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Current Concepts and Future Perspectives of Stem Cell Therapy in Peripheral Arterial Disease

Kereena Chukka[1]*, Gnaneswar Atturu[1], Ashok Reddy Somu[1], Prem Chand Gupta[1]

[1]Department of Vascular & Endovascular Surgery and Interventional Radiology, CARE Hospitals, Hyderabad, India

***Corresponding author:** Dr Kereena Chukka, Lead Clinical Scientist, Department of Vascular & Endovascular Surgery and Interventional Radiology, CARE hospitals, Hyderabad, India; Email: chukkakereena@gmail.com

Mini Review

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Abstract

Some advanced stage peripheral arterial disease (PAD) patients will not eligible for revascularization strategies. From the last two decades stem cell therapy (SCT) has been explored as an alternative therapy for no option advanced stage PAD patients. Therapeutic motif of this novel therapy is to promote the collateral vessel formation that will improve the blood flow to ischemic leg that in turn can prevent major amputations. This mini review provides the brief outline of the use of autologous and allogeneic SCT for the treatment of advanced stage PAD.

Keywords: Stem Cell Therapy, Peripheral Arterial Disease, Regenerative Medicine, Critical Limb Ischemia (CLI), Autologous, Allogeneic

Abbreviations: SCT: Stem Cell Therapy; PAD: Peripheral Arterial Disease; CLI: Critical Limb Ischemia; BM: Bone Marrow; EPCs: Endothelial Progenitor Cells; TACT: Therapeutic Angiogenesis Using Cell Transplantation; ISCT: International Society for Cell Therapy.

Introduction

Regenerative medicine using stem cells to treat human diseases has gained significant momentum in the scientific community. The discovery and isolation of endothelial progenitor cells by Asahara et al. in 1997, has paved way for the use of SCT in the management of several cardiovascular diseases. Peripheral artery disease is a type of cardiovascular disease that affects more than 230 million people worldwide and is defined as ischemia in the lower limb due to narrowing of arteries, most commonly due to atherosclerotic plaque accumulation [2]. PAD is associated with increased risk of cardiovascular diseases, stroke and limb loss [3].

Critical limb ischemia (CLI) is the progressive form of PAD in which severe obstruction of blood flow leads to rest pain, ulcers, and/or gangrene with a significant risk of amputation, morbidity, and mortality. Revascularization is essential at this stage and if it fails or is not feasible, amputation becomes inevitable. Amputation has a high rate of mortality (25~50%), of which 5~20% occur during the perioperative period. The prognosis is generally poor with a 5-year survival rate of less than 50%. The re-amputation rate can also be as high as 30%. SCT has emerged as a promising therapeutic strategy especially in patients with CLI with no revascularization options. In the present review, we aim to update the information on the current evidence for usage of autologous and allogeneic stem cell therapy in the

management of PAD and the future perspectives.

For the first time, Asahara, et al. [1] isolated endothelial progenitor cells (EPCs) from blood. EPCs are a type of stem cells, derived from bone marrow (BM) and are mainly found in the embryo and umbilical cord blood. These cells are capable of forming new capillaries and small arteries. The exact marker for EPC's is yet to be finalized but has predominantly CD34+ and VEGFR2+ markers. Other makers like CD117 and CD133 are also noted by researchers [4,5]. In the early years, the angiogenesis potential of stem cells in ischemic limbs was proved in animal models [6-9]. Based on these studies, SCT was introduced in the management of patients with PAD. The First human trial named 'therapeutic angiogenesis using cell transplantation' (TACT) was conducted in Japan in 2002 [10]. Several clinical trials have shown their results using different types of stem cells harvested from the same person (autologous) or from healthy donors (allogenic). Although the results were encouraging and showed neovascularization and limb salvage in most of these studies, SCT has not yet become the standard therapy for PAD patients. There are several reasons for this, and these reasons need to be understood both by the clinicians and researchers to guide the future research on SCT in the management of PAD.

These studies were heterogeneous in terms of the isolation process, SCTs used, the mode of administration and the outcome measures. In majority of the studies, SCTs were harvested from the same patients (autologous BM-SCT). There were only few studies that reported the therapeutic potential of allogeneic SCTs derived from healthy donors (Allogeneic SCT). Although autologous harvesting has several advantages, these cells will also be senile and may not have the maximum regenerative potential. In contrast, Allogeneic SCTs are human BM cells harvested from young and healthy donors, and hence could have better regenerative potential. One major drawback of allogeneic SCTs is that it requires a robust supply chain to maintain the sterility and potency of stem cells.

The source for autologous stem cell harvesting and the cell type used varied in studies. Bone marrow aspirate was the commonly used source for harvesting stem cells. Other sources included peripheral blood and adipose tissue. Irrespective of the source, all SCTs require ex-vivo processing to harvest the stem cells. This ranged from simple centrifugation to complex ex-vivo methods to culture the cells to boost the therapeutic response. This is a key cause for heterogeneity and should be addressed by future researchers by narrowing down the therapeutic options.

There is no standard test for identifying multi-potent MSCs. The minimum criteria to describe the multi-potent MSCs according to International Society for Cell Therapy (ISCT) are expression of cell surface makers of CD73, CD90 and CD105, low or lack of expression of cell surface makers of CD34, CD45, CD14, CD19, HLA-DR and multi-lineage differentiation capacity [11]. Apart from clinical trials, it is not routinely feasible to identify the concentration of stem cells with specific cell surface markers in the SCT. This could affect the individual outcomes and need to be addressed in future studies.

Most of the studies have reported excellent results in the short and medium term. Studies with long term follow up are required to understand the safety profile and sustainability of therapeutic benefit. Studies are also required to expand the use of SCTs in less severe cases and in patients who have undergone successful revascularization. Application of SCT in early stages could halt or reverse the progression of PAD. Such studies would help in guiding the policy makers and regulators in make the right decision.

Conclusion

Several studies have reported that the PAD patients who treated with autologous and allogeneic cell therapies had improvement in structural and functional measures and outcomes. However, the heterogenesity of the studies, legal regulations, availability and lack of long-term results has hampered its wider application. Future studies should understand the current limitations and address them.

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