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Autologous bone marrow transplant for the treatment of patients who have experienced heart failure

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PRIORITISING SUMMARY

REGISTER ID: **000033**

NAME OF TECHNOLOGY: **AUTOLOGOUS BONE MARROW TRANSPLANT**

PURPOSE AND TARGET GROUP: **FOR THE TREATMENT OF PATIENTS WHO HAVE EXPERIENCED HEART FAILURE**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- ☒ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- ☐ Yes — ARTG number
- ☐ No
- ☒ Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States & Brazil	✓		
Germany	✓		
Italy	✓		
Belgium	✓		

IMPACT SUMMARY:

Autologous bone marrow derived stem cells are used to compensate for the loss of cardio-myocytes as a result of injury to the myocardium (eg myocardial infarction). This technique would only be made available in specialist cardiac facilities.

BACKGROUND

Heart failure or acute myocardial infarction results in injury to the surrounding heart muscle, due to the death of cardiomyocyte cells. Once advanced heart failure has developed and severe myocardial remodelling has occurred, there are few treatment options available to patients, with the only definitive therapy being heart transplantation. The goal of cell therapies such as transplantation of skeletal myoblasts and bone marrow mononuclear cells is to intervene in this process early enough to repair the injured myocardium, preventing permanent injury and thus avoiding the need for heart transplantation (Ott et al 2005). This prioritising summary will focus on the transplantation of autologous bone marrow cells.

Bone marrow consists of a two types of stem cells: mesenchymal and haematopoietic. Mesenchymal stem cells can produce fat, cartilage and bone. The haematopoietic stem cell fraction of bone marrow gives rise to >95% of the body's three types of blood cell in the circulation, leukocytes (including lymphocytes, monocytes and macrophages), erythrocytes (red blood cells) and thrombocytes (platelets). Recent research has demonstrated that both mesenchymal and haematopoietic stem cells have the capacity to differentiate into other lineages of cells, including cells with a cardiac phenotype (cardiomyocytes), that they have the ability to self-renew and preferentially migrate to the infarct region of the myocardium. Tissue injury is thought to be a major factor influencing the differentiation of these cells to other lineages (Haider and Ashraf 2005).

Bone marrow cells are harvested from patients and fractionated to remove red blood cells and platelets. A number of methods have been developed for the delivery of the prepared bone marrow cells to the site of injury. Cells may be delivered as a stand alone treatment, surgically as an adjunct to coronary artery bypass grafting or percutaneously as an adjunct to reperfusion. Surgical delivery is by its nature, highly invasive, and not well tolerated by patients with greatly reduced left ventricular function. Some trials have utilised multiple epicardial punctures through an open chest during revascularisation procedures. Other less invasive methods include thoracoscopic injection, ultrasound guided coronary sinus injection, endoventricular injection and percutaneous catheter based intracoronary delivery. The ideal method of delivery will depend on the clinical situation (Ott et al 2005).

CLINICAL NEED AND BURDEN OF DISEASE

In Australia, the age-standardised rate of acute myocardial infarction public hospital admissions has been steadily decreasing since the early 1990s, corresponding to a decline in the incidence of AMI. However, the absolute number of admissions has remained steady or increased due to the increasing average age and overall growth of the population. In Australia, AMI occurs predominantly amongst those aged 40 years and over (97 per cent), with almost two-thirds occurring among people aged 65-90 years of age. Men are twice as likely to be admitted than women (Mathur 2002).

In Australia, the number of public hospital separations for patients with acute myocardial infarction, in 2003-04, was 46,885. Of these, there were 30,795 male and 16,089 female separations, representing a total of 270,125 patient days. This equates to a rate of 519 separations per 100,000 population, aged 40 years and over. One in four Australians experiencing a heart attack or AMI will die within an hour of the first symptoms and almost nine in ten coronary deaths will occur before the patient reaches hospital. In Australia, the National Cardiovascular Disease and Diabetes Database recorded that in the year 2000, 14,616 persons died from AMI at a rate of 76.3 per 100,000 (AIHW 2006).

In New Zealand, the number of public hospital separations for patients with acute myocardial infarction, in 2002-03, was 11,582 and of these, there were 7,272 male and 4,310 female separations. Provisional 2002 data reported 3,252 deaths with an underlying cause of AMI (data supplied by the NZ Health Information Service).

DIFFUSION

Autologous bone marrow transplantation for cardiac regeneration is not currently practiced in Australia or New Zealand.

COMPARATORS

Patients experiencing AMI require prompt and complete restoration of blood flow in the infarcted artery, i.e. reperfusion. Reperfusion strategies for patients who have experienced AMI include pharmacological treatment, percutaneous coronary intervention (PCI) or surgical measures such as a coronary artery bypass graft (CABG) surgery (American Heart Association 2006). Of the patients admitted to acute care hospitals in Australia during 1999-00, 30 per cent received either cardiac catheterisation, PCI or CABG (Mathur 2002).

EFFECTIVENESS AND SAFETY ISSUES

Wollert et al (2004) conducted the BOOST trial, a randomised controlled trial of 60 patients who had undergone a successful percutaneous coronary intervention (PCI) for myocardial infarction (level II Intervention evidence). Patients were randomly allocated to either the control group (n=30) that received optimum post-infarction medical care, or to the treatment group (n=30) that received intracoronary transfer of autologous bone marrow cells (BMC) 4.8 ± 1.3 days after PCI. Bone marrow cells were infused into the infarct-related artery 6-8 hours after they were harvested via the central lumen of an over-the-wire balloon catheter. The balloon was inflated inside the stent to occlude the vessel and to allow maximum contact time for the BMC. This process was repeated 4-5 times with the artery reperfused for three minutes between occlusions. MRI was performed at baseline and at 6 months follow-up. No patients died, experienced adverse events associated with BMC transfer or were lost to follow-up. Results at 6 months are described in Tables 1 and 2.

At six months follow-up the global left ventricular ejection fraction of the treatment group was significantly higher when compared to the control group (p=0.0026). In addition, significant improvements were noted in the treatment group compared to controls for regional left ventricular ejection fraction (p=0.04) and systolic wall motion in the border zone of the infarct area (p=0.03) *but not* in the systolic wall motion of the infarct region itself (p=0.32). Improvements did not correlate with the number of nucleated cells or haemopoietic colony forming cells that were infused into the infarct related coronary artery.

Table 1 Left ventricular parameters at 6 months follow-up

	Baseline		6 months		Change		BMC treatment effect*	p
	Controls	BMC group	Controls	BMC group	Controls	BMC group		
LVEDV index (mL/m²)	81·4 (16·9)	84·2 (17·2)	84·9 (21·9)	91·7 (26·0)	3·4 (11·1)	7·6 (20·0)	4·0 (−4·4 to 12·5)	0·32
LVESV index (mL/m²)	40·6 (16·9)	43·0 (14·7)	42·6 (23·5)	42·4 (23·9)	2·0 (11·1)	−0·6 (14·9)	−3·2 (−9·7 to 3·3)	0·33
Global LVEF (%)	51·3 (9·3)	50·0 (10·0)	52·0 (12·4)	56·7 (12·5)	0·7 (8·1)	6·7 (6·5)	6·0 (2·2 to 9·9)	0·0026
LVM index (g/m²)	78·2 (18·3)	82·7 (18·7)	71·7 (14·2)	71·9 (14·6)	−6·5 (12·8)	−10·8 (10·6)	−2·5 (−7·3 to 2·3)	0·30
LE (mL)	30·3 (17·4)	33·0 (21·1)	19·8 (9·8)	18·9 (12·2)	−10·5 (10·6)	−14·1 (13·0)	−2·2 (−5·4 to 1·0)	0·18

BMC=bone-marrow cell. Data are mean (SD) unless otherwise stated. *Treatment effects expressed as differences in least-squares means (ANCOVA model) with 95% CI. LVM=left ventricular mass. LE=late contrast enhancement. There were no differences between groups at baseline.

LVEDV = left ventricular end-diastolic volumes, LVESV = left ventricular end-systolic volumes, LVEF = left ventricular ejection fraction, LE = late contrast enhancement

Table 2 Regional left ventricular ejection fraction and systolic wall motion at 6 months follow-up

	Baseline		6 months		Change		BMC treatment effect†	p
	Controls	BMC group	Controls	BMC group	Controls	BMC group		
Regional LVEF (%)	47·8 (9·7)	46·3 (10·6)	48·9 (15·2)	53·0 (15·5)	1·1 (11·8)	6·7 (9·5)	5·7 (0·2 to 11·3)	0·04
Systolic wall motion (mm), infarct region	3·9 (1·8)	4·4 (1·9)	4·9 (2·9)	5·9 (2·5)	1·0 (2·5)	1·5 (2·1)	0·6 (-0·6 to 1·8)	0·32
Systolic wall motion (mm), border zone	6·8 (1·6)	7·0 (1·7)	6·8 (2·1)	8·0 (2·1)	−0·1 (2·2)	1·0 (1·9)	1·1 (0·1 to 2·1)	0·03

BMC=bone-marrow cell. Data are mean (SD). Treatment effects are expressed as differences in least-squares means (ANCOVA model) and 95% CI. There were no differences between groups at baseline.

Meyer et al (2006) reported 18 month follow-up data on the BOOST trial. There was no significant difference between the control and BMC treatment groups at 18 months for the majority of parameters, including the global left ventricular ejection fraction (p=0.27) (Table 3). However, an improvement in the speed of left ventricular ejection was observed with a significantly higher speed in the BMC group when compared to controls (p=0.001). The authors conclude that further work is needed in the area to increase the number of BMCs that graft to the myocardium.

Table 3 Left ventricular ejection fraction at 18 months follow-up

	Control (n = 30)	BMC (n = 30)	*P* Value
LVEF at baseline (%)	51.3 ± 9.3	50.0 ± 10.0	
LVEF at 6 months (%)	52.0 ± 12.4	56.7 ± 12.5	
LVEF at 18 months (%)	54.4 ± 13.0	55.9 ± 14.7	0.27

Preliminary results from the REPAIR-AMI randomised controlled trial were recently reported to the American Heart Association conference in November 2005 (level II Intervention evidence). Patients were randomised to receive intracoronary infusion of BMCs (n=101) into the infarct-related artery during stop flow (3 x 3 minutes infusion of 3.3 ml) or placebo (n=103) 3-6 days after infarction. All patients underwent follow-up at 4 months. There were two deaths in both the BMC and placebo group. In addition, in the placebo group two patients developed heart failure and five patients had a recurrent myocardial infarction. At 4 months follow-up there was a significant improvement in LVEF in the BMC group compared to the placebo group (p=0.021) (Table 4).

Table 4 Left ventricular ejection fraction at 4 months follow-up

	Placebo (n = 92)	Bone Marrow (n = 95)	*P* Value
LVEF at baseline (%)	47 ± 1	48 ± 1.5	0.31
LVEF at 4 months (%)	50 ± 1.5	54 ± 1.1	0.021
P value (within group)	< 0.001	< 0.001	
Absolute change in EF (%)	5.5 ± 0.7	3 ± 0.7	0.014

LVEF = left ventricular ejection fraction

Patients with a greater degree of left ventricular dysfunction (LVEF <49%) at baseline benefited more from BMC therapy as in this subset of patients, the absolute change in LVEF in the BMC group was 7.5% vs 2.5% in the placebo arm (p = 0.002). In addition, delaying time to infusion was associated with better outcomes. Patients in the BMC arm treated 5 days after myocardial infarction had the largest improvement in LVEF. There was no difference in the absolute change of global LVEF in patients who received treatment ≤ 4 days after MI. Clinical endpoints at 4

months were similar in both groups, however there was a trend towards an increased rate of myocardial infarction in the placebo group. Mortality rates, rehospitalisation due to heart failure, and revascularisation rates were similar in both arms. However, the combined endpoint of death, myocardial infarction and rehospitalisation due to heart failure was significantly lower in the BMC group (p=0.033) (Cleland et al 2006; Schächinger 2005).

Another good quality (level II Intervention evidence) study was conducted by Janssens et al (2006). Patients in the BMC group (n=33) and the placebo group (n=34) all received PCI within five hours from symptom onset, and for those patients in the BMC group, bone marrow was harvested one day after PCI. MRI was conducted to assess left ventricular function at baseline and at four months follow-up. There was no significant difference in global LVEF between the BMC and placebo groups (*p*=0.36), however there was a significant reduction in the size of the infarction in the BMC group (*p*=0.036) (Table 5).

Table 5 Left ventricular parameters at 4 months follow-up

	Baseline		4 months		Difference		Treatment effect*	p
	Control (n=30)	BMSC (n=30)	Control(n=30)	BMSC (n=30)	Control (n=30)	BMSC (n=30)		
LVEDV index (mL/m²)	83·1 (14·7)	81·2 (14·0)	85·9 (19·5)	84·1 (20·8)	2·8 (15·0)	2·8 (15·2)	0·997 (0·915 to 1·086)	0·95
LVESV index (mL/m²)	44·4 (12·3)	42·2 (10·5)	45·0 (17·9)	41·0 (15·5)	0·6 (11·6)	−1·1 (11·2)	0·980 (0·861 to 1·115)	0·76
Global LVEF (%)	46·9 (8·2)	48·5 (7·2)	49·1 (10·7)	51·8 (8·8)	2·2 (7·3)	3·4 (6·9)	1·036 (0·961 to 1·118)	0·36
LV mass index (g/m²)	64·5 (15·8)	57·0 (11·0)	58·7 (11·1)	50·9 (9·6)	-5·8 (11/9)	−6·1 (6·8)	0·931 (0·864 to 1·003)	0·06
Late contrast enhancement (g)	22·3 (16·1)	20·6 (14·3)	14·7 (9·3)	10·3 (8·0)	-7·9 (8·5)	−10·2 (7·9)	0·717 (0·530 to 0·971)	0·036
Systolic wall thickening in infarct area (%)	21·8 (19·21)	23·6 (17·9)	23·7 (18·9)	29·3 (21·7)	1·9 (21·4)	5·7 (24·4)	4·99 (−5·3 to 15·3)	0·35
Systolic wall thickening in border zone (%)	32·7 (15·4)	36·6 (18·9)	38·4 (21·1)	40·8 (17·2)	5·7 (18·8)	4·2 (22·6)	−0·84 (-10·5 to 8·9)	0·87

BMC=bone-marrow cell. Data are mean (SD) unless otherwise stated. *Treatment effects expressed as differences in least-squares means (ANCOVA model) with 95% CI. LVM=left ventricular mass. LE=late contrast enhancement. There were no differences between groups at baseline.

COST IMPACT

There is currently no costing information available on the use of autologous bone marrow transplantation for cardiac remodelling. The in-vitro processing of bone marrow for autologous stem cell transplantation as an adjunct to chemotherapy is available on the Medicare Benefits Schedule as item number 13760, which attracts a fee of $660.05. Costings will vary depending on time and mode of delivery of stem cells.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No other issues were identified in the sources examined.

OTHER ISSUES

No other issues were identified in the sources examined.

CONCLUSION:

There are a number of good quality studies included in this summary which described the use of bone marrow cells for autologous transplantation for patients who have experienced a myocardial infarction. Significant improvements were reported by some studies in surrogate outcomes, such as left ventricular ejection fraction, at short-term follow-up. These results were conflicted by another study which reported no significant improvement. Long-term follow-up may indicate that no benefit is afforded to patients who have undergone bone marrow transplant. Most authors agree that more work needs to be under taken to ascertain the optimal cell type to be used for

transplantation, how many cells to use and the timing of cell transfer. In addition studies need to present long-term follow-up data.

HEALTHPACT ACTION:

Despite the lack of long-term follow-up data, HealthPACT are of the opinion that this technology is likely to enter the Australian health system soon and therefore recommended a horizon scanning report.

SOURCES OF FURTHER INFORMATION:

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Wollert, K. C., Meyer, G. P. et al (2004). 'Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial', *Lancet,* 364 (9429), 141-148.

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LIST OF STUDIES INCLUDED

Total number of studies
Level II Intervention evidence 3

SEARCH CRITERIA TO BE USED:

Bone Marrow Cells
Cell Differentiation
Cell Fusion
Cell Lineage
Heart/physiology
Myocardial Contraction
Myocardial Infarction/*surgery
Regeneration
*Stem Cell Transplantation
Ventricular Function, Left
*Bone Marrow Transplantation
*Heart Catheterization
Heart Failure, Congestive/etiology/*surgery
Transplantation, Autologous