NARRATIVE REVIEW

Mesenchymal stem cell therapy for treatment of osteoradionecrosis of mandible in head and neck surgery patients - A way forward into the future with promising clinical Outcomes

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Abstract

Managing osteoradionecrosis is an integral part of complication management in head and neck cancer patients. While essentially an infection, the management of this complication has a considerable task for head and neck surgeons. While various measures have been discussed for the management, stem cells injection therapy is a potential management option. Mesenchymal stem cell therapy provides the local tissue with growth factors and proliferative cells that can aid a radiated tissue in the healing process. The article intends to review the bedrock of the pathology, ranging from pathophysiological and the epidemiological concerns to sparking a potential discussion on the use of mesenchymal stem cell therapy in osteoradionecrosis of mandible in head and neck cancer surgery and thus the ensuing future of the regenerative medicine. Moreover, the article has considered the management option in a developing nation thus explaining the procedural as well as the financial pitfalls and has highlighted the potential loop holes to be addressed in the management of osteoradionecrosis with stem cell therapy.

Keywords: Stem cell therapy; osteoradionecrosis; Stem cell; Mesenchymal stem cells; Head and Neck

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Introduction

Osteoradionecrosis is the scourge of head and neck cancers invading the bone particularly the mandible. The pathophysiological basis of the disease is based on the lack of vascular richness of the region. Mandible is a bone that provides structural integrity to the jaw. With necrosis setting in, there can be local as well as disseminated complications and side-effects of the disease process. There are numerous challenges that one can face in the conventional treatment modalities that can be offered in such patients. Stem cell therapy is a potentially uncharted territory that holds great promise in restoration of vascular richness to the local tissue. The implications of mesenchymal stem cells are a realm to ponder. These can essentially prove to be either a way out or just another dead end, but the mechanism of regenerative medicine holds true in these key areas hence need to be evaluated. This review intends to highlight the epidemiological basis of the disease process, the pathophysiology governing the entity, stem cells therapy and regenerative medicine as a potential way out of this conundrum.

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Osteoradionecrosis – Epidemiology and causes

Osteoradionecrosis (ORN) is a common adverse effect of radiation therapy in high doses for head and neck cancer[1]. Exposed necrotic bone that fails to granulate over 3 months defines ORN and this complicates up to 5%-15% of patients[2]. Mandible is more prone to ORN as compared to maxilla as the latter has a richer blood supply.[3]

Besides exposed bone other symptoms include purulent or serosanguinous discharge, pain, limitation in mouth opening and infections[4]. This can further complicate into an abscess, sepsis, malnutrition and death (5).Current treatment modalities include using broad spectrum antibiotics, topical corticosteroids, hyperbaric oxygen therapy or antioxidant agents (i.e. pentoxifylline, tocopherol), but these modalities have modest benefit at best with incomplete resolution. Aggressive mandibulectomy becomes inevitable to arrest progression[5].

Stem cells have recently gained momentum with advances seen in tissue engineering. They are self-renovation, multipotent progenitor cells with the power to transform into multiple well-defined lineages. Mesenchymal stem cells (MSCs) can aid in tissue regeneration especially those with an impaired healing capacity, as seen in certain studies that have demonstrated the therapeutic role of bone marrow derived mesenchymal stem cells on ORN in swine and rat

models[6].

Pathophysiology

Development of ORN impedes vital functions such as speaking, masticating and even mouth opening. It can be described as a failure of wound healing as a result of metabolic tissue disturbances and homeostasis[7]. Marx described osteoradionecrosis as wound with failure to heal as a result of hypo-cellular and hypo-vascular tissue with lack of oxygen supply[6]. Store et al used DNA hybridisation to suggest that the bacterial infestation of exposed bone due to dermal thinning after radiation caused ORN[3, 6-8].

Radiation-induced fibro atrophic theory, explains the development of ORN in three different stages. The initial pro-fibrotic stage, in which by an acute inflammatory response is triggered by radiation-induced reactive oxygen species (ROS) along with chemokines causing endothelial cell damage[9]. The second stage is constitutive organized stage in which loss of cytokines (i.e., interleukins (IL), tumour necrosis factor-α (TNF-α), FGF-β and TGF-β1) along with damage to the vascular endothelial barrier results in the accumulation of myofibroblasts (MFB). Fibro atrophic stage is the last stage in which local metabolic alterations and bone fragility ends up as ORN[10]. Generation of MFB plays the central role in this theory due to their rapid proliferation rate, producing large amounts of extracellular matrix protein and collagen, thus causing an imbalance between formation and mortification in the exposed tissue. Due to this, bony matrix is replaced with fibrous tissue, causing ORN[10].

Current treatment options and their challenges

Due to the debilitating effects and functional loss seen with surgical interventions, medical management of ORN has been largely advocated as first line in literature. This has led to the use of drugs like pentoxifylline, clodronate, doxycycline, tocopherol owing to their effects based on the reversal of reactive oxygen species[11]. Other conservative options such as ultrasound therapy and hyperbaric oxygen therapy are also being considered(3). Delaina and Lefaix postulated that necrosis of vessels, tissue hypoxia led to ultimate fibrosis[12]. Based on this theory hyperbaric oxygen (HBO) therapy was considered the standard of treatment for ORN. But Annane et al. in a, double blinded randomised controlled trial, demonstrated no benefit from HBO therapy, which makes its use in ORN controversial[8, 9].

A phase II clinical trial has reported the mucosal and bone healing effects of pentoxifylline (PTX), tocopherol and clodronate (PENTOCLO) among this study cohort which comprised of 18 patients of which 16 showed complete recovery[11]. Whereas Epstein et al reported a 57% recovery rate as preliminary results on conservative management[13]. Chlorhexidine being an anti-bacterial for Gram-positive and Gram-negative bacteria, combined with debridement has also shown promising results in bone closure. Ultrasound therapy to establish revascularisation is still under experimental trials but may soon add up to the conservative management protocols[13]. But the conservative therapy is expensive and many drugs await FDA approval and the treatment continues over months.

Surgical options mostly recommended for advanced cases may include sequestrectomy, ostectomy, radical resection followed by reconstruction most common being the free fibular flap. However, it is safe to say that fruitful results are usually attained by combining both the options together as removal of the devascularised bone will provide a medium for these therapies to produce maximum impact[2].

Regenerative medicine/Stem cell therapy – Idea and physiology

Regenerative medicine can be simply defined as the process of replacing human tissues or organs to restore normal functions. It works by using human body as a bioreactor to boost the body's own potential to heal and regenerate in vivo. It employs cellular transplantation and scaffolds according to type of tissue and functioning of head and neck sub-sites.[2]

Scaffolds provide a 3-D framework to induce cell differentiation for establishment of normal functioning of the organs. These Scaffolds can be made by multiple ways including de-cellularising tissue, 3-D printing, hydrogels, customising and electro spinning[2].

In regenerative medicine, paracrine signalling is used in Immune response modulation. Multiple kinds of stem cells, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs) are used in this modulation[14].

Mesenchymal stem cells and osteoradionecrosis

MSCs have opened new opportunities in regenerative medicine owing to their broad range of healing and aesthetic functions. These were discovered initially in bone marrow for support of haematopoiesis. They have been taken from almost every type of connective tissue and showed tissue regeneration equally for all including cases of trauma and inflammation[2]. They are spindle

shaped, non-haematopoietic cells that are plastic-adherent with ability to regenerate and differentiate[2]. Various mesenchymal surface markers such as CD90, CD44, CD73, and CD105 are expressed by these cells. Bone marrow, fat cells and dental pulp are a few sources[2].

The Challenges faced during the in-vitro formation of these stem cells is most importantly the time-consuming nature of cell culture which can reduce the cell differentiation potential significantly. Moreover, the proliferation and differentiation potential of the isolated MSCs is also affected by the choice of donor site for cell isolation. The perks of MSCs lies in their anti-inflammatory properties that can be described by the secretion of potent immunoregulatory factors inhibiting activity of T-helper cells, thus improving differentiation and leading to an increase of anti-inflammatory cytokines secretion. MSCs also prevent the antigen-presenting function of dendritic cells and macrophages[14].

The mesenchymal stem cell regenerative mechanisms

The therapeutic effect of MSC in ORN surrounds angiogenesis, immunomodulation, bone regeneration and ferroptosis regulation. The literature reveals that exosomes which are secreted by MSC can promote angiogenesis. Angiogenesis with MSC is enhanced by Notch and Jagged 1 signalling when stimulated with hypoxia-inducible factor-1 α (HIF-1α). Similarly, every parent cell for the mesenchymal exosome has a different pathway; human-induced pluripotent stem cells work when induced by the PI3K/Akt signalling pathway. Exosomes retrieved by human placenta-derived MSCs enables the angiogenic with increase in VEGF and miR-126 by stimulation of nitric oxide[3].

MSC-exosomes have proved to improve survival of neutrophils in congenital neutropenic subjects, in turn showing their efficacy to fight acute infection[15]. In labs, MSC-exosomes displayed immunomodulation by anti-inflammatory function by changing inflammatory cytokines secretion profile while in vivo, they exhibit immunomodulation pathway by antigen presenting cell (APC) mediated manner[15]. Exosomes are found to promote M2 polarization of macrophages which reduces M1 related cytokines, for example IL-6, IL-12, TNF- α & causes enhancement of IL-10 and TGF-β[1, 3].

Ferroptosis is a form of iron dependent, nonapoptotic type of cell injury which is gaining support for treatment of tumours. A lipid dynamics regulation protein named Prominin-2 helps emergence of multi-vesicular bodies and exosomes with ferritin content, preventing ferroptosis by transporting iron out of the cells. The exosomes that enroll in the ferroptosis resistance in tumour cells may reduce ORN by influence on the osteogenesis-related cells with ferroptosis resistance. The biocompatible nature and effectiveness of MSC exosomes is high. This ability might harbour an innovative idea for treating ORN by regulating ferroptosis[16].

The best time for stem cell administration is still unclear and asks for more endeavours, the literature is divided on the fact that the stem cells should be administered at the time of surgery as preventive therapy or after insult is evident (after ORN)[6]. Xiu et al has reported the effect of irradiation activated gingival fibroblast to have an inhibitory effect on the osteogenic differentiation of human bone mesenchymal stem cells (hBMSCs) , miR-23a/CXCL12 regulate osteogenic differentiation of hBMSCs, use of human gingival fibroblasts in radiation therapy to have preventive role in ORN by secreting exosomal miR-23a[17].

Future in a third world country

The clinical application of MSC is a challenge in actual clinical settings, but the field has proven itself to be promising in vitro and in early phase clinical trials. The field attracts further research in a prospective pattern involving patients and to look for a preventive or therapeutic course of ORN with MSC. In Pakistan, the are many obstacles in the roadmap of stem cell therapy, lack of skilled centres, poor socioeconomic status, lack of funds are a major hurdle. Yet, many centres are working in the recent advancements we emphasize on need of independent research centres for stem cell biology and to start patient-based trials.

Human organ transplant authority (HOTA) has developed guidelines (http://www.pmrc.org.pk/stem_cell_protocol.htm) for different diseases like thalassemia, leukaemia, lymphoma, spinal cord injury, myocardial infarction keeping in mind the religious sensitivities and customs of Pakistan. Oral cavity squamous cell carcinoma and its complications are a major disease burden in the largest city of country and related stem cell research is needed. Along with research, improvement in social services in post-transplant period and patient education is emphasized.

Conclusion

Stem cell therapy, though a promising avenue of research and one-day use in patients suffering from osteoradionecrosis of mandible. However, it carries a number of legal as well economic implications that needs to be further analysed. Our review should compel further studies into the subject to ensure safety as well as efficacy

of the therapy.

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