8.5	-	11	= 0.01	III	II
Gyongyosi 2009 [11]*	82	30	51	27	38.4 ± 5.8	42.9 ± 10.4	42.8 ± 9.7	5	= 0.01	II	I
		30	55	28	37.7 ± 6.0	41.3 ± 9.0	41.7 ± 9.2	5	= 0.03	II	I
Pokushalov 2009 [12]	109	55	61	48	27.8 ± 3.4	32.8 ± 6.2	32.3 ± 4.1	4	= 0.02	III	II
Flores-Ramìrez 2010 [13]	7	7	56	6	28.0 ± 6.7	-	38.8 ± 10.3	10	< 0.01	III	I
Turan 2011 [14]	56	38	62	20	46.0 ± 10.0	-	52.0 ± 8.0	6	= 0.01	III	I
Makkar 2012 [15]	436	25	52	25	39.0 ± 12.0	39.0 ± 12.0	-	-	n.s.	IV	IV
Hare 2012 [16]	96	30	63	26	27.1 ± 9.6	-	27.7 ± 9.3	-	n.s.	III	II
Honold 2013 [17]	154	133	60	133	40.3 ± 10.9	-	43.5	-	n.s.	II	II
Malliaras 2014 [20]	31	17	-	-	42.4 ± 8.9	-	48.2 ± 10.3	-	n.s.	I	I
Heldman 2014 [19]*	65	33	61	22	35.7 ± 8.5	35.8 ± 8.5	35.8 ± 8.5	-	n.s.	II	II
				22	35.9 ± 11.1	36.3 ± 11.1	36.3 ± 11.1	-	n.s.	II	II
Nassseri 2014 [18]	60	30	62	28	26.2 ± 5.6	33.0 ± 8.0	-	7	< 0.05	IV	II
Trifunovic 2015 [21]	30	15	56	15	35.9 ± 4.7	-	45.4 ± 4.9	10	< 0.001	III	I
Mathiasen 2015 [22]	60	40	66	36	28.2 ± 9.3	34.4 ± 3.8	-	6	< 0.0001	III	II
Florea 2017 [23]*	15	15	67	12	37.6	-	35.5	-	n.s.	-	-
	15	15	66	15	30.1	-	33.8	4	< 0.04	-	-
Aceves 2020 [24]	29	20	62	20	31.0 ± 2.0	49.0 ± 2.0	50.0 ± 1.0	19	< 0.001	III	I
Makkar 2020 [8]	142	90	55	76	39.9 ± 6.0	40.4 ± 7.7	-	-	n.s.	II	II
Ulus 2020 [25]*	54	25	62	25	29.0	-	34.4	5	< 0.04	-	-
		12	57	12	27.4	-	31.1	-	n.s.	-	-
Quayyum 2023 [26]	139	81	67	44	34.2 ± 7.90	32.5 ± 5.2	-	-	n.s.	II	II
Quayyum 2023 [27]	167	133	66	84	31.6 ± 7.2	30.0 ± 5.2	-	-	n.s.	II	II

*Protocol details are reported in the Reference; **mean ± SD.

Table 2. Stem cells source and transplantation route

Trials [Ref. N.]	Cells		Transplantation route		% LVEF increase
	*Source**	*Cells number*	*Intracoronary*	*Intramyocardial*	
Erbs 2005 [9]	PBC (133+)	69 ± 14 × 10^6	+		16
Stamm 2007 [10]	BMC (133+)	25-34 × 10^6		+	11
Gyongyosi 2009 [11]**	BMC	1300 ± 1.64 × 10^6	+	+	5
		200 ± 68 × 10^6			5
Pokushalov 2009 [12]	BMC	41 ± 16 × 10^6		+	4
Flores-Ramìrez 2010 [13]	PBC (133+)	103 ± 164 × 10^6	+		10
Turan 2011 [14]	BMC (133+)	99 ± 25 × 10^6	+		6
Makkar 2012 [15]	CDC	12-17-25 × 10^6	+		-
Hare 2012 [16]	MESC	20-100-200 × 10^6		+	-
Honold 2013 [17]	PBC	183 ± 101 × 10^6	+		-
Malliaras 2014 [20]	BMC	12.5-25 × 10^6	+		-
Heldman 2014 [19]	PBC	N/A		+	-
Heldman 2014 [19]	MESC	N/A		+	-
Nassseri 2014 [18]	BMC (133+)	5 × 10^6	+		7
Trifunovic 2015 [21]	BMC	70.7 ± 32.4 × 10^6		+	10
Mathiasen 2015 [22]	MESC	21.5 × 10^6		+	6
Florea 2017 [23]**	MESC	20 × 10^6		+	4
		100 × 10^6			
Aceves 2020 [24]	PBC (133+)	400 × 10^6		+	19
Makkar 2020 [8]	CDC	12-17-25 × 10^6	+		-
Ulus 2020 [25]**	MESC	21-26 × 10^6		+	5
	MESC	70 × 10^7			
Qayyum 2023 [26]	MESC	100 × 10^6		+	-
Qayyum 2023 [27]	MESC	110 × 10^6		+	-

*PBC: peripheral blood-derived progenitor cells; BMC: bone marrow-derived progenitor cells; CDC: cardiosphere-derived cells; MESC: mesenchymal stem cells. N/A: not available. **Protocol details are reported in the Reference.

Recently, we reviewed 34 randomized trials in the period 2000 to 2020 that recruited 3,142 patients evaluating the efficacy of stem cells transplantation on LVEF increase at 6 months after acute myocardial infarction. Despite the considerable number of patients evaluated, results demonstrated uncertain efficacy of this therapeutic approach. In fact, 20 trials showed a significant LVEF increase while 14 trials did not show LVEF improvement [29]. These controversies have stimulated this review aimed to explore the efficacy of stem cells transplantation in patients affected by chronic ischemic heart disease without heart failure after myocardial infarction. To this end we searched clinical trials in PubMed and Cochrane library and selected 24 trials published from 2005 to 2023 that enrolled 1,824 patients.

Baseline myocardial function of transplanted patients was severely impaired with left ventricular ejection fraction between 26% and 46%. Thirteen trials reported a statistically significant absolute and relative percent LVEF increase at 6/12 months after stem cells transplantation whereas 11 studies did not report benefit. Furthermore, no difference in outcome was reported between patients transplanted either via intracoronary or intramyocardial route. NYHA class decreased from severe to mild/moderate in 10 trials in which a significant LVEF increase was reported at 6/12 months after stem cells transplantation.

Cell type of transplanted cells could affect the efficacy of the transplantation procedure. Of interest, BMC and PBC stem cells were utilized for transplantation in all studies showing positive results. Even more interesting, LVEF increase was about double in patients transplanted with BMC or PBC CD133+ stem cells compared to patients transplanted with CD-

133- cells. This finding is in keeping with recent studies reporting that transplanted BMC CD133+ cells improve functional exercise capacity in patients with severe ischemic cardiomyopathy [30, 31]. Of note, CD133+ cells represent the most immature cell population which has shown to efficiently regenerate ischemic myocardium in pre-clinical models [32].

Cell dose could be an important determinant of the efficacy of stem cell transplantation because high cell number increases costs and adverse effects while low cell number could lead to unsatisfactory results. However, there are few studies evaluating dose-effect relationship.

Caution should be exercised in the evaluation of the results reported in the current narrative review and in our previous study [29] including a total of 4,966 patients affected by acute and chronic ischemic heart disease due to different stem cells utilized, transplant protocols and endpoints. Moreover, statistical significance of data analysis is limited by the small number of patients treated in some studies which affects the value of the results.

Conclusions

Overall, the results of published studies on this topic are contradictory to achieve a conclusion on efficacy regarding the long-term effectiveness of stem cells therapy to improve cardiac function and quality of life. Therefore, large multicenter randomized clinical trials are needed to identify optimal type and dose of transplanted stem cells as well as to determine the better transplantation protocol.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Francesco Puppo, Department of Internal Medicine, University of Genoa, Viale Benedetto XV, n. 6, 16132 Genoa, Italy. E-mail: puppof@unige.it

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