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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]

Immunohistochemical staining of retrobulbar adipose tissue in GO showed an increase HLA-DR expression, an activation of intercellular adhesion molecule 1 (ICAM-1), and a marked infiltration of activated T-cells, especially CD4, and macrophages (CD68) on retrobulbar fat. The perimuscular connective tissue showed an accumulation of CD4/CD8 T-cells, ICAM-1 and B-cells; and retrobulbar muscle tissue exhibit an increase of CD4, CD8 and CD68.[28] Th1-type cytokines predominate at initial GO stages, especially IL-1, a proinflammatory cytokine that is the key point in this stage. Proinflammatory cytokines (IFN-γ, TNF-β, and IL-2) produced by T-helper Th1 subtype have been found within the retroocular tissues. Th2-type cytokines appear in the late GO phase,[33,34] IL-4, IL-5, and IL-10 signal entry into the recovery phase.[21]

GAG synthesis by retroocular fibroblasts is stimulated by IL-1α, IFN-γ, and TGF-α. The early predominance of IFN-γ favours local inflammation and GAG production in vitro. IL-1α, IL-4, PDGF, insulin-like growth factor, and TGF-β stimulate fibroblast proliferation in vitro, while glucocorticoids diminish this effect.[21] IL-1 produced by macrophages and fibroblasts stimulates synthesis of GAGs by orbital fibroblasts. IL-1 receptor antagonist (IL-1RA) and soluble IL-1 receptor (sIL-1R) inhibit this GAG production.[35]

L-selectin and ICAM-1 levels are elevated in patients with active GO.[36,37] ICAM-1 levels have been positively correlated with GO severity measured with the Total Eye Score or activity assessed by the CAS.[38] An increase of soluble intercellular adhesion molecule-1 (sICAM-1) has been found in Graves' hyperthyroidism patients just before the onset of GO.[38] Serum ICAM-1 levels decrease in corticosteroid responsive patients[36] and changes in sICAM-1 levels during glucocorticoid therapy closely parallel changes in degree of inflammation. Changes in sICAM-1 serum concentrations correlate with the degree of periorbital inflammatory activity in GO and the response to glucocorticoid treatment.[39,40] When tested in a cell adhesion assay, GO sera containing elevated concentrations of sICAM-1 were found to enhance the attachment of peripheral blood mononuclear cells (PBMC) to interferon-gamma (IFN-γ)-treated retroocular fibroblasts in a dose-dependent manner.[39,40]

4. Radiotherapy for Graves' disease

In a very interesting survey, an estimated annual number of 1600 GO cases are treated in German RT departments.[41,42] With an 88% consensus, stages II–V are the typical indications for RT. Total RT doses in the range of 15–20 Gy were recommended by 76% of institutions, and conventional fractionation was the commonest (57%). Approximately 50% would prescribe salvage RT, and total doses in the range of 20–40 Gy were considered to be acceptable.

The role of RT in the management of GO is still controversial. However, recent randomized clinical trials have, with one exception, confirmed that orbital RT is an effective and safe therapeutic procedure for GO. Orbital RT has been used for over 60 years to treat thyroid eye disease alone or in combination with glucocorticoids or orbital decompression surgery. However, numerous observational and randomized controlled trials have yielded conflicting results concerning its efficacy.

The advantage of RT over glucocorticosteroids is that it is well tolerated with no common side effects.[43] While the established RT schedule is 20 Gy in 10 daily fractions, some studies suggest that lower doses may be sufficient for patients showing soft tissue signs without ocular dysmotility.[44] The duration of symptoms before RT has been found to be of great importance. Matthiesen et al.[16] reported that patients treated within <6 months from the onset of symptoms had worse results than those treated in the 6–12 month duration of the presence of orbitopathy. Kouloulias et al.[8] reported a median time of irradiation after the onset of GO of 9 months. A correct management of GO should include adequate patient counselling, concerning therapy outcomes, risks related to treatments, timing and the need for a long lasting follow-up. Despite the fear of radiation-induced tumours, this adverse event has so far not been reported in follow-up studies, even in the setting of reirradiation for GO.[16,45] On the contrary, radiation induced retinopathy has been documented in low quality technique treatments and with the coexistence of diabetes mellitus.[46] Cataract as late radiation toxicity is rarely seen when lens receive <10% of the prescribed radiation dose.[47] The new radiotherapy techniques improve the side effects of radiotherapy treatment.[48]

5. Anti-inflammatory mechanisms of LD-RT. Hypothesis for use LD-RT Graves' disease

Despite orbital irradiation at total doses of 10–20 Gy delivered at a rate of 1.8–2 Gy/day during 5–10 days is usually recommended, low-dose fraction irradiation has an anti-inflammatory role for benign diseases.[7] The inflammatory response is a tightly regulated process that involves a sequence of leucocyte–endothelium interactions, called rolling, adhesion and migration to the interstitial space (Fig. 1).[49]

Low-dose irradiation induces an increase in levels of TGF-β1, which is maximum 24 h after irradiation and returns to basal levels at 72 h. LD-RT in vivo studies have also shown a decrease of pro-inflammatory cytokines levels like IL-1β.[50]

Analysing the effects of LD-RT on an experimental model of acute systemic inflammation in mice, we found that LD-RT (0.1, 1.3 or 0.6 Gy) caused decreased adhesion of leukocytes in intestinal venules, and that and the anti-inflammatory action of RT did not depend on changes in ICAM-1 expression. LD-RT also induced overexpression of TGF-β1. This anti-inflammatory effect was maintained for 48 h after irradiation and lost at 72 h.[5,6]

Low doses of irradiation (0.2–0.8 Gy single dose) have shown to stimulate, in orbital fibroblasts, the production of IL-1 receptor antagonist, a potent inhibitor of pro-inflammatory IL-1, which were stimulated to a lesser degree with higher doses of irradiation (1–2 Gy single dose).[51] Overall, these data indicate that LD-RT can have a role in the treatment of GO diminishing inflammation.

Considering the pathogenesis of Graves' it is conceivable that LD-RT may provide a maximum anti-inflammatory effect while decreasing the late adverse events.

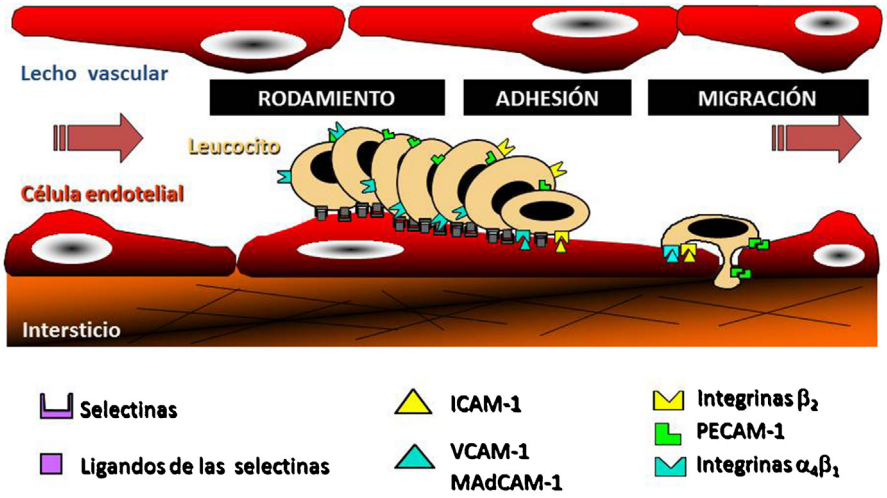

Fig. 1 – Diagram of steps of recruitment of circulating leukocytes. ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cellular adhesion molecule 1; MAdCAM-1, mucosal adressin cell adhesion molecule-1; PECAM-1, platelet-endothelial cell adhesion molecule 1

6. Conclusions

RT administered at high doses induces production of pro-inflammatory cytokines in immune cells and endothelial cells. Paradoxically, LD-RT acts upon cells that participate in the inflammatory response, producing an anti-inflammatory effect. This anti-inflammatory effect has been demonstrated in vitro studies, in experimental in vivo studies and in clinical studies. The efficacy of LD-RT has been demonstrated experimentally by lowering clinical inflammatory parameters and improving histological markers in various models of arthritis, with doses ranging from 0.5 to 1.5 Gy. In vitro studies suggest that LD-RT has a potent anti-inflammatory effect, inhibiting leucocyte-endothelium interactions at doses under 0.7 Gy.

Graves' disease is an inflammatory and autoimmune disorder related to thyroid disease. RT is an alternative treatment option. Considering current knowledge of pathogenesis Graves' disease, we propose that using lower doses of RT in the range 0.1–0.3 Gy could maximize anti-inflammatory effects and minimize toxicity, in contrast the dose fractionation treated with doses ranging from 1 to 2 Gy.

Properly designed and powered clinical studies are necessary to determine the most efficacious treatment dose and schedules, and to establish the role of LD-RT in the therapeutic algorithm of inflammatory conditions in Graves' disease.

Authors' contributions

MA and SS designed the review and performed the literature research. The manuscript was written for MA, SS and JP. PL, AR, AB, VL, MB and JP read and revised. All authors approved the final manuscript.

Conflict of interest

None declared.

Financial disclosure

None declared.

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