Turk J Hematol 2006; 23:188-192

RESEARCH ARTICLE

Retrospective analysis of results of short-term low dose interferon-α-2b combined with PUVA in the treatment of early stage mycosis fungoides

Fahri Şahin[1], Işıl Kılınç Karaarslan[2], Nur Akad Soyer[1], Filiz Vural[1], Serkan Ocakcı[1], Günseli Öztürk[2], Kezban Pınar Özen[1], Güray Saydam[1]

[1]Department of Hematology, Ege University Faculty of Medicine, Izmir, Turkey
✉ *saydamguray@yahoo.com*
[2]Department of Dermatology, Ege University Faculty of Medicine, Izmir, Turkey

Received: *Jun 20, 2006* • ***Accepted:*** *Aug 09, 2006*

ABSTRACT

Early-stage mycosis fungoides (MF) can be treated with different regimens such as oral photo-chemotherapy (Psoralen and UVA-PUVA). There have been some studies showing the effectiveness of combination of interferon (IFN) with PUVA. In this study, we aimed to evaluate retrospectively the patients with early-stage MF treated with IFN + PUVA.

Six patients with the diagnosis of early stage (Ia-IIa) MF between June 2003 and May 2005 were enrolled in this study. IFN combined with PUVA was started and followed by IFN maintenance in complete response (CR) patients. Patients achieving CR were followed up at monthly intervals until relapse. Interferon-α-2b was administered at a dose of 3 MU 3 times a week and PUVA was applied 3 times a week.

There were 4 female and 2 male patients, aged 32-75 years (mean 54.3 years). Four patients were at stage Ia, one patient at Ib and one patient at stage IIa according to TNM staging. Four of 6 patients (66%) achieved CR and 2 of 6 (33%) achieved partial response (PR). No grade 3-4 side effects due to IFN were detected, and no progression was observed during the treatment. All patients have been under treatment as planned.

Low dose of IFN-α-2b plus PUVA was found to be successful in achieving excellent clinical responses in patients with early-stage MF. This treatment modality was very well tolerated.

Key Words: PUVA, interferon-α-2b, mycosis fungoides

ÖZET

Erken evre mikozis fungoides tedavisinde PUVA ile kombine kısa süreli interferon α 2B tedavi sonuçlarının retrospektif değerlendirilmesi

Erken evre mycosis fungoides (MF) oral photo-chemotherapy (Psorolevand UVA-PUVA) gibi metotlarla tedavi edilebilir. Literatürde, PUVA ile birlikte interferon (IFN) kullanımının başarılı olabileceğine dair yayınlar mevcuttur. Bu çalışmada, retrospektif olarak, IFN+ PUVA ile tedavi ettiğimiz erken evre MF hastalarının değerlendirilmesi amaçlanmıştır.

Haziran 2003-Mayıs 2005 tarihleri arasında tedavi edilen 6 erken evre (Ia-IIa) MF hastası bu çalışmaya alınmıştır. IFN ve PUVA kombine olarak başlanmış ve yanıt alınan hastalarda IFN ile devam edilmiştir. Tam yanıt alınan hastalar aylık peryodlarla izlenmiştir. Interferon-α-2b haftada 3 gün 2 milyon ünite (MÜ) /gün kullanılmış, PUVA haftada 3 gün yapılmıştır.

Dört kadın ve 2 erkek hastanın ortalama yaşları 54.3 (32-75) idi ve tümör nod metastaz (TNM) evreleme sistemine göre, 4 hasta evre Ia, 1 hasta evre Ib ve 1 hasta da evre IIa idi. Altı hastanın 4'ünde (%66) tam yanıt elde olunurken, 2 hastada (%34) parsiyel yanıt alınabildi. Hiç bir hastada evre 3-4 toksisite gelişmedi. Tedavi esnasında hiç bir hastada progresyon saptanmadı. Tüm hastalar planlandığı şekilde halen takip ve tedavi altındadır.

Düşük doz IFN-α-2b ve PUVA kombinasyonu, erken evre MF hastalarında yanıt eldesinde oldukça başarılıdır ve hastalar tarafından iyi tolere edilmektedir.

Anahtar Sözcükler: PUVA, interferon-α-2b, mycosis fungoides

INTRODUCTION

Mycosis fungoides (MF) is the form of cutaneous T-cell lymphomas (CTCL) that represent non-Hodgkin lymphomas. MF is a common indolent form of CTCL that may appear in the skin generally as pruritic, long-standing patches, plaques, cutaneous tumor, or dissemination to visceral sites, lymph nodes and peripheral blood [1]. Sézary syndrome (SS), the leukemic variant of MF, is characterized by pruritic infiltrative erythroderma, general lymphadenopathy, and presence of circulating atypical mononuclear cells with hyper-convoluted nuclei [2]. Approximately 200 years after the first description of lesions of CTCL as 'MF', immunophenotyping studies revealed that it was actually one of many CTCLs, typically of the CD4+/CLA+/CCR4+ T cells phenotype [3]. The median survival time from diagnosis was less than two years for late-stage disease, but 10-12 years for early-stage MF confined to the skin [4].

Treatment of MF includes a variety of modalities, among them topical corticosteroids, retinoids, oral psoralen plus ultraviolet light (PUVA), total skin electron beam therapy (TSEBT), extracorporeal photochemotherapy (ECP), topical and systemic chemotherapies, adenosine analogs, monoclonal antibody therapy, and interferons (IFN) [5-13]. In preliminary studies, IFN was used alone or combined with PUVA or other agents [14]. In the literature, Bunn *et al.* [13] first reported that IFN was an effective agent in the treatment of advanced MF patients. After the first report, some studies have demonstrated significant response rates of 45% to 65% in heavily pretreated patients [15]. In these studies, different doses of IFN (high-dose or low-dose) were used in treatment. However, the optimal IFN dose, schedule, and duration are still not clear [14].

In the literature, there are some studies that have assessed the efficacy, tolerability, and agreement of IFN-α-2b + PUVA in the treatment of early-stage MF patients [14]. In this study, we aimed to evaluate retrospectively patients with early-stage MF treated with low-dose IFN-α-2b + PUVA in the Hematology and Dermatology Departments of Ege University Hospital.

MATERIALS and METHODS

Six patients followed in the Departments of Hematology and Dermatology with the diagnosis of early (stage Ia-IIa) MF between June 2003 and May 2005 were included in the study. The characteristics, stage of disease, duration of disease and history of prior therapy of the six patients are listed in Table 1. Duration of the disease was defined as the interval between the first diagnostic cutaneous biopsy and beginning of the treatment.

In all patients, biopsy specimen was obtained before therapy for routine histopathological examination and immuno-histochemical analysis. The diagnosis of MF was based on light microscopic evidence of a dermal infiltrate of atypical lymphocytes with cerebriform nuclei, epidermal exocytosis of these cells, and the presence of microabscesses [15].

The disease was staged according to the Committee on Staging and Classification of CTCLs by Bunn and Lamberg [16]. For staging, patients were examined for evidence of lymphadenopathy and hepatosplenomegaly. Furthermore, complete blood count, chemistry panel, examination of blood smear for circulating Sézary cells, and computerized tomography of the chest and abdomen were performed.

IFN combined with PUVA was started and maintained until the end of the evaluation. IFN-α-2b was subcutaneously administered at a dose of 3 MU three times a week, 2-4 hours prior to PUVA treatment. Photochemotherapy was performed with oral 8-methoxi-psoralen 0.6 mg/kg 2 hours before UVA radiation, three times a week. At the end of the combination therapy, patients who achieved complete response (CR) were required to continue maintenance therapy with IFN-α-2b indefinitely.

During the study, blood counts and chemistry panel were monitored monthly. Clinical assessment was performed at baseline and at the end of the four-week treatment period. Response criteria to treatment were defined as follows: CR, with no signs of active disease and disappearance of all lesions, and partial response (PR), with reduction of lesions of more than 50% compared to start of therapy. At the end of the therapy, a second biopsy was performed in all patients who achieved CR. Biopsies were obtained from the zone of a cleared lesion adjacent to a pretreatment biopsy site. Patients achieving CR were followed up at monthly intervals until relapse. Toxicity was graded according to World Health Organization (WHO) criteria.

Table 1. Demographic features and clinical conditions of all patients

	Sex	age(yr)	Stage	Disease duration (month)	Duration of PUVA (session / j)	Duration of IFN+PUVA (month)	Dose of IFN (x 3/ week)	Response (CR/PR)	Response duration (month)	Time to response (month)
case 1	M	72	Ia	48	144 1472j	6	3mü	PR	4	2
case 2	F	58	Ia	72	74 512j	20	3mü	CR	18	2
case 3	M	32	Ia	60	25 140j	16	3mü	CR	6	10
case 4	F	55	Ia	72	45 327j	9	3mü	CR	7	2
case 5	F	76	Ib	244	115 816j	17	3mü	CR	11	6
case 6	M	62	IIa	84	69 319j	21	3mü	PR	18	3

RESULTS

The characteristics of the six patients are listed in Table 1. There were 4 female and 2 male patients. The median age was 54.3 years (range, 32-75 years). Four patients were at stage Ia, one patient at stage Ib and one patient at stage IIa according to TNM staging. Disease duration was 96.6 months (range, 48-244 months).

Four of 6 patients (66%) achieved CR and 2 of 6 (33%) achieved PR. The median time to achieve the CR was 5 months (range, 2-10 months). The median duration of overall response was 10.6 months (range, 4-18 months).

No grade 3-4 side effects due to IFN were detected. No progression was observed during the treatment. All patients have been under treatment as planned.

DISCUSSION

There are many therapeutic options for the treatment of patients with MF. PUVA, topical chemotherapy and TSEBT are some of the palliative therapies for treatment, especially in early-stage MF patients. But these therapies are less effective in patients with advanced MF[14]. Furthermore, neoplastic clones are detectable at distant sites even in the presence of clinically localized skin disease. Palliative therapies may not prevent systemic spread [17].

Beneficial effects of PUVA have been reported in several studies [18]. It has been reported an 83% CR rate for PUVA in early-stage MF patients. IFNs is naturally occurring cytokines [19]. They are produced by eukaryotic cells in response to stimulation by a variety of agents. They have been synthesized by recombinant technique for clinical use. Antitumor effect of IFN seems to be mediated by induction of cell cycle arrest and apoptosis in selected cells using the Jak-Stat pathway [20]. Immunestimulatory effects on some cells, including cytotoxic T-cell, macrophages, and natural killer cells, are other effects [20]. The efficacy of IFN-α in CTCL was first described by Bunn *et al.* in 1984 [13]. They demonstrated a 45% objective response rate in heavily treated patients with advanced disease using high-dose IFN (50 MIU/m^2 three times a week). Different dose schedules for IFN as monotherapy were used in other studies.

Some very promising results have been obtained using the combination IFN-α and PUVA. In a 15-patient study, Kuzel *et al.* [15] reported an 80% CR with a median duration of 24 months with combination of IFN-α (6-30 MU three times a week) and PUVA. Mostow *et al.* reported a 100% CR in five PUVA refractory patients treated with combination of IFN-α (3-6 MU daily and 9 MU three times a week) and PUVA. Then, Kuzel *et al.* reported a study of 39 patients with MF and SS (stage IB-IVB) treated with IFN-α (6-30 MU three times a week) and PUVA [15]. In this study, there was a 62% CR with a median duration of 28 months. In their 63 patients treated with IFN-α (6-12 MU three times a week) and PUVA,

Chiarion-Sileni *et al.* [14] reported a 75% CR with a median duration of 32 months. The 5-year overall survival rate was 91% and the 5-year disease-free survival was 75%. In this study, nine patients had recurrence (19%), and five patients obtained a second CR with the same therapy. Furthermore, Kuzel *et al.* [15] showed that by using lower dose, only two patients needed to stop therapy due to IFN-α toxicity.

Rupoli *et al.* [17] reported a 76% CR with combination of IFN-α-2b (induction phase: 18 MU/week and maintenance phase: 6 MU/week) and PUVA in 25 early-stage MF patients. The authors suggested that the combination of low-dose IFN-α with PUVA should be sufficient to maintain antitumor activity.

Anadolu *et al.* [18] reported a 57% CR with combination of IFN-α (3 MU three times a week) and PUVA in seven patients with early stage MF. In this study, three patients with late-stage MF were treated with IFN-α (3 MU three times a week) and PUVA and the rate of CR was 33.3%. The authors concluded that PUVA and IFN-α (3 MU three times a week) is an effective therapy for early-stage MF with minimal side effects.

Stadler *et al.* [21] compared IFN-α (9 MU three times a week) and PUVA versus IFN-α (9 MU three times a week) and acitretin in early-stage CTCL patients. The rate of CR was 70% in the IFN+PUVA group and 38.1% in the IFN+acitretin group. Time to response was significantly shorter in the IFN+PUVA group than in the IFN+acitretin group (18.6 vs 21.8 weeks).

Our results show similar CR rates (66 %) to those reported previously in trials. Low doses of IFN-α-2b plus PUVA has been found to be successful in achieving excellent clinical responses in patients with early-stage MF. Furthermore, this treatment modality was very well tolerated.

References

1. Willemze R, Kerl H, Sterry W, Berti E, Cerroni L, Chimenti S, Diaz-Perez JL, Geerts ML, Goos M, Knobler R, Ralfkiaer E, Santucci M, Smith N, Wechsler J, van Vloten WA, Meijer CJ. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. Blood 1997;90:354-71.
2. Kazakov DV, Burg G, Kempf W. Clinicopathological spectrum of mycosis fungoides. J Eur Acad Dermatol Venereol 2004;18:397-415.
3. Girardi M, Heald PW, Wilson LD. The pathogenesis of mycosis fungoides. N Engl J Med 2004;350:1978-88.
4. Toro JR, Stoll H Jr, Oseroff AR. Prognostic factors and evaluation of mycosis fungoides and Sézary syndrome. J Am Acad Dermatol 1997;37:58-67.
5. Zackheim HS, Kashani-Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Arch Dermatol 1998;134:949-54.
6. Knobler RM, Trautinger F, Radaszkiewicz T, Kokoschka EM, Micksche M. Treatment of cutaneous T-cell lymphoma with a combination of low-dose interferon alfa-2b and retinoids. J Am Acad Dermatol 1991;24:247-52.
7. Roenigk HH Jr, Kuzel TM, Skoutelis AP, Springer E, Yu G, Caro W, Gilyon K, Variakojis D, Kaul K, Bunn PA Jr et al. Photochemotherapy alone or combined with interferon alpha-2a in the treatment of cutaneous T-cell lymphoma. J Invest Dermatol 1990;95(Suppl 6):198-205.
8. Van Vloten WA, Vroome H, Noordijk EM. Total skin electron beam irradiation for cutaneous T-cell lymphoma. Br J Dermatol 1985;112:697-702.
9. Armus S, Keyes B, Cahill C, Berger C, Crater D, Scarborough D, Klainer A, Bisaccia E. Photopheresis in the treatment of cutaneous T-cell lymphoma. J Am Acad Dermatol 1990;23:898-902.
10. Kemme DJ, Bunn PA. State of the art therapy of mycosis fungoides and Sézary syndrome. Oncology 1992;6:31-42.
11. O'Brien S, Kurzrock R, Duvic M, Kantarjian H, Stass S, Robertson LE, Estey E, Pierce S, Keating MJ. 2-Chlorodeoxyadenosine therapy in patients with T-cell lymphoproliferative disorders. Blood 1994;84:733-8.
12. Hesketh P, Caguioa P, Koh H, Dewey H, Facada A, McCaffrey R, Parker K,bNylen P, Woodworth T. Clinical activity of a cytotoxic fusion protein in the treatment of cutaneous T-cell lymphoma. J Clin Oncol 1993;11:1682-96.
13. Bunn PA Jr, Ihde DC, Foon KA. The role of recombinant interferon alfa-2a in the therapy of cutaneous T-cell lymphomas. Cancer 1986;57:1689-95.
14. Chiarion-Sileni V, Bononi A, Fornasa CV, Soraru M, Alaibac M, Ferrazzi E, Redelotti R, Peserico A, Monfardini S, Salvagno L. Phase II trial of interferon-alpha-2a plus psoralen with ultraviolet light A in patients with cutaneous T-cell lymphoma. Cancer 2002;95:569-75.
15. Kuzel TM, Roenigk HH Jr, Samuelson E, Herrmann JJ, Hurria A, Rademaker AW, Rosen ST. Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sezary syndrome. J Clin Oncol 1995;13:257-63.
16. Bunn PA Jr, Lamberg SI. Report of the Committee on Staging and Classification of cutaneous T-cell lymphomas. Cancer Treat Rep1979;63:725-8.

17. Rupoli S, Barulli S, Guiducci B, Offidani M, Mozzicafreddo G, Simonacci M, Filosa G, Giacchetti A, Ricotti G, Brandozzi G, Cataldi I, Serresi S, Ceschini R, Bugatti L, Offidani A, Giangiacomi M, Brancorsini D, Leoni P. Low dose interferon-alpha2b combined with PUVA is an effective treatment of early stage mycosis fungoides: results of a multicenter study. Cutaneous-T Cell Lymphoma Multicenter Study Group. Haematologica 1999;84:809-13.

18. Anadolu RY, Birol A, Sanli H, Erdem C, Tursen U. Mycosis fungoides and Sezary syndrome: therapeutic approach and outcome in 113 patients. Int J Dermatol 2005;44:559-65.

19. Bunn PA Jr, Foon KA, Ihde DC, Longo DL, Eddy J, Winkler CF, Veach SR, Zeffren J, Sherwin S, Oldham R. Recombinant leukocyte A interferon: an active agent in advanced cutaneous T-cell lymphomas Am Intem Med 1984;101:484-7.

20. Pichardo DA, Querfeld C, Guitart J, Kuzel TM, Rosen ST. Cutaneous T-cell lymphoma: a paradigm for biological therapies. Leuk Lymphoma 2004;45:1755-65.

21. Stadler R, Otte HG, Luger T, Henz BM, Kuhl P, Zwingers T, Sterry W. Prospective randomized multicenter clinical trial on the use of interferon -2a plus acitretin versus interferon -2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. Blood 1998 Nov 15;92:3578-81.