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EDITORIAL

Regenerative medicine for osteonecrosis of the femoral head

PRESENT AND FUTURE

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One of the notable exceptions to the paradigm of self-healing bone is osteonecrosis of the femoral head (ONFH). In this disease, obstruction of blood supply and increased intraosseous pressure to the femoral head subsequently cause death of osteocytes. Necrotic bone cannot continually repair itself, and consequently microfractures accumulate and progress to structural collapse.[1] The high incidence of ONFH in young patients (20 to 40 years old), in particular, creates major treatment dilemmas.[2] While immediate good results of arthroplasty are appealing to both patients and surgeons, the high chances of failure in the long remaining lifespan justify attempts to preserve the femoral head. Therefore, regenerative medicine for bone regeneration finds a good niche in the treatment of ONFH.[3] Considering that the pathogenesis of ONFH is related to cell death, replenishing cells that can make bone or vasculature in situ is an appealing concept. Core decompression procedure, in which part of a necrotic bone is removed to alleviate pain and possibly cure the disease, provides unique circumstances for adding cell therapy to the procedure with minimal additional morbidity. In addition to cell-based therapy, non-cellular therapies including growth factor, exosome, and gene therapy may be employed to regenerate bone in ONFH.

Cells used for regenerative treatment

The prototype application of a cell therapy in ONFH is the injection of bone marrow aspirate concentrate (BMAC) in the cavity created by core decompression, with a view that these cells may restore the trabecular bone in the necrotic femoral head.[3-5] Encouraging results have been reported by several groups.[4-8] However, other groups have found no notable difference between treated patients and control patients.[9,10] Overall, the value of most studies is rather limited because of low numbers of patients and brief follow-up periods. A prospective, double-blinded trial has provided a higher level of evidence for the effectiveness of BMAC implantation at a five-year follow-up.[11]

Increasing knowledge and characterization of stem cells have promoted the use of these cells instead of BMAC in regenerative medicine for ONFH. Among various cell types, mesenchymal stromal/stem cells (MSCs) derived from bone marrow have been put forward as the top candidate.[12] However, application of ex vivo expanded autologous bone MSCs is a more complicated process than using BMAC. In addition, they are controlled by regulatory authorities.[13] Most studies reporting the application of MSCs are uncontrolled case series except for a few controlled studies. On the other hand, a meta-analysis of stem cell therapy in ONFH has shown that complications are all minor with an unremarkable rate (2.8%).[14] While heterogeneous methods of application make it difficult to directly compare individual studies, there is an increasing perception that BMAC or bone marrow MSC (BMSC) treatment has reasonable, if not remarkable, effects in early stage (Ficat I or II) ONFH in terms of symptomatic relief and preventing progression of femoral head collapse.[15-17] While BMSC is the most used stem cell type in ONFH, adipose stem cells (ASCs) offer several advantages as a cell source for regenerative medicine. ASCs are more easily and less painfully obtained than BMSCs.[18] They are not only more abundant in fatty tissues,

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but also have greater proliferative potential compared with BMSCs.[19] ASCs additionally have the advantage of promoting angiogenesis.[20]

Allogenic MSCs have economic advantages compared with autologous MSCs because allogenic cells can be made available as an 'off the shelf' product, although they carry the chance of disease transmission and immunological rejection.[16] In this sense, there are arguments on whether allogenic MSC should be appropriate for non-lethal diseases such as ONFH. On the other hand, considering that the proliferative and osteogenic potential of MSCs from ONFH patients is reduced,[21-24] allogenic MSCs derived from healthy donors might be effective in treating those patients. Umbilical cord-derived MSCs may prove to be a good candidate because of high cell yield and low immunogenicity.[25]

Delivery of the cells

The optimal number of implanted cells, which is comparable to the dose of a drug, needs to be determined in cell therapy for the reason of economy and therapeutic effects, as well as to avoid possible complications from overdose. BMAC and stromal vascular fraction are a mixture of cells, with a small proportion of stem cells. Also, each kind of adult stem cell is expected to have different survival and osteogenic potential. Based on current reported studies, the number of used cells ranges from 10^6 to 10^9, and the most frequently used dose is 10^8 cells.[6-10,26] Still, the optimal number remains to be determined for each type of cell. Cells have most commonly been delivered at the time of core decompression.[3,6-11,26] A couple of studies have also shown that therapeutic cells may be effectively delivered via intra-arterial infusion to treat ONFH.[27,28] However, general applicability and safety of these methods need further investigation.

Given the high cost of regenerative therapy, only patients who will show a high chance of successful results may be indicated for this form of treatment. Post-collapse ONFH may not be indicated for stem cell therapy,[29] as implantation of BMAC after core decompression could not lead to any improvement in the clinical course of stage III ONFH.[30] Thus, only early-stage (stage I or II) patients may be considered for this form of treatment. Also, it has been reported that patients with post-traumatic ONFH have better outcomes than patients with non-traumatic ONFH, suggesting that hips with a systemic cause of the disease would show less favourable response to regenerative medicine than those with localized causes.[6] Furthermore, it has been found that those with smaller lesion sizes may achieve better results, which is also the case with core decompression without additive cell therapy.[31] Therefore, hips with pre-collapse, smaller size, probably traumatic ONFH are better candidates for regenerative therapy. A recent study using autologous BMSCs reported that the mean threshold residual lesion volume for progression of collapse was 10% (standard deviation 6%) at three months after implantation.[32]

Safety is one of the critical concerns in the application of cell therapy. Key features of stem cells such as self-replication, long lifespan, and multidifferentiation are also shared by cancer cells. This means that stem cells can undergo malignant transformation, which poses a key obstacle in the safety of stem cell implantation.[33] Immune rejection can also limit the clinical use of allogenic stem cells for ONFH. However, current literature so far shows no severe complications in stem cell implantation for ONFH.[14,34,35] Therefore, it can be proposed that the application of stem cells for the treatment of ONFH is relatively safe. Nevertheless, longer follow-up results are still needed to ensure its safety. As in vitro cell expansion process is necessary, the entire process must be controlled and standardized so that cells may retain their phenotype and functional potential, and avoid possible microbial contamination.[33]

One hitherto unheeded and uncharacterized aspect of stem cell therapy in ONFH is the in vivo fate of implanted cells. Although stem cells are implanted with the hope that they will engraft to the recipient area and undergo differentiation into osteogenic cells, whether implanted cells will survive on the site has not been investigated yet. Without adequate vascular supply, these cells will suffer from hypoxia, hypoglycaemia, lack of nutrients, and piling up of waste products. In ONFH, the scanty vascularity at the recipient site may render the local microenvironment unfit for the survival of stem cells. These circumstances may account for unsatisfactory results of stem cell implantation in controlled studies. Most implanted cells probably go through massive cell death within a short period of time, exerting a degree of paracrine effect before they die. Thus, if the survival and engraftment of implanted cells are to be promoted so that these cells become osteogenic cells and regenerate bone within the implanted area, augmentative measures to enhance the angiogenic potential of implanted cells will be necessary.[3]

Other methods such as gene therapy and exosome have been explored. Gene transfer of therapeutic genes can be employed to enhance therapeutic efficiency of MSCs. Bone morphogenetic protein-2 (*BMP*-2), vascular endothelial growth factor (*VEGF*), basic fibroblast growth factor (*bFGF*), and platelet-derived growth factors (*PDGFs*) are candidate genes that can be transferred to promote osteogenic and angiogenic properties of MSCs. As gene transfer techniques which mostly use viral vectors further complicate the safety issue of cell therapy, gene-modified MSCs have not yet been applied to treat ONFH patients. As all data on gene-modified MSCs are from animal experiments, the efficiency and safety in patients are not presently known and await evaluation in clinical trials.[36-38] Growth factors may be directly implanted in the lesion site to enhance osteogenesis and angiogenesis. However, direct implantation of growth factors is complicated by practical problems of peptide therapy, such as an extremely short half-life and side effects with systemic or high-dose administration. The combined use of carrier

materials is thus necessary to enable controlled release and practical application of growth factors. Recombinant BMPs and fibroblast growth factor 2 (FGF-2) have been used for clinical application in combination with various carriers.[39-43] The therapeutic benefit of MSCs is known to be mostly attributable to factors they secrete.[44] In addition to growth factors and cytokines, cells communicate with neighbouring or distant cells via extracellular vesicles (EVs) including exosomes, which are EVs smaller than 150 nm in diameter.[45] Exosomes isolated from human MSCs showed preventive effects in a rat model of ONFH by exerting proliferative and antiapoptotic effects,[46] and by promoting angiogenesis.[47]

Numerous studies have reported positive results. However, it remains unclear whether regenerative medicine can be the game-changer in the treatment of ONFH that genuinely alters the natural history of the disease. While well-controlled randomized studies recruiting adequate numbers of patients are necessary to define the place of treatment, the nature of regenerative treatment, including the cost and individual difference in donor cell characteristics, makes it rather difficult to perform. In the case of cell therapy, because an outcome observed from a type of cell source cannot be projected to another type of cells, precise definitions of cell sources and types are mandatory. Also, distinguishing between culture-expanded and native cells is necessary as well as between autologous and allogenic sources. In addition to scientific concerns, regulatory issues complicate regenerative therapies. The implantation of culture-expanded cells needs approval from regulatory agencies in most developed countries, which is even more strict for allogenic or genetically modified cells, adding to the cost of cell therapy. Nevertheless, given that failure to revitalize necrotic bone inevitably leads to joint arthroplasty in young patients, further efforts need to be dedicated to the research and advancement of regenerative medicine for ONFH.

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