Low Dose Psoralen Plus Ultraviolet A (PUVA) Is an Effective and Safe Method for the Treatment of Chronic Graft Versus Host Disease

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Abstract

Background: Chronic graft versus host disease (ch.GVHD) is the most frequent late complication after allogenic stem-cell transplantation. Systemic immunosuppressive agents are usually required to control the disease. Psoralen plus UVA (PUVA) has been used for the treatment of ch.GVHD with variable beneficial effects. The objective of this study was to assess the efficacy and safety of a relatively lower dose of oral psoralen compared with previous reports, for the treatment of ch.GVHD patients with PUVA.

Methods: Eleven patients who received allogenic bone marrow transplantation and had severe progressive ch.GVHD that was unresponsive to conventional immunosuppressive treatments were treated with oral 8-methoxypsoralen (0.2 mg/kg, up to 10 mg) two hours before exposure to UVA.

Results: The patients received a median of 43 treatments (range: 18 to 72). Mean cumulative dose of UVA was 200.5 J/cm2 (range, 116.5-306.5 J/cm2). In four of the 11 patients, there was a complete resolution of cutaneous ch.GVHD and the remaining seven patients achieved partial response with PUVA treatment. Complete and partial remission was observed in four and six patients with lichenoid lesions, respectively, but all of the four patients with sclerodermoid GVHD showed partial response to PUVA treatment. We observed no side effects like phototoxicity, nausea and vomiting, and exacerbation of GVHD. Liver enzymes raised in five patients, causing no significant morbidity for them.

Conclusion: Low-dose psoralen plus UVA can be a safe and effective therapy for chronic cutaneous GVHD. Although the number of treatments and total cumulative exposure to UVA was rather high in our study, we observed no phototoxic reaction or severe irreversible liver damage due to phototherapy, which may be because of a relatively lower dose of methoxsalen used in our patients. Psoralen plus UVA is effective particularly in lichenoid GVHD lesions but sclerodermoid lesions may also benefit from this therapy. *(Iran J Dermatol 2008;11: 137-142)*

Keywords: bone marrow transplant, phototherapy, ultraviolent A

Introduction

Chronic graft versus host disease (ch.GVHD) remains the most frequent late complication after allogenic hematopoitic stem-cell transplantation, and represents the major cause of morbidity and mortality in long-term survivors[1]. Clinically and histologically, two different forms of chronic cutaneous GVHD can be distinguished: Lichenoid and Sclerodermoid. Immunosuppressive agents such as prednisolone and cyclosporin are used in the treatment of ch.GVHD. These therapies cause significant morbidity and mortality particularly due to superimposed opportunistic infections[2]. Psoralen plus UVA (PUVA) has been used for the treatment of GVHD with variable beneficial effects[1-7].

To date, the appropriate dose of psoralen and the amount of exposure to UVA are not determined

weighting the efficacy of PUVA treatment against its side effects. In this case series of patients with ch.GVHD resistant to standard immunosuppressive treatments, we used phototherapy with a lower dose of oral psoralen compared to previous reports. We have described the efficacy and cutaneous and systemic side effects of PUVA treatment in our patients.

Patients and Methods

Patients:

Eleven patients (7 male, 4 female, age: 6-31 years) who received an allogenic bone marrow transplantation (BMT) and had severe progressive ch.GVHD unresponsive to conventional immunosuppressive treatments were referred to our clinic for PUVA therapy between the years 2001 and 2003. All patients received HLA-identical allogenic bone marrow transplantation from siblings. The diagnosis of cutaneous ch.GVHD was established by clinical examination by two dermatologists and an oncologist, along with histological study. These patients developed ch.GVHD at a median time of eight months (range, 5 to 20 months), after BMT. For prophylaxis of acute GVHD, patients had received cyclosporin and prednisolone, and in one patient thalidomide was added. Chronic GVHD was treated with corticosteroids alone or in combination with cyclosporin, thalidomide or azathioprin. All the patients or their parents signed an informed consent before beginning PUVA therapy. All the patients were maintained on their previous conventional immunosuppressive protocol of treatment. Before commencing PUVA therapy, despite a mild elevation of liver enzymes in seven patients, there were no significant systemic abnormalities due to ch.GVHD. All patients had a normal baseline eye examination performed by an ophthalmologist and negative antinuclear antibodies.

Phototherapy schedule:

Psoralen and UVA were administrated in a standard fashion in a cylindrical stand-up radiator equipped with 48 PUVA fluorescent bulbs. Low dose oral 8-methoxypsoralen (0.2mg/kg, up to 10 mg) was used two hours before exposure to UVA. Appropriate eye protection was provided in the cabin and on the day of therapy. Genital area was shielded in males during exposure. The treatment was given three times a week on nonconsecutive days (Saturdays, Mondays, and Wednesdays). The initial dose of UVA was 0.5 J/cm2 and in the absence of phototoxic reactions, increments of 0.5 J/cm2 were given every two treatment sessions. Phototherapy was continued for at least 12 weeks. The treatment was stopped if complete response was achieved or no additional clinical improvement was detected for at least 4 weeks.

Patients were visited weekly by a dermatologist and monthly by an oncologist. All patients were instructed to make six monthly follow-up visits by a dermatologist after finishing PUVA treatment for the evaluation of long-term side effects of the treatment. Full blood counts and liver function tests were checked before the treatment and monthly thereafter. In the cases of oral involvement, the patients were advised to open their mouths in the cabin during the phototherapy.

Table 1: *Profile of 11 patients with chronic GVHD treated with PUVA*

Case	Age/Sex	Diagnosis	History of acute GVHD	GVHD prophylaxis	GVHD Onset after BMT	Skin involvement	Extra-cutaneous involvement	Skin Biopsy before treatment
I	19/M	AML	+	P + CyA	8 mo	Lichenoid + mucosal	Hepatic	Lichenoid
II	21/M	Aplastic Anemia	+	P + CyA	8 mo	Mixed lichenoid & sclerodermoid+ mucosal	Hepatic	Sclerodermoid
III	29/F	CML	+	P + CyA	6 mo	Lichenoid + mucosal	-	Lichenoid
IV	30/F	CML	+	P + CyA	6 mo	Lichenoid + mucosal	-	Lichenoid
V	20/F	AML	+	P + CyA	20 mo	Sclerodermoid	-	Sclerodermoid
VI	15/M	Fancony Anemia	+	P + CyA	12 mo	Mixed lichenoid & sclerodermoid	-	Lichenoid
VII	6/M	Major Thalassemia	+	P + CyA	5 mo	Lichenoid + mucosal	Hepatic	Lichenoid
VIII	11/F	Major Thalassemia	+	P + CyA	6 mo	Lichenoid + mucosal	Hepatic	Lichenoid
IX	27/M	CML	+	P + CyA + T	5 mo	Lichenoid + mucosal	Hepatic	Lichenoid
X	22/M	CML	+	P+ CyA	12 mo	Mixed lichenoid & sclerodermoid	Hepatic	Lichenoid
XI	28/M	CML	+	P+ CyA	8 mo	Lichenoid + mucosal	Hepatic	Lichenoid

P= Prednisolone, CyA= Cyclosporin A, T= Thalidomide, AML= Acute Myelocytic Leukemia, CML= Chronic Myelocytic Leukemia, M=Male, F=Female, mo=Months

Table 2: *Details of treatment with PUVA in 11 patients with GVHD*

Case	Chronic GVHD therapy	Dose of psoralen (mg)	Total number of PUVA treatments	Total cumulative UVA dose (J/cm^2)	Number of treatments to the onset of improvement	Total cumulative dose to the onset of improvement
I	P+ CyA	10	61	275	22	39.5
II	P+ CyA	10	72	306.5	13	25
III	P+ CyA	10	41	120	25	44.5
IV	P+ CyA	10	45	206.5	21	63.5
V	P+ CyA	10	41	298	16	72
VI	P+ CyA	10	43	167.5	10	25
VII	P+ CyA+T	10	52	116.5	29	42.5
VIII	P+ CyA	10	40	143	12	21.5
IX	P+ CyA	10	46	172.5	23	42.5
X	P+ CyA	10	18	-	-	-
XI	P+ CyA	10	19	-	-	-

P= Prednisolone, CyA= Cyclosporin A, T= Thalidomide

Table 3: *Outcome of treatment with PUVA in 11 patients with GVHD*

Case	Clinical Response	Side effect	Pathological Response	Six month follow- up	Current status
I	CR for lichenoid and mucosal	Mild LFT elevation*	CR	Remission	Remission
II	CR for lichenoid and mucosal PR for sclerodermoid	-	PR	Remission	Remission
III	CR for lichenoid and mucosal	Sever LFT elevation**	CR	Remission	Remission
IV	PR for lichenoid and mucosal	-	CR	Remission	Remission
V	PR for sclerodermoid	-	CR	Remission	Remission
VI	CR for lichenoid PR for sclerodermoid	Mild LFT elevation	-	Remission	Death
VII	PR for lichenoid and mucosal	Mild LFT elevation	-	Remission	Death
VIII	PR for lichenoid and mucosal	Mild LFT elevation	-	Death	Death
IX	PR for lichenoid and mucosal	-	-	Remission	Remission
X	PR for lichenoid and sclerodermoid	-	-	-	Worsening
XI	PR for lichenoid and mucosal	-	-	-	Remission

CR= Complete Remission, PR= Partial Remission, LFT= Liver Function tests
* Mild LFT Elevation= less than three times of normal range
** Severe LFT Elevation= three times or greater than the normal range

Clinical and pathological response:

Cutaneous complete response was considered as resolution of all the clinical evidence of active skin lesions. It means disappearance of lichenoid lesions with acceptance of remaining post lesional hyperpigmentation and softening of sclerotic patches in sclerodermoid ch.GVHD lesions. Cutaneous partial response was defined as resolution of 50% or greater decrease in skin lesions. Likewise, complete and partial response of oral lesions of ch.GVHD was defined as resolution of all the active lesions in oral mucosa and 50% or greater decrease in oral lesions, respectively. Pathologically, the response was defined as significant decrease in the dense collagen bundles for sclerodermoid type and resolution of lichenoid infiltration in the presence of melanophages for lichenoid type.

Results

Patients' demographic data are shown in table 1. The patients received a median of 43 treatments (range, 18 to 72). Median number of treatment sessions before the onset of clinical improvement was 21 sessions (range, 10 to 29). Mean cumulative dose of UVA was 200.5 J/cm2 (range, 116.5-306.5 J/cm2). In four of the 11 patients, there was a complete resolution of cutaneous ch.GVHD and the remaining seven patients achieved a partial response with PUVA treatment. All of the ten patients with lichenoid skin lesions responded to therapy (4 completely, 6 partially). Clinically, pure sclerodermoid lesions were observed in one patient and mixed lichenoid/ sclerodermoid lesions were seen in three patients, all of which showed partial response to PUVA treatment. In patient II and VI that presented with diffuse lichenoid and localized areas of sclerodermoid GVHD, lichenoid changes resolved completely while the sclerodermoid lesions responded partially. Four of seven patients with intraoral GVHD responded completely to PUVA and two patients responded partially.

Biopsy was performed in five patients after PUVA treatment. Patients I, III and IV who had lichenoid patterns showed complete response. Biopsies in patients II and VII who had a pure

sclerodermoid pattern and a mixed pattern with lichenoid lesions, respectively, showed partial remission. The treatment courses and outcomes are shown in tables 2 and 3 correspondingly.

Phototherapy was generally well tolerated. We observed no side effects like phototoxicity, nausea and vomiting and exacerbation of GVHD. Liver enzymes rose mildly (< three times) in four patients during the course of therapy. Treatment was stopped in patient III due to marked elevation in liver function tests (≥ three times) but phototherapy was reinstituted after returning of the liver enzymes to normal values with no consequent abnormality. Patient X discontinued treatment after 18 sessions because of the worsening of a crusted erosive lesion on his upper back and neck. Patient XI left the treatment program deliberately at 19th session. Both of them had partial response when discontinued the treatment. Patient II developed multiple periungual pyogenic granulomas during the course of therapy but all lesions resolved with cryosurgery. Overall, one patient died of systemic GVHD-related complications, during the follow-up period. She died due to sepsis after finishing the course of PUVA treatment. The observed clinical responses remained unchanged on the first six-month follow-up. To date (February 2006), we have followed up the patients for a mean duration of five years and their clinical status is shown in table 3. No cutaneous neoplastic lesions have been observed on follow-ups to date.

Discussion

Although evidence based data is lacking, some authors have used PUVA therapy for the treatment of chronic cutaneous GVHD after allogenic bone marrow transplantation[3, 4-8]. Psoralen and UVA may alter effector cells in ch.GVHD. It has an effect on effector lymphocytes, blocks antigen presenting and co-stimulatory signals (cytokines like IL-1), and induces clonal anergy by langerhans cells[3]. Psoralen and UVA is able to deplete surface markers of langerhans cells and inactivate T-cell responses to mitogenic and antigenic stimuli that results in decreased IL-2 production. It can also decrease IL-1, IL-6 and IL-8 production in peripheral mononuclear cells[9, 10].

In our series, all patients responded to PUVA treatment with complete remission in 36% and partial remission in 64%. Vogelsang et al. reported a response rate of 77% to PUVA treatment in a series of 40 patients with chronic cutaneous GVHD[3]. Aubin et al. reported a response rate of 70% in seven patients with ch.GVHD although one of them was treated by UVB[4].

We observed that PUVA could be a safe and effective therapy for chronic cutaneous GVHD in conjunction with systemic immunosuppressive agents. Complete and partial response was observed in four and six patients (40% and 60%) with lichenoid lesions, respectively, but all four patients with sclerodermoid GVHD showed only partial response to PUVA treatment. This suggests that PUVA treatment is effective particularly in lichenoid GVHD lesions but sclerodermoid lesions may also benefit from this therapy.

Poor response of sclerodermoid GVHD to PUVA treatment has been reported by Vogelsang et al.[3] but Kapoor et al.[6] and Kerscher et al.[11] have reported a high response rate in sclerodermoid GVHD. Jampel et al. reported five patients with lichenoid GVHD who showed clinical improvement by PUVA therapy but the only patient with sclerodermoid lesions did not respond to therapy[5]. A favorite response of sclerodermoid GVHD to UVA1 is reported by Pinton et al.[12]. We also observed that phototherapy was not tolerated in patient X who had some erosive skin lesions. Although his lichenoid and sclerodermoid lesions responded partially, the erosions worsened on phototherapy. We think that further studies concerning the efficacy and/or hazards of phototherapy on erosive lesions in ch.GVHD seem necessary.

In our series, the median number of treatment sessions was 43 (range: 18-72) which is higher than many previous studies, namely, 22 (range: 2-64)[3], 22 (range: 2-43)[5], and 20 (range: 3-117)[4]. The median number of treatment sessions before the onset of clinical improvement was 21 (10-29) which is more than 15.5 (2-19) reported by jampel et al.[6] Mean cumulative exposure to UVA was 200.5 J/cm2 (range, 116.5-306.5) that is more than some other studies, namely, 146.3 J/cm2 (range: 5.5-1094)[3], 123 J/cm2[5], 86,6 J/cm2[4]. The dose of psoralen used in previous studies was 0.3 to 0.6 mg per kg of body weight[3,4-6] which is higher than 0.2 mg/kg (maximum of 10 mg) that was used in our patients.

Short-term side effects of PUVA are due to 8-methoxypsoralen or direct effects of PUVA on the skin[2]. Methoxypsoralen may cause phototoxicity, nausea and vomiting and hepatic damage, all of which are dose dependent[13]. Phototoxicity and PUVA burns are reported in two and one patient, respectively, in the five patients studied by Jampel et al.[5]. In Vogelsang's study, three patients

developed PUVA burns with blistering and marked erythema and treatment was interrupted in four other patients due to symptoms of phototoxicity (painless erythema)[3].

Although the number of treatments and total cumulative exposure to UVA was relatively higher in our study, we observed no phototoxic reactions. This may be due to a lower dose of psoralen used in our patients. Other reasons that might contribute to the lower phototoxic reactions in our patients is starting the UVA with a relatively low dose regardless of their skin phototype (Fitzpatrick's III-IV), and more caution in increasing the UVA doses throughout the treatment sessions. Based on diffuse skin involvement and receiving several medications, we actually treated our patients with a protocol similar to erythrodermic patients. As a result, we suggest that this kind of therapy together with preventing phototoxicity may increase patients' compliance without necessarily decreasing the efficacy of PUVA therapy. Higher median number of treatment sessions and mean cumulative dose of UVA in our study does not necessarily represent higher risk of long-term side effects such as skin cancers. We think that this risk not only depends on the amount of UVA but also relies mainly on the prescribed dosage of 8-methoxy-psoralen, which makes skin nearly one thousand times more sensitive to UVA. In our protocol, the dosage of psoralen was approximately less than half of the other studies, so our higher number of treatment sessions and UVA dose theoretically do not seem harmful.

Seven patients developed hepatic involvement of GVHD before treatment with PUVA. During the therapy, liver enzymes rose mildly in three patients, which did not interfere with continuing the treatment. The remaining four patients showed no further elevations in liver enzymes. We stopped PUVA treatment in one patient with severe elevation of liver enzymes (three times greater than the normal value) whose tests were normal before PUVA therapy. After liver enzymes returned to normal, phototherapy was re-instituted in this patient with an even lower dose of Psoralen which did not result in any consequent side effects. We think that patients with mild elevations in liver enzymes can tolerate PUVA therapy and go on with the treatment, even though they might show very mild further rises in the enzymes during the treatment. On the other hand, patients who have normal liver enzyme tests before therapy may show marked elevations in these tests during the treatment. We suggest that lower doses of methoxsalen are particularly convenient for ch.GVHD patients who are at risk of hepatic damage and concurrently take a number of other hepatotoxic drugs.

Although we observed no late complication of PUVA treatment in our patients, the relatively short follow-up period does not allow for firm conclusions.

Six of seven patients (87%) with oral lesions responded to PUVA treatment as three complete and three partial responders. As our patients were instructed to open their mouths during phototherapy, the clinical response may be inferred as its local effect on the oral mucosa. Vogelsang et al. used a glass fiber extension of a UVA source for intraoral application and claimed a homogenous intraoral exposure to UVA. They reported a response rate of 87% (6 of 7 patients) similar to ours[3]. Because using intraoral devices can result in a superior exposure of oral mucosa to UVA, similarity between our data and other studies that have used such devices may be in favor of a systemic effect for PUVA in resolving mucosal lesions. Resolution of the oral lesions of ch.GVHD despite delivery of the PUVA only to the skin has been reported previously[14]. We can not justify whether the mucosal response was due to local or systemic effect of PUVA. Further clinical trials may help to explain this problem.

We think that low-dose psoralen plus UVA can be a safe and effective therapy for chronic cutaneous GVHD in conjunction with systemic immunosuppressive agents. We think that randomized controlled trials are warranted to further assess the optimal dose of psoralen and UVA in the treatment of chronic cutaneous GVHD.

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