Evaluation of narrow band UVB therapeutic effect on chronic mucocutaneous graft versus host disease lesions: A case series

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Background: Chronic graft versus host disease (cGVHD) is a major cutaneous complication of bone marrow transplantation (BMT). Although milder forms of this process may be associated with a lower incidence of tumor recurrences, it is mandatory to develop a more efficient and less harmful therapeutic approach.

Methods: This case-series study enrolled 7 patients diagnosed with chronic mucocutaneous GVHD. We divided the patients into three major categories based on the type of skin lesions: sclerodermoid, lichenoid, and mixed. Patients received several packs of narrow band UVB (NBUVB) phototherapy. Each pack contained ten sessions of NBUVB (311 nm) with a duration of at least ten seconds and a fixed radiation dosage (6 mj/cm^2) during the treatment.

Results: There were 3 patients diagnosed with lichenoid skin lesions, 2 with sclerodermoid lesions, and 2 had mixed cGVHD lesions. During the follow up period one patient was excluded due to a lower respiratory tract infection. The mean response ratio was 42% with a mean satisfaction level of 5.5 out of 10. The lichenoid group had the best, most rapid response. There were no serious adverse effects reported.

Conclusion: Narrow band UVB phototherapy is useful as an adjuvant therapeutic modality in cutaneous lichenoid and intraoral cGVHD with no serious adverse effects.

Keywords: chronic graft versus host disease, phototherapy, narrow band ultraviolet B, bone marrow transplantation

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INTRODUCTION

Chronic graft versus host disease (cGVHD) is a major cutaneous complication of bone marrow transplantation (BMT) with high mortality and morbidity. Chronic graft versus host disease usually begins about 3 months after BMT. Since the milder forms of this process may be associated with a lower incidence of tumor recurrence, it is mandatory to find a more efficient, less harmful therapeutic approach [1].

Chronic graft versus host disease is seen in

approximately 25% of patients who survive more than 6 months. It is classically divided into lichenoid and sclerodermoid forms. Lichenoid lesions are characterized by violaceous, lichenoid papules usually on the extremities and mucosal involvement present with lichen planus-like lesions and leukoplakia. The more advanced sclerodermoid cGVHD is characterized by plaques of dermal sclerosis and eventually by generalized scleroderma [1,2].

Improvements in therapy guidelines are necessary considering the major effects of GVHD on quality of life [2-4]. The standard first-line therapy is daily oral corticosteroids either alone or in combination with cyclosporine or systemic tacrolimus. However, improvement of the cutaneous GVHD is not always achieved with the above-mentioned systemic and/or topical treatments and carries the potential to cause severe morbidity and mortality [5].

Narrow band Ultraviolet B (NBUVB) and UVA have immunomodulatory effects. Reduction in the number of epidermal dendritic cells has been seen following phototherapy [6]. The antigen presenting process and suppressor T cell behavior seems to be altered. Other theories suggest higher tissue metalloproteinase activity and improvement in cytokine interactions [7].

In recent years, NBUVB (311–313 nm) has been found to be a beneficial adjuvant treatment in patients refractory to first-line immunosuppressive drugs. Compared with psoralen and UVA (PUVA) and immunosuppressive agents, NBUVB is less expensive, has a lower risk of delayed hypersensitivity reactions, along with fewer cosmetic discomforts and bone marrow suppression. There are no expected gastrointestinal and hepatic adverse effects and drug toxicity [7,8]. This treatment is also associated with a lower risk of carcinogenicity [9].

PARTICIPANTS AND METHODS

In this case-series study, we enrolled seven patients diagnosed with cGVHD following BMT. Both a dermatologist and hematologist examined the patients. Bone marrow transplantation was performed because of acute lymphoblastic leukemia (ALL) and Fanconi anemia in two patients, acute myeloblastic leukemia (AML) in two, and chronic myelogenous leukemia (CML) in the other patients.

We obtained a complete medical history from each patient, in addition to an ophthalmology consult and antinuclear antibody (ANA) profile. A total of 7 (3 lichenoid, 2 sclerodermoid, and 2 mixed) patients started phototherapy. During the study, patients received standard systemic suppression therapy.

Patients received several packs of NBUVB phototherapy on their bodies. The duration of each package was at least four consecutive weeks. Each package contained 10 treatment sessions of NBUVB (311 nm), approximately three non-consecutive sessions per week, with a duration of at least 10 seconds per session. Although we increased the duration of radiation in each treatment session, the intensity was fixed (6 mj/cm^2). We photographed all of the present primary lesions before and after complete clinical response, and during the follow up period.

The radiation source was a cabin composed of 24 lamps (Philips Lighting BV, Roosendaal, Netherlands). Maximum intensity of the ranged from 310-315 nm with a the peak of 311 nm. The radiation dosage was controlled by a Waldman UVB detector (Waldmann, Villingen-Schwenningen, Germany).

Duration of radiation and number of the phototherapy packages were determined based on clinical response and probable complications of aggravation, incompliance, etc. according to an expert opinion. We took into consideration the possibility of carcinogenicity and covered critical areas such as the eyes and genitalia by a protective device (mechanical and/or chemical antisolar). Patients with mucosal involvement were requested to keep their mouths open during the radiation treatments.

A dermatologist evaluated all study patients prior to each session. Clinical response was determined as erythema, scaling, and development of hypopigmentation in the active lesions compared to the initial lesions.

We divided clinical response into three groups: complete (>75%), partial (25%-75%) and weak (<25%), which was estimated by a dermatologist (expert opinion).

An evaluation was performed on the degree that patients could open their mouths (height) in order to obtain an objective parameter for improvement in patients with intraoral lesions. This percentage was also based on an expert opinion.

The follow up period continued for three months after treatment.

Study proposal was approved by the local ethics committee. Patients consented to enter the study and signed written consent forms.

RESULTS

Although all patients received NBUVB phototherapy, one was excluded because of a lower respiratory tract infection in the third month of therapy.

There were three patients diagnosed with the lichenoid type, two had the sclerodermoid type, and two patients had the mixed type. The mean body surface area of involvement was 55.7% at baseline which reduced to 42% at the end of the follow up period. The mean patient satisfaction rate was 5.3 out of 10.

The mean body surface area of involvement before treatment was 51%, whereas it was16.6% after the treatment sessions in the lichenoid group, with a response ratio of 53.3%.

In the sclerodermoid group, the mean body surface area of involvement at baseline was 55% and 25% after treatment, with a response ratio of 32.5%. The mixed group had a baseline mean body surface area of involvement of 60%, which reduced to 20% after treatment, with a response ratio was of 35%.

We observed no serious complications during the three month follow up period. The mean numbers of phototherapy sessions were 39 (lichenoid), 43 (sclerodermoid), and 31 (mixed types).

The mean total radiation dosages were 21124 mj/cm^2 (lichenoid), 19960 mj/cm^2 (sclerodermoid), and 16640 mj/cm^2 (mixed types).

The mean treatment duration was 84 days for the lichenoid group, 98 days for the sclerodermoid group, and 64 days for the mixed group.

The lichenoid group had a mean initial open mouth height of 3.15 cm and a final open mouth height of 3.75 cm. These values were 4 cm (initial) and 5.75 cm (final) in the sclerodermoid group, whereas the mixed group had a mean open mouth height of 4.75 cm (initial) and 5 cm (final).

During this trial no cases reported any recurrence or BMT failure.

At the end of the study and during the three month follow up all patients experienced decreases in immunosuppressive drug doses compared to the initial doses.

DISCUSSION

Chronic GVHD may be resistant to standard immunosuppressive therapy. PUVA is limited by a wide range of unwanted effects. A novel improved form of UVB phototherapy, NBUVB, has been proven to be very effective in T-cell mediated dermatoses since it impacts the skin's immunity through antigen presenting cells, cytokines, and apoptotic pathways [6-9].

Although all patients experienced some benefit from the treatment, as predicted, we observed the best response in the lichenoid group with minimal complications and maximum satisfaction rates.

In a study by Grudmann-Kollmann *et al.*, ten patients with GVHD who did not respond to common immunosuppressive therapy received NBUVB. Of these, seven had complete response and three showed significant responses during the treatment course [7].

Enk *et al.* studied five cGVHD patients (sclerodermoid in two patients, lichenoid in one patient and intraoral cGVHD in two patients) unresponsive to standard immunosuppressive drugs. The patients received adjuvant UVB phototherapy. The patient with lichenoid GVHD experienced complete clearing of the cutaneous lesions [9].

Brazzelli *et al.* reported complete responses in 80% of cGVHD pediatric cases (8 patients) after a median number of 29 treatments which corresponded to a median of 7.5 weeks (52 days) of treatment. The average cumulative dose was 28.71 j/cm^2. Only two patients reported partial remission [10].

Response characteristics and criteria determination were controversial in the sclerodermoid clinicopathology state. Atkinson *et al.*, used different measure including skin physical examination (structure, texture, pigmentation and thickness), ultrasound, open mouth height, patient satisfaction rate, and skin biopsy because of the lack of GVHD grading [11]. According to their findings, in both the treatment and follow up periods, patients showed partial responses, however they were well satisfied with smoothness, less skin rigidity, and higher open mouth height [11]. In the Enk *et al.* study, both

patients with sclerodermoid changes had significant relief of pruritus but showed no changes in their sclerodermoid skin lesions. Intraoral lesions cleared in one patient [9].

In the present study, one of the patients in the sclerodermoid group had flexion deformity and was wheelchair-bound from the beginning of the treatment. Despite dramatic improved, that patient expired because of causes not related to NBUVB. The partial effect on sclerodermoid cGVHD might be explained by the inability of UVB radiation to reach the dermis, which is the main location of the pathological events that characterize sclerodermoid cGVHD [8,9].

Although lichenoid lesions showed better response in the mixed group, we did not observe any complete responses.

Mucosal involvement improved satisfactorily in all of three groups This improvement was especially observed in the sclerodermoid group and considered to be the main reason for patient satisfaction in this group.

Elad *et al*. found that intraoral UVB was a valuable modality in the treatment of resistant cGVHD. In their study, intraoral UVB irradiation (0.02 mj/ cm^2) was administered 2 or 3 times per week for two patients. Both reported early, satisfactory responses [12].

In our study the extent and severity of mucocutaneous involvement significantly decreased. Patients noted improvements in quality of life. At the end of the trial and during the three month follow up period, we noted that the immunosuppressive drug dosage decreased compared to the first dosages in all patients, which might be due to the positive effect of NBUVB.

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