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Total Body Irradiation in Systemic Sclerosis: Moving from Contraindication to Indication?

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1. Abstract

Scleroderma is an autoimmune disease characterised by increased collagen synthesis and fibrosis affecting the skin, subcutaneous tissue and other organs. The systemic form, systemic sclerosis, affects multiple organ systems and is incurable, with treatment aimed at relieving symptoms and slowing disease progression. Localised scleroderma can progress to systemic sclerosis, with early involvement of the lungs and kidneys being key factors in morbidity and mortality. Conventional treatments include corticosteroids and immunosuppressive drugs, but long-term success remains elusive, with less than 50% of patients surviving five years. The aetiology of the disease is a combination of genetic, environmental and immunological factors. Radiotherapy, typically used in cancer, has historically been contraindicated in scleroderma due to its potential to accelerate fibrosis. However, low-dose total body irradiation (TBI) combined with haematopoietic stem cell transplantation (HSCT) has shown promise. This case study describes a 46-year-old man with progressive generalised scleroderma who underwent TBI and HSCT. Despite disease progression on conventional therapy, TBI at 8 Gy in four fractions followed by HSCT resulted in significant clinical improvements, including reduced skin sclerosis and improved lung function, without acute TBI-related toxicity. At 17 months, the patient showed significant functional improvement and stable lung function, although some skin sclerosis remained. This case supports the potential of low-dose TBI and HSCT in stabilising and possibly regressing systemic sclerosis. Further research is recommended to elucidate the role of TBI in the treatment of systemic sclerosis.

2. Introduction

Scleroderma is an autoimmune connective tissue disease characterized by increased collagen synthesis and fibrosis in the skin, subcutaneous tissues and other areas of the body. Localized form of scleroderma only affects the skin and the structures directly under the skin, whereas the systemic form, also called systemic sclerosis, affects many organs and systems. Systemic sclerosis is a serious disease without any proven cure, the goal of treatment is to relieve symptoms and to slow the progression of the disease. Localized scleroderma may progress to systemic sclerosis by time, early involvement of lungs and kidneys is the primary factor in morbidity and mortality [1]. Corticosteroids and other immunosuppressive drugs including cyclophosphamide, azathioprine, hydroxychloroquine and mycophenolate are used in the treatment. Despite research on biological and disease-modifying antirheumatic medications, none has demonstrated long-term success yet. Less than 50% of patients receiving traditional therapy survive for five years [2,3]. Though the precise origin of systemic sclerosis is unknown, a mix of genetic, environmental, and immunological variables are considered to be responsible [10]. Radiotherapy is a medical modality using ionizing radiation in the treatment of cancers and some benign diseases characterised by abnormal proliferation of cells. Radiotherapy is occasionally used in some rheumatic diseases, in those unresponsive to systemic treatment to

stop progression and to provide regression of the disease. However, past experiences showed that high-dose radiation can accelerate fibrosis in patients with scleroderma, thus radiotherapy has usually been considered as an absolute contraindication for the treatment of systemic sclerosis, and also a relative contraindication for the cancer patients with scleroderma [4]. Plenty of reports from cancer patients treated with high-dose radiation are available where radiation caused fibrosis in subcutaneous tissues and internal organs resulting in severe late effects in the skin, lungs, and other organ systems. However, the rate of subcutaneous fibrosis has been significantly low in clinical trials where much lower doses of radiation is delivered by total body irradiation (TBI), immunoablation and haematopoietic stem cell transplantation (HSCT). Reports from pilot studies of autologous HSCT in scleroderma patients have shown improvement in skin sclerosis and stabilisation of lung functions [5-9]. This article presents our experience in a patient who underwent TBI and HSCT after being diagnosed with progressive generalized scleroderma.

	Pre-OCIT	17th month
Pulmonary functions		
• **FVC**	**59 %**	**42 %**
• **FEV**	**69 %**	**52 %**
• **FEV1/FVC**	>85%	>85%
Renal functions	**Normal**	**Normal**
Rodnan skin score	**42**	**20**
Fine motor skill	**limited**	**Improvement**
HAQ score	**1.30**	**0.45**

3. Materials Methods

A 46-year-old man with symptoms of weight loss, pain in several joints, oedema, stiffness and cough was evaluated and diagnosed with generalized scleroderma with lung and renal involvement. The patient had 40 kg loss of body weight over the past year, accompanied by thinning and loss of hair, dry mouth and eyes, dysphagia, generalized oedema and shortness of breath. He had a mask-like facial appearance, generalized thickening of the skin (modified Rodnan skin score of 42), ulcers at fingers, generalized hypohyperpigmention, and mechanical hand deformities. The wrist, metacarpophalangeal and proximal interphalangeal joints were painful on palpation, active and passive movements were restricted. Pulmonary reserves were reduced, breath sounds were reduced in both lungs and peripheral pulses were very weak. Pulmonary function tests (PFT) were performed where FVC was 59%, FEV 69% and FEV1/FVC >85122%; many huge capillaries and bleeding spots were seen on capillaroscopy. He was treated with combinations of sulfasalazine, azathioprine, hydroxychloroquine, corticosteroid, methotrexate and cyclophosphamide. The disease progressed rapidly and Rituximab and mycophenolate mofetil were started, however no response was observed. The patient was considered as "treatment-resistant active scleroderma" and HSCT was planned with TBI in the conditioning regimen.

4. TBI Technique

The SCOT (The Scleroderma: Cyclophosphamide or Transplantation) regimen was decided, and a total dose of 8 Gy TBI with 2 Gy per fraction was planned in total 4 fractions in two days for lymphoablation prior to CD34+ HSCT. The radiation dose limits for lungs and kidneys were 2 Gy. The first fraction delivered from two lateral open fields while the patient was seated and without any protection for lungs and kidneys. Other three fractions were delivered from anterior and posterior fields in seating position, using individualized shielding blocks for lungs and kidneys. Position of the blocks were verified by ultrasonography for kidneys and by KV portal imaging for lungs.

5. Results

Patient tolerated the treatment well, no TBI-related acute toxicity was recorded. After a follow-up of 17 months although sclerodactyly and skin hardening secondary to scleroderma was persisting in both hands, lesions on the both extremities and the face were significantly reduced, significant functional improvement was present in tasks requiring fine motor movements such as grasping and reaching for objects. Rodnan skin score reduced to 20. No abnormalities of the renal functions and no significant deterioration of PFT (FVC 42%, FEV1 52%, and FEV1/FVC >85124%). The quality-of-life questionnaire (HAQ-DI), which assessed daily living tasks such general self-care and dressing, eating, sitting up, hygiene, walking, and grasping, showed a considerable improvement compared to pre-transplantation (HAQ Score 1.3 pre-transplant and 0.45 at the14th month).

6. Discussion

There is no known cure for systemic sclerosis. A range of immunosuppressive drugs may provide short to medium term benefit, however failed to stop ultimate disease progression in many patients. Several clinical studies reported promising results with hematopoietic stem cell transplantation in patients unresponsive to immunosuppressive treatment. Autologous HSCT is a procedure in which a patient's own stem cells are collected, stored, and then reinfused after conditioning regime of high-dose chemotherapy or irradiation. This treatment aims to "reboot" the immune system in by the elimination of defective immune cells attaching patients' own healthy cells. Improved skin and lung functions, reduction of fibrosis and inflammation, and a decrease in death rates are some of the possible advantages of HSCT for those with systemic sclerosis [11,12]. However, it is important to keep in mind that autologous HSCT is a high-risk procedure with potentially serious adverse effects and has a risk of mortality. Patients having a diagnosis of scleroderma who received high-dose radiation for the treatment of a cancer are under risk of serious toxicity. Radiation itself causes serious tissue damage which often results in fibrosis in long-term.

Scleroderma patients already has fibrosis in their tissues, and the fibrinogenic effects of radiation can add additional toxicity which may cause serious impairment or even mortality. Scleroderma patients whom had chest wall irradiation due to breast cancer experienced increased rate of radiation-related side effects, such as arm oedema, necrosis of the chest wall, brachial plexopathy, pneumonitis, and severe skin fibrosis with retractions and fistulae [13-15]. At present radiation is considered as a relative contraindication for breast-conserving surgery in scleroderma patients with breast cancer [16]. However, most clinical data comes from curative or adjuvant radiotherapy experience to treat the locoregional tumours where high doses of radiation in the range of 50-70 Gy was required. No data related to toxicity of low-dose radiation (10-12 Gy) to whole body among the scleroderma patients is available. There are few reports describing use of TBI as the conditioning regimen for HSCT in the patients with scleroderma [17]. Despite its demonstrated effectiveness, HSCT is still not commonly used. Among these reports the use of TBI and anti-thymocyte globulin as a conditioning regimen has emerged as a promising treatment option for patients with systemic sclerosis after the publication of the SCOT research. In the SCOT study, the dose to lungs and kidneys was limited to 2 Gy by using individualized pulmonary and kidney shielding. However, keeping the dose to lungs and kidneys below 2 Gy is not an easy task. TBI is usually applied in a seating position and contouring these organs using the CT slices taken while the patient lying flat on the CT couch will not accurately define their localizations. Verification of the position of kidneys using ultrasonography and lungs by X-ray may be a good solution coupled with real time dose verification using TLD chips or silicon diode dosemeters. Craciunescu et al. evaluated the renal protection and dosimetry of TBI in scleroderma patients where strict dose limits of 2 Gy was required and discussed the technique, challenges, and dosimetry of renal shielding. The results of this study demonstrated that the kidneys' exposure to radiation was significantly reduced by the renal shielding methods applied in this research. The study also shown that age, sex, body mass index, and other characteristics can affect the dosimetry of the total body irradiation [18]. It was pointed out as a result that patients receiving TBI should have their dosimetry parameters thoroughly assessed. The use of helical tomotherapy or VMAT for TBI was suggested by several authors, providing treatment in a lying position thus better positioning of the patients, and CT-based simulation and planning. Although these techniques for TBI are increasingly becoming common practice in the United States and Europe there is still a lack of clinical expertise and some concerns remain [19-21]. Ladbury et al. evaluated the effect of intensity-modulated total body irradiation (IM-TBI) for HSCT in in 14 scleroderma patients. The goal of the study was to assess the safety and effectiveness of this technique. Patients who had HSCT with IM-TBI conditioning was associated with favourable outcomes, including a decline in disease activity and a reduction in skin fibrosis. Although major adverse effects were uncommon, side effects were also recorded, including acute toxicity, gastrointestinal toxicity, and haematological toxicity [22]. In this paper we reported the a patient who underwent SCOT in our department and was followed up for 17 months. The favourable results with stabilization of disease progression without any significant toxicity is encouraging, and the dose limits and the technique can be considered in patients undergoing HSCT for systemic sclerosis.

7. Conclusion

HSCT may slow progression of the disease in patients with progressive scleroderma by providing disease stabilization and possible regression. Ensuring adequate pulmonary and renal protection, low-dose TBI used in the conditioning regimen seems to be a safe treatment. Further research is recommended to understand the role of TBI in the treatment of systemic sclerosis.

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