Radiotherapy Improves the Disability in Patients with Secondary Progressive Multiple Sclerosis

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ABSTRACT

Background: Multiple sclerosis (MS) as a complex neurological abnormality is marked with loss of myelin and axons due to chronic inflammatory and autoimmune responses. The modulatory properties of the low dose radiation (LDR) on inflammatory and immune responses have well known.

Objective: The current research aimed to assess the impacts of LDR on the disability in patients suffering from MS.

Material and Methods: This experimental pilot study was done on 10 patients with secondary progressive multiple sclerosis (SPMS). After magnetic resonance imaging, the SPMS patients were treated by LDR at a daily dose of 2 Gray for 5 consecutive days (totally 10 Gray dose) using a linear accelerator. The extent of the disability was evaluated one week after the completion of radiotherapy using expanded disability status scale (EDSS).

Results: After receiving radiotherapy, the patients had a feeling of wellbeing of some sort. The mean of EDSS was significantly reduced after radiotherapy compared with before irradiation (7.4±0.45 vs 6.35±1.18; P<0.017). EDSS more decreased in younger SPMS patients (P=0.0001), and in the women after LDR (P=0.027).

Conclusion: Radiotherapy can reduce fatigue and EDSS in patients with SPMS. The age and gender of patients may influence the LDR efficacy.

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Keywords

Human; Autoimmune Disease; Multiple Sclerosis; Radiotherapy; Disability

Introduction

Multiple sclerosis (MS) is a complicated demyelinating illness of nerves in the central nervous system (CNS) due to chronic inflammatory and immune responses [1]. MS affects around 2.5 million persons worldwide, and women are at higher risk than men (approximately with 2:1 ratio), worldwide [1]. The prevalence of MS in Kerman is 57.3 per 100,000, with the women to men ratio of 3:1 [2]. The MS is mainly classified to 4 types based on the expression of the clinical patterns, including relapsing-remitting (RRMS), primary progressive (PPMS), secondary progressive (SPMS) and progressive relapsing (PRMS) [1]. The rupture of the blood-brain barrier (BBB) and massive leukocytes accumulation [including dendritic cells (DCs) lymphocytes, monocytes and macrophages] into the CNS are key phenomenon

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happen during MS [1, 3]. T Lymphocytes, in particular, Th1- and Th17 cell-mediated responses promote pathogenic reactions while regulatory T (Treg) and Th2 cells play protective role during MS [4-6]. The microglia (as the brain-resident macrophages) and astrocytes also contribute to the immunopathologic process of the MS by releasing proinflammatory cytokines [7]. Experimental autoimmune encephalomyelitis (EAE), an inducible disorder in rodents, is considered as a reliable model for assessment of developing drugs for possible treatment of MS [1].

Experimentally, it has been demonstrated that low and high dose of radiation exerts different effects on the leukocytes as Th1 cell responses were induced by low dose radiations while Treg cells are triggered by high dose radiation [8]. Low-dose ionizing radiation (LDR) has also been shown to have modulatory influences on the generation of the proinflammatory cytokines and chemokines [9, 10]. It has been also reported that high dose radiation downregulates the expression of costimulatory molecules on human DCs and reduces their capacity to present antigen to specific T cells [11]. High dose radiation also impairs the immune function in mice so that reduces lymphocyte proliferation, the percentage of CD8+ T, and the cytokine production [12]. Moreover, high dose radiation enhances the Th2 cell-related responses [11]. Furthermore, the human Th17 cells are highly susceptible to radiation-induced senescence, indicating that radiation has damping effects on these cells [13]. Ionizing radiation promotes Th2 cell immune response while reduces Th1 cell immune responses in experimental animal models and survivors of atomic bomb. Th1/Th2 diversion toward Th2 cells may be an important reason for radiation-induced immunosuppression [8, 14, 15]. Collectively, radiation may have beneficial effects on the autoimmune disease through modulation of immune system, although its doses, timing and treatment program need fundamental standardization.

The beneficial effects of LDR was indicated in animal models of EAE, collagen-induced arthritis and systemic lupus erythematosus, leading to the attenuation of the disease severity accompanied with reduced levels of IL-6 and IFN-γ and enhanced number of Treg cells [16]. According to our knowledge, the effects of LDR on MS patients was not evaluated, yet. Here, a radiotherapy program was applied in patients with MS to clarify beneficial effects.

Material and Methods

Patient selection

This experimental pilot study was conducted on patients with secondary progressive multiple sclerosis (SPMS) disease in Kerman MS center (affiliated to Iranian MS Association) and diagnosis was done based on the McDonald's Revised Criteria. Advanced (disabled) patients with a physical disability levels that is higher than 6 and fully-aware patients were selected. In the brain magnetic resonance imaging (MRI) scan of participants, the pituitary height was equal to or more than 6 mm. The investigators didn't change anything in the preceding treatment protocol. This study was carried out after approval of the local ethics committee and then registered in Iranian Registry of Clinical Trials (IRCT20111217008436N4). The inclusion criteria for the patients were signing an informed consent after a complete walkthrough (this radiotherapy was unprecedented for the MS patients).

Radiotherapy technique

This study used linear accelerator (Elekta, China), which is the most usual procedure of therapeutically radiation. All patients were treated in supine position. Thermoplastic pillows and masks were used to fixate the patients. Placed the required markers, all patients went through brain CT-scan imaging (Simax, Poland) with a slice thickness of 5 mm. The treatment field included the sellar region plus a margin of 1 cm. The investigators took pains

not to involve the cranial nerve and tract, as far as possible. To this end, a shield was applied in special cases. All patients were treated with lateral and parallel opposite fields, at a daily dose of 2 Gray for 5 consecutive days, totally 10 Gray using a linear accelerator.

Assessment of the expanded disability status scale (EDSS)

EDSS is commonly applied in clinical evaluations to estimate the disability of MS patients [17], and is also a clinical scoring system, ranging from 0 to 10, in which 0 indicates no disability and 10 refers to death due to MS [17]. Here, the extent of the disability was evaluated one week after the completion of radiotherapy using EDSS.

Statistical analysis

The extent of the EDSS was indicated as mean±standard error of mean (SEM). The *student t-test* was applied to compare the differences in variable and the P-value of less than 0.05 was defined to be significant. The data were analyzed by statistical SPSS software (version 22, Chicago, IL, USA).

Results

This pilot study was conducted on 10 secondary progressive MS patients with EDSS of 7.4±0.45. The average age of patients was 42.6±7.0 years old, and the average duration of disease was 13±4.7 years. After receiving the 10 gray radiotherapy, the patients had a feeling of wellbeing of some sort. One week later, the patients' physical examination was performed, and the EDSS was significantly reduced to 6.35±1.18 (P=0.017) (Figure 1). The EDSS reduction was not significantly associated with relapse of MS attacks (P=0.530), the height of hypophysis (P=0.609), and the duration of disease (P=0.420). The EDSS reduction was significantly associated with the age and gender of patients (the EDSS more decreased in younger MS patients (P=0.0001), and in the women compared to men (P=0.027) (Table 1). The MS patients at the initial sages with visual abnormalities displayed a better response to radiotherapy compared to patients with paraparesia (P=0.004).

Discussion

Radiotherapy with similar doses used in this

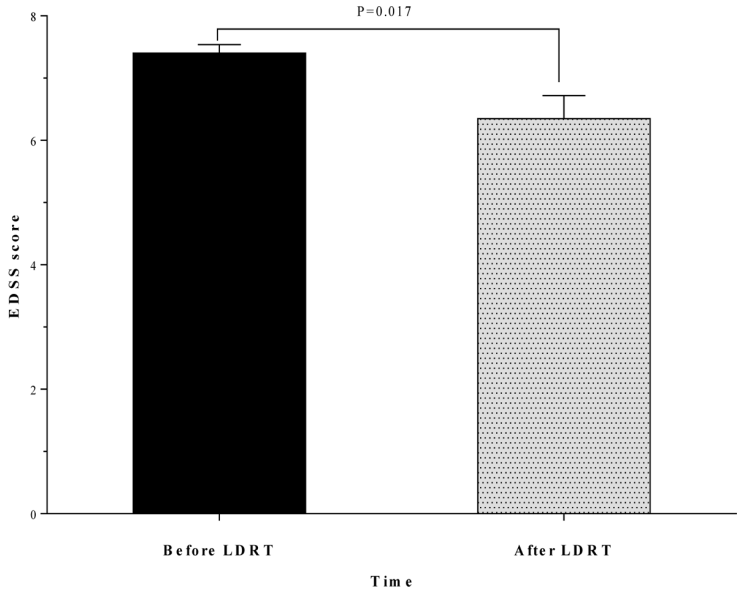

Figure 1: Expanded Disability Status Scale (EDSS) score before and following low dose radiation therapy (LDRT). In total patients, the EDSS score was significantly reduced compared with before LDRT (P=0.017).

Table 1: Comparison of the expanded disability status scale (EDSS) score before and following low dose radiation therapy (LDRT) according to gender.

Group	Gender	Number	·EDSS score before LDRT	EDSS score after LDRT	*P* values
Multiple sclerosis patients	Men	3	7.33±0.44	6.50±0.86	*0.44
	Women	7	7.42±0.13	6.28±0.43	**0.027
	Total patients	10	7.40±0.14	6.35±0.37	***0.017

·The scores of expanded disability status scale (EDSS) were shown as mean±standard error of mean (SEM). *The difference of the EDSS score of men patients before and after low dose radiation therapy (LDRT) was not significant. **The EDSS score in women patients after LDRT was remarkably reduced compared with before radiation (P=0.027). ***In total patients, the EDSS score was remarkably reduced compared with before radiation (P=0.017).

study has been also applied in patients with Graves' Ophthalmopathy [18, 19]. A LDR program has been also applied on the disease symptoms in patients with knee osteoarthritis, although no benefit effects were observed [20]. Here, the results indicated that a radiotherapy using LDRT remarkably mitigated EDSS in SPMS patients. In agreement with our findings, in an animal model of EAE, it was indicated that repeated 5 Gy-gamma irradiated-mice with EAE expressed lower pathologic alterations and clinical grades than non-irradiated mice with same disorder [21]. Irradiation is thought to delay the progression of the pathologic reactions and ameliorates the disease signs in EAE mice. Irradiation slightly reduced the TNF-α production in EAE mice [21]. The levels of IL-6, which act as an inducer of pathogenic Th17 cells, and the frequency of auto-reactive B cells were also reduced in EAE mice [21]. The serum levels of anti-MBP antibody were also reduced in the in the radiation-exposed-EAE mice compared with in non-exposed EAE animals. Irradiation also reduced the IL-17 quantities in EAE animals. The percentage of Treg cells in the radiation exposed-EAE mice was remarkably higher than that non-irradiated animals with EAE [21].

We observed that female patients exhibit better response to radiotherapy. Before radiotherapy, men and women did not exhibit remarkable difference concerning the EDSS grade. Although the prevalence of MS is greater in women compared to men, it was reported that women experience less severe diseases compared to men and men with MS exhibit worse neurodegeneration compared with women [22]. The male gender has been associated with shorter time between MS onset to reaching to certain disability levels compared to female gender [22, 23]. The atrophy of subcortical gray region and cognitive impairment were observed worse in men compared women with MS [22, 24, 25]. Thus, it seems that the MS-related pathological mechanisms may partly differ in men and women, affecting their responses to any therapeutic program such as radiotherapy.

We also observed that younger patients exhibit better response to radiotherapy. The results of a study indicate that young adult patients with MS exhibit greater disease activity and higher lesions in their CNS [26]. Thus, immnopathologic mechanisms in younger patients may be more sensitive to the radiotherapy effects. Moreover, effective CNS-related repair mechanisms in young MS patients may explain their better response to treatment compared to older patients, even in the presence more inflammatory responses and greater lesions [27]. The better response of the younger patients to radiotherapy may be also attributed to the progression of the disease with age.

Although the results of this study indicate the attenuating impacts of a radiotherapy on the EDSS grades, there are major concerns reading the radiotherapy as some important side

effects were related to this method, especially development of some malignancies. As for the limitations of this research, the effects of radiotherapy on the immune and inflammatory parameters were not parts of our research project. We need more long-term studies and patients with lower disabilities (EDSS: 4.5–6.0) to confirm the positive and lasting outcomes of radiotherapy. Our patients were in advanced stages, and suffered from axonal loss, thus the reversibility couldn't be produced.

Conclusion

In summary, LDR can reduce fatigue and EDSS in SPMS patients. However, the age and gender of patients may influence the LDR efficacy.

Authors' Contribution

HA. Ebrahimi contributed to the study conception and design, supervision of study, data analyses, writing the first draft of the manuscript; MH. Larizadeh contributed to data collection, data analyses, writing the first draft of the manuscript; M. Saba contributed to data collection, data analyses: writing the first draft of the manuscript; A. Jafarzadeh contributed to data analyses and interpretation and revision of the manuscript. All the authors read, modified, and approved the final version of the manuscript.

Ethical Approval

The Research protocol was by the ethical committee of Kerman University of Medical Sciences and registered with an ethic code: IR.KMU.REC.1396.1920.

Informed Consent

The patients were enrolled into the study if they agreed and informed written consent was also obtained from them.

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Conflict of Interest

None

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