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

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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 (Psoralevand UVA-PUVA) gibi metotlarla tedavi edilebilir. Literatürde, PUVA ile birlikte interferon (IFN) kullanımının başarılı olabileceği dair yayınlar mevcuttur. Bu çalışmada, retrospektif olarak, IFN+ PUVA ile tedavi ettigimiz erken evre MF hastalarının değerlendirilmesi amaçlanmıştır.


Dört kadın ve 2 erkek hastanın ortalama yaşları 54.3 (32-75) idi ve tümör nod metastazı (TNM) evreleme sisteminine göre, 4 hasta evre Ia, 1 hasta evre Ib ve 1 hasta da evre Ila idi. Alın hastanın 4’ünde (%66) tam yant elde olunurken, 2 hastada (%34) parsiyel yant alınıbıldi. Hiç bir hasta evre 3-4 toksisite gelişmedi. Tedavi esnasında hiç bir hasta progressyon saptanmadı. Tüm hastalar planlandığı şekilde halen takip ve tedavi alındı.

Düşük doz IFN-α-2b ve PUVA kombinasyonu, erken evre MF hastalarında yant 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 \[3\]. 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-methoxypсорalen 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.
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 Ila 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. Furthermore, neoplastic clones are detectable at distant sites even in the presence of clinically localized skin disease. Palliative therapies may not prevent systemic spread.

Beneficial effects of PUVA have been reported in several studies. It has been reported an 83% CR rate for PUVA in early-stage MF patients. IFNs is naturally occurring cytokines. 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. Immuno-stimulatory effects on some cells, including cytotoxic T-cell, macrophages, and natural killer cells, are other effects. The efficacy of IFN-α in CTCL was first described by Bunn et al. in 1984. They demonstrated a 45% objective response rate in heavily treated patients with advanced disease using high-dose IFN (50 MIU/m² 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. 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. 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,

<table>
<thead>
<tr>
<th>Sex</th>
<th>age (yr)</th>
<th>Stage</th>
<th>Disease duration (month)</th>
<th>Duration of PUVA (session / j)</th>
<th>Duration of IFN + PUVA (month)</th>
<th>Dose of IFN (x 3/ week)</th>
<th>Response (CR/PR)</th>
<th>Response duration (month)</th>
<th>Time to response (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>case 1</td>
<td>M</td>
<td>72</td>
<td>Ia</td>
<td>48</td>
<td>144 / 1472</td>
<td>6</td>
<td>3mü</td>
<td>PR</td>
<td>4</td>
</tr>
<tr>
<td>case 2</td>
<td>F</td>
<td>58</td>
<td>Ia</td>
<td>72</td>
<td>74 / 512</td>
<td>20</td>
<td>3mü</td>
<td>CR</td>
<td>18</td>
</tr>
<tr>
<td>case 3</td>
<td>M</td>
<td>32</td>
<td>Ia</td>
<td>60</td>
<td>25 / 140</td>
<td>16</td>
<td>3mü</td>
<td>CR</td>
<td>6</td>
</tr>
<tr>
<td>case 4</td>
<td>F</td>
<td>55</td>
<td>Ia</td>
<td>72</td>
<td>45 / 327</td>
<td>9</td>
<td>3mü</td>
<td>CR</td>
<td>7</td>
</tr>
<tr>
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<td>F</td>
<td>76</td>
<td>Ib</td>
<td>244</td>
<td>115 / 816</td>
<td>17</td>
<td>3mü</td>
<td>CR</td>
<td>11</td>
</tr>
<tr>
<td>case 6</td>
<td>M</td>
<td>62</td>
<td>Ila</td>
<td>84</td>
<td>69 / 319</td>
<td>21</td>
<td>3mü</td>
<td>PR</td>
<td>18</td>
</tr>
</tbody>
</table>
Chiarión-Sileni et al. 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. showed that by using lower dose, only two patients needed to stop therapy due to IFN-α toxicity.

Rupoli et al. 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. 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. 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


