One Decade of Stem Cell Therapy for Bone Marrow: What is Missing?

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The use of autologous bone marrow cells in humans is celebrating ten years now, in an area where Brazilian cardiology has international recognition because of its pioneering initiative[1]. One decade ago the first cases were treated in patients with terminal chronic ischemic heart disease, which were published two years later[2]. The article by Vilas Boas et al[3], published in this issue of the *Archives*, represents another pioneering effort in the field of cardiology in Brazil: the application in Chagas disease (CD). In this issue, the authors present a case series of 28 patients with heart failure due to CD with NYHA functional class III and IV who underwent transplantation of bone marrow-derived mononuclear cells (BMC) by coronary injection.

Like all scientific evidence, the articles on cellular therapy must undergo a process of critical evaluation. For this purpose, besides the general criteria for a therapy-related article[4], we have learned through these ten years that some specific considerations must be made about BMC articles.

Firstly, it should demonstrate which cells were injected (and their subtypes), viability and degree of functionality. Especially when a study is negative[5]. In 2006, the same issue of the NEJM was presented in two studies with similar methodologies in the setting of acute myocardial infarction: a study suggesting benefit and another not suggesting benefit, which generated much controversy at that time[6,7]. The authors have devoted to understand why there was such a difference and today we know that the negative study had used cells with depressed functional capacity. Thus, the main questions to be asked are: which cells were injected? What functionality and viability tests were made and what is the experience of the group that accomplished it?

Another key point for the study on BMC relates to adverse events. We are usually interested in the risk-benefit of a new therapy. In the case of cell therapy, there has not been so far major adverse events established[8]. If that fact is proven, the criteria for clinical decision making changes to the extent that the risk-benefit ratio becomes favorable.

In the study by Vilas Boas et al[3], 240 million cells were injected intracoronarily. Although there is no functional or cell typing test, viability was high (96%) and the testing center has extensive experience in this area. There were no adverse events related to cell harvesting or implantation. In a six-month follow-up, four deaths were reported, with improvement in clinical parameters (NYHA, quality of life, 6-minute walk test) and echocardiographic parameters (LVEF).

When we consider the evidence available, a systematic review of BMC in the setting of chronic ischemic benefits EF in these patients[8]. Interestingly, there is a disproportion between the improvement in EF and marked clinical improvement. Data from five years of our group showed a higher than expected survival and quality of life assessment by SF-36 and Minnesota in the general population in the same age group[9]. It could be argued that quality of life data are subjective and reflect a positive psychological influence. This fact is mischaracterized by the performance of patients in exercise testing, also disproportionately better than EF gains sustainable in the long term (psychological influences do not usually have five-year effects). The more serious the condition of patients, the more these have benefited from the performance of EF[9].

One possible explanation could be a complex multi-dimensional mechanism of action, unlike chemical agents (working in a specific point in the pathophysiological cascade). Although BMC have their ability to transdifferentiate into cardiomyocytes discussed to these days, they have demonstrated angiogenic capacity, and capacity to restore the intrinsic nervous system of the heart and heart supporting tissue rearranging the cardiac collagen that modulates inflammation[10].

After ten years, why do we still not have any definitive evidence in cell therapy? Simply because the BMC are not patentable; they do not generate any funding interest. This shows how important is the role of the industry in developing new cardiovascular technologies. In the case of CD, a more robust evidence sponsored by the Ministry of Health has demonstrated no benefits for patients[11]. Unfortunately, the study provides data on the functionality of cells administered, which will always keep us wondering: BMC therapy does not benefit CD, or the injected cells were not appropriate?

Keywords

Stem cells; therapeutics/trends; bone marrow.

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