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Review

Radiotherapy for Graves' disease. The possible role of low-dose radiotherapy

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ABSTRACT

Immunomodulatory effects of low-dose radiotherapy (LD-RT) have been used for the treatment of several benign diseases, including arthrodegenerative and inflammatory pathologies. Graves' disease is an autoimmune disease and radiotherapy (RT) is a therapeutic option for ocular complications. The dose recommended in the clinical practice is 20 Gy (2 Gy/day). We hypothesized that lower doses (<10 Gy total dose, <1 Gy/day) could results in higher efficacy if we achieved anti-inflammatory and immunomodulatory effects of LD-RT.

We review current evidence on the effects of RT in the treatment of Graves' disease and the possible use of LD-RT treatment strategy.

1. Introduction

Graves's ophtalmopathy (GO) is an inflammatory disorder of the orbit and the most frequent manifestation of Graves' disease. GO is characterized by an excessive deposit of glycosaminoglycan (GAGs), an inflammatory infiltrate, and an overproduction of cytokines. Cytokines contribute to the local inflammatory process in the orbit.

GO is mostly associated with Graves' disease, and is its main extrathyroidal manifestation, but it can also occur in patients with Hashimoto's thyroiditis or rarely in euthyroid patients. GO is an autoimmune process with autoantibodies directed against thyrotropin receptor (TSRH). GO affects both orbits and involves orbital tissue, extraocular muscles, periorbital connective/fatty tissue and the lacrimal gland.[1] An excessive GAGs production and an infiltration of the orbital connective/fatty tissue and extraocular muscles by

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lymphocytes, predominantly T cells and macrophages are evident. The result is an increased volume of the extraocular muscles and orbital connective and adipose tissues, thus many clinical manifestations, like proptosis, are related mechanically to this increase in tissue volume.

Orbital radiotherapy (RT) is one of the proposed treatments. Usually, total doses of 10–20 Gy (1.8–2 Gy/day) are recommended. RT has a dual effect, inducing the production of pro-inflammatory citokines at high-doses per fraction while the opposite effect has been shown at low-doses per fraction.[2–7]

Excellent reviews have been published on the pathogenesis, clinical manifestations and treatment of ophtalmopathy and Graves' disease.[8] This review is restricted to data related with the possible use of low-dose per fraction (<1 Gy/day) and low-dose RT (LD-RT) (<10 Gy total dose).

2. Graves' ophthalmopathy and treatment options

GO is the major extrathyroidal manifestation of Graves' disease. GO is an invalidating and disfiguring disease affecting appearance and functioning of the eyes as well as impairing the quality of life of patients.[9–11] The symptoms of GO result from the inflammatory and fibrotic reactions in the retroorbital space. Exophthalmos, impaired muscle involvement, diplopia, blurred vision, periorbital oedema, chemosis, lid retraction and compressive optic neuropathy may be present. The most typical presentation symptoms include proptosis, pain, tearing, visual impairment and rarely blindness.[8]

Management of GO should be based on individualized analysis after thorough evaluation of each patient and requires a multidisciplinary approach from a team of physicians, including endocrinologists, ophthalmologists, radiologists, radiation oncologists and orbital surgeons.[12] Treatment should be provided in specialized centres, in the context of a multidisciplinary team to avoid consequences of delays in intervention and in optimizing therapy.

The treatment of GO is conditioned by the severity of the disease. The restoration of the euthyroid state and avoiding of hypothyroidism are essential in mitigating the progression of orbitopathy, this includes antithyroid drugs, surgery and radio-iodine. Corticosteroids have been used in the treatment due to the anti-inflammatory and immunomodulatory properties. Corticosteroid therapy provides relief of pain, retrobulbar pressure and oedema. intravenous glucocorticoid therapy is the treatment of choice in the active phase and surgical treatment in the inactive phase. The use of corticosteroids is associated with a considerable number of adverse events, especially in patients suffering from diabetes mellitus, hypertension, cardiovascular disorders, obesity and gastrointestinal diseases.[13] RT and cyclosporine in combination with corticosteroids are alternatives when monotherapy with steroids is insufficient during the active phase.

The thyroid function and the severity of GO should always be considered when making a treatment plan for GO. The European Group of Graves' Orbitopathy (EUGOGO) classifies GO severity based on subjective symptoms and objective signs into three categories: mild, moderate to severe and sight-threatening.[14] The last category is of major importance as these patients are at a risk of vision loss.

Patients of sight-threatening GO appear to have dysthyroid optic neuropathy or corneal breakdown and need immediate intervention.[14] On the other hand, the activity of GO refers to the presence of inflammatory signs. It can be measured through the clinical activity score (CAS) based on the classical features of inflammation. In this way, one point is given for each of the following features: spontaneous retrobular pain, pain of attempted up- or down gaze, conjunctival redness, redness of the eyelid, swelling of the caruncle or plica, swelling of the eyelid and chemosis. A score $\geq$3 represents active GO.[15] Orbital RT for GO is a well-established treatment modality for patients, as a sole therapy or in combination with glucocorticosteroids.[16,17]

Treatment of moderate or severe active disease has been limited to steroids and retrobulbar RT, particularly in the case of eye muscle involvement.[9,18–20] In the relatively rare case where vision is threatened, emergency decompression surgery can be performed. The proptosis, motility, or cosmetic concerns associated with stable GO are commonly remedied with surgical intervention.

3. Pathogenesis Graves' disease

GO is an autoimmune disorder, but the pathogenic mechanisms is not fully understood. Antibodies against the TSHR are believed to be the responsible for unregulated production of thyroid hormone; nevertheless IGF-1 receptor (IGF-1R) is also being considered a contributing autoantigen.[21] Autoimmunity in the orbital space is likely triggered by autoreactive T lymphocytes reaching the orbit and recognizing antigens shared by the thyroid and the orbit. Activation of various antigen-presenting cells produces a chronic inflammation. Secretion of cytokines causes expansion of the orbital fibroadipose tissue and infiltration/enlargement of extraocular muscles.[22]

The orbital fatty connective tissue increases and extraocular muscles are diffusely infiltrated by lymphocytes,[23,24] mainly T lymphocytes and macrophages. B cells, produce antibodies at least against TSHR.[25] Progression of GO is due to recruitment of activated T cells that amplifies the B cell response.[26] During the initial stages of GO, orbital infiltration by T cells activate fibroblasts, which produce extracellular matrix, differentiate to adipocytes and proliferate.[26] Fibroblasts, in turn, can initiate the early T cell infiltration of the orbit secondary to IL-16 and RANTES secretion, due to its chemoattractant proprieties, that promote T cell migration.[27] An orbital volume increase is due to fibroblasts proliferation, and adipocyte and GAGs accumulation, whereas fibroblast infiltration of extraocular muscle fibres leads to fibrosis.[28] Fibroblasts are the key cell in the pathophysiology of GO and the main target of the autoantibodies directed against TSHR. Fibrocytes in GO express high TSHR levels,[29] and triggering of this receptor results in TNF and IL-6 production.[30] Orbital fibroblasts produce GAGs as well as they also differentiate to either myofibroblasts or to lipofibroblasts.[31,32]