Effectiveness of interferon α in mycosis fungoides therapy

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Post Dermatol Alergol 2012; XXIX, 1: 51–55

Abstract

Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma. Skin manifestations are generally the first signs of the disease. Many topical and systemic therapeutic alternatives are utilized in MF treatment, but there is no defined curative treatment regimen. One of the successful agents is interferon-α (IFN-α), which shows appreciable responses, especially in combination therapy with psoralen and ultraviolet A (PUVA). However, the optimal IFN dose, schedule, and duration of therapy are still not determined. We describe 2 patients suffering from MF, being treated at the Clinic of Dermatology, Venereology and Allergology in Gdansk, including IFN and phototherapy with very satisfactory results.

Key words: interferon-α2a, mycosis fungoides, PUVA, UVB311.

Introduction

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) and is characterized by the malignant proliferation of mature helper T lymphocytes [1]. It is usually associated with an indolent clinical course with episodes of remissions and subsequent relapses. Skin manifestations are generally the first signs of the disease. Patients present erythematous, sometimes poikilodermatous and scaly, long-standing patches, plaques, or tumoral lesions with an occasional itch. In patients with early disease stages, life expectancy is normal, however follicular MF has a worse prognosis than the classic type of MF. In approximately 30% of patients there is extracutaneous involvement, which is associated with a poor prognosis [2].

There are two therapeutic modalities in mycosis fungoides: skin-directed and systemic treatments. Most patients respond well to skin-targeted therapy, which may include topical chemotherapy (nitrogen mustard or carmustine), topical corticosteroids, topical retinoids, phototherapy including ultraviolet A and B radiation, oral psoralen plus ultraviolet light (PUVA), radiotherapy, excimer laser, photodynamic therapy, and total skin electron beam therapy [3-5]. Systemic therapy, generally reserved for more extensive, advanced or refractory disease, is often used in combination with skin-directed treatments [4]. A number of systemic treatment options, such as cytotoxic chemotherapy and biologic agents, enhance the host immune system response to neoplastic T cells. The most commonly used biologic response modifiers are interferon-α and bexarotene, which is a novel retinoid-X-selective retinoid [6, 7]. At present, any type of available therapy (with the exception of hematopoietic cell transplantation) for MF is curative [4].

Skin-targeted therapies are first-line agents in early-stage disease but they are also useful in patients with advanced-stage disease. Systemic chemotherapy is not the treatment of choice in early-stage MF, because it does not improve survival as compared with skin-targeted therapy [8]. For some patients with early stages of the disease only careful observation is recommended. Complete responses have rarely been obtained in patients with heavily pretreated and advanced disease [9].

Case reports

Two patients suffering from MF have been treated at the Department of Dermatology, Venereology and Allergology of Medical University in Gdansk including IFN therapy with very satisfactory results. One of them, a 36-year-old man was admitted to hospital with erythroderma, very

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high fever and in poor general condition. The stage of MF was assessed as III (T4N0M0). Treatment has started with prednisone and cyclosporine obtaining a partial recovery followed by progression before admission to hospital, because of suspicion of adverse drug reaction (chlorprothixene taken because of depression); erythroderma and palmoplantar hyperkeratosis. Another medication was methotrexate (20 mg per week), which was discontinued after 4 weeks due to staphylococcal sepsis. Finally IFN-α was included (Roferon) at a dose of 3 MU 3 times weekly obtaining a partial improvement after 2 months of therapy, while hyperkeratosis persisted. The complete treatment schedule included IFN-α to which the patient responded after 84 days. During this therapy the patient also received 5 sessions of soak PUVA and 2 treatments of UVB 311 in accordance with the second skin phototype, what has allowed to achieve CR (Figures 1 A-B, 2 A-B). During the interferon (IFN) therapy, the patient complained of weakness and night sweats, but only at the beginning of the treatment. The treatment has been continued thanks to kind cooperation of the Regional Oncological Center in Gdansk and Dermatological Department of Elblag Regional Hospital (due to the patient's place of residence).

The second patient was a 58-year-old woman, diagnosed with folliculotropic MF based on clinical features and histopathological examination of the skin slice, with widespread pruritic papules with concomitant characteristic perifollicular collocation on the trunk and buttocks (Figure 3). There were no mucin deposits in histopathological examination. We initially applied PUVA plus acitretin at a dose of 25 mg daily for 1 year. However, because of persistent itching and just partial remission, methotrexate was added at a dose of 15 mg per week. The patient received seven rounds of MTX and prednisone was given because of arthralgia diagnosed by the rheumatologist, at an initial dose of 30 mg daily, reduced to 10 mg, without improvement of skin lesions. Finally, IFN treatment was started at a dose of 3 MU 3 times weekly.

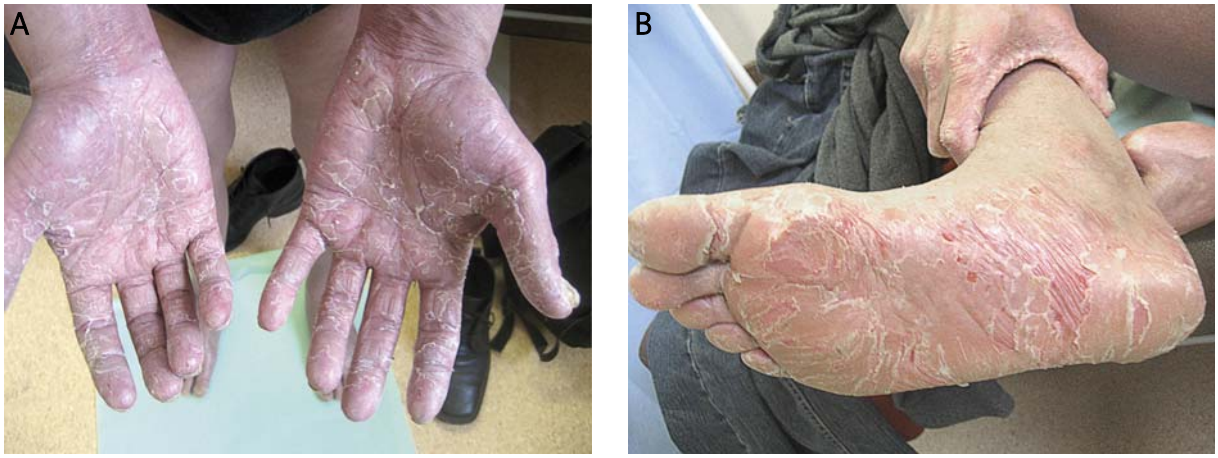

Figure 1 A-B. Palmoplantar hyperkeratosis after 76 days of treatment with IFN-α

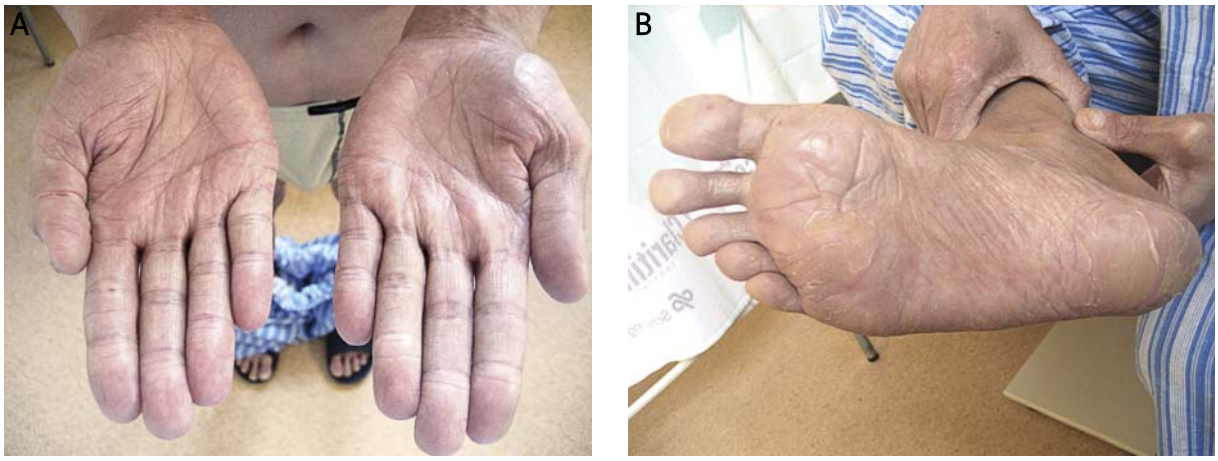

Figure 2 A-B. The improvement of local palms and soles after 84 days of IFN-α therapy, 5 sessions of soak PUVA and 2 sessions of UVB (8 days later than Figure 1)

After 2 weeks of IFN therapy, UVB 311 irradiation was added, yielding, after 6 doses of UVB 311 exposure, a spectacular remission, especially resolving the problem of severe pruritus. But because of influenza-like syndrome, weakness, malaise, anorexia symptoms, arthralgia, leucopenia and neutropenia, which occurred during the second week of IFN therapy, the agent was discontinued for 7 days, after which blood parameters returned to normal. The dose of IFN was reduced to 1.5 MU 3 times a week, thanks to kind cooperation of the Regional Oncological Center in Gdansk, and UVB311 was continued with better tolerance and good response (Figures 4 A-B).

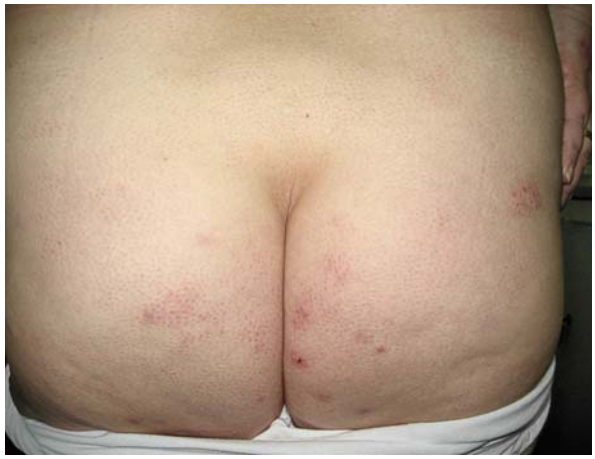

Figure 3. Folliculotropic MF: widespread pruritic papules on the buttocks

Discussion

Recombinant interferon-α (IFN-α) is named type I IFN as it binds to IFN cell surface receptors type 1. There are two major forms of IFN-α: IFN-α-2a (Roferon) and IFN-α-2b (Intron), which are differently purified and have different amino acid substitution at position 23. There are also the pegylated forms of IFN-α-2a, IFN-α-2b and αcon-1, but neither of them has been reported to be used in clinical trials in MF [10]. Elimination half-life is 3-8 h for IFN-α-2a and 2-3 h for IFN-α-2b for both subcutaneous and intramuscular injections [11].

Interferons are cytokines with immunoregulatory, antiproliferative, antiangiogenic, and antiviral effects [12]. The mechanism of IFN-α action is not completely understood. However, studies have shown inhibition of IL-4 and IL-5 production by T cells and SCs, under the influence of IFN [13]. In combination with radiation, IFN-α has been reported to have a potential effect on radiation enhancing blockage at the G2-M phase of the cell cycle [14].

The first report on the effectiveness and toxicity of IFN in the treatment of patients with advanced cutaneous

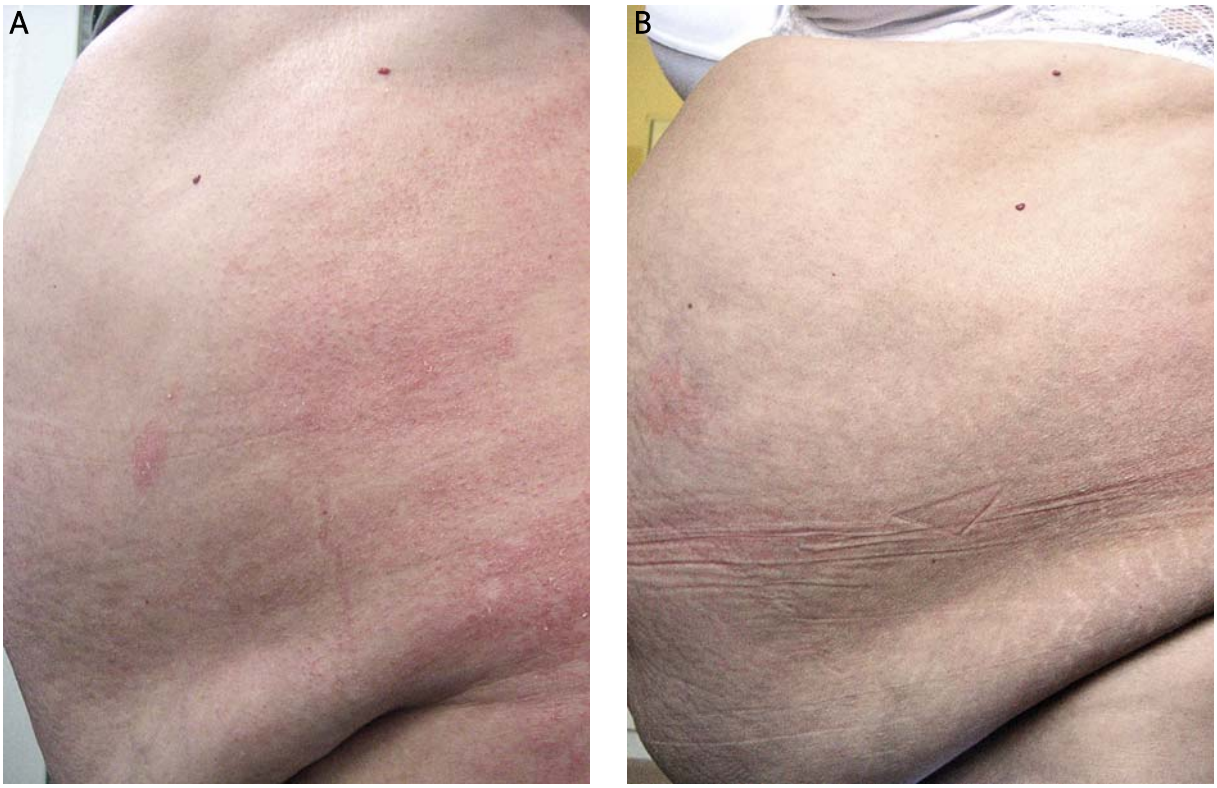

Figure 4. A – Folliculotropic MF; numerous pruritic perifollicular papules before addition of UVB 311 to IFN-α therapy. **B** – Remission of skin lesions just after 6 UVB 311 sessions (9 days later)

T-cell lymphomas was published in 1984. The maximal tolerated dose of IFN-α (50×10^6 U/m^2 body surface area), used intramuscularly 3 times weekly, was highly effective in treatment of disease refractory to at least two standard therapies. However, none of 20 patients had complete response (CR). Almost half of the patients had partial response in the first 4 weeks of therapy. Both cutaneous and extracutaneous lesions, including the size of palpable lymph nodes and the number of circulating malignant cells, definitely improved [15].

Interferon-α was used at doses ranging from about 3 million units (MU) three times weekly to 9 or 12 MU daily [16]. In spite of short periods of IFN therapy at high doses, it showed a dose-related toxicity. A strong correlation between dose and efficacy has never been confirmed [7, 17].

Interferon-α has been reported to be effective at each stage of MF. Clinical response rates have been reported for 45-74% and complete response rates for 10-27% of treated patients [18, 19]. Significantly, the highest complete response was achieved in patients of the early-stage group compared with the advanced-stage group [20]. The efficacy of IFN was higher than that of chemotherapy (high-dose methotrexate, etoposide) and serotherapy such as TIOI monoclonal antibody and antithymocyte globulin.

To improve effectiveness of IFN monotherapy, combinations with other agents were introduced into the treatment of MF. Some very encouraging results have been observed using the combination of IFN-α and PUVA [21], retinoids [17, 22] or extracorporeal photopheresis [23]. Kuzel *et al.* [24] reported the results of combined treatment of IFN-α2a (6-30 MU TIW) and PUVA. Complete response was achieved in 80% of patients, with a median duration that approached 2 years. The combination of PUVA and IFN-α2b of 2-5 MU 3 times weekly demonstrated higher response rates (a median of overall response rate – 98%, CR rate – 84%) and longer duration of response than PUVA or IFN-α alone [18, 19, 21, 25, 26]. They have been shown to be effective in patients with refractory to PUVA early-stage MF and less in advanced-stage patients. A 2-year progression free survival was observed in 100% of patients with early-stage disease and 27% of patients in the advanced-stage group. In each case the number of PUVA treatments and the dose of IFN-α2b necessary to produce response were reduced [18, 27]. This combination was more effective than IFN-α plus acitretin [28].

The lack of complete responses was probably the cause of the rapid dose reductions in some cases. Initially, when interferon was administered in very high doses, all patients required dose reductions to 50% of the initial dose, during the initial 3 months of therapy [15]. This approach always alleviated a toxicity within several weeks after dose reduction [20]. Major complications associated with the use of IFN include influenza-like syndrome with myalgia, chills, mild fever, malaise and fatigue. Moreover, anorexia, weight loss, depression, rashes and hypotension were often observed. Hematologic toxicity was mild, including neutropenia and thrombocytopenia; not dose limiting [29]. Febrile responses were most severe in the first week of therapy. Subsequently re-escalated doses of interferon causedtachyphylaxis to the major dose-limiting influenza-like syndrome. Perhaps escalating doses should be applied, however the optimal IFN dose and schedule is still an unresolved issue.

We used low doses of IFN-α in our patients, because such proceeding minimizes the risk of side effects. According to world literature, time to response is in the order of weeks and the treatment should be carried out at least for 1 year, if the tolerance is good.

In conclusion, IFN is a treatment of choice for patients with MF helping to delay the introduction of chemotherapy, especially in erythroderma, as a single agent or as a part of combined therapy with phototherapy. It has been shown that the use of chemotherapy in patients with MF did not lead to prolongation of their survival, therefore recommending drugs with different mechanism of action, such as IFN. According to the Polish guidelines, the section of skin lymphomas of the Polish Lymphoma Research Group established last year, treatment of choice in early stages of MF (IA-IIA) is a therapy being possibly the least aggressive one, as at this stage of disease patients have normal life expectancy [30]. Interferon-α is recommended as second-line in monotherapy at doses of 3 to 5 MU daily, or in combination with PUVA, retinoids, bexarotene and methotrexate. For advanced-stage disease (IIB-IV) IFN-α should generally be considered as first-line therapy. To increase the effectiveness of IFN-α, it can be combined with PUVA, retinoids, bexarotene and additionally methotrexate (IIB) or extracorporeal photopheresis (III-IV). In folliculotropic MF, because of the depth of infiltration, phototherapy should be used only in combination with IFN and retinoids or bexarotene [31]. Psoralen plus ultraviolet light should be added in the case of more widespread pruritus and bexarotene if the response is suboptimal [9].

Nowadays, there is no possibility of free IFN treatment of patients with cutaneous lymphoma in dermatological out-patient departments in Poland. However, those patients can receive IFN without the costs of the medicament in oncological or hematological ambulatories. That means that therapy of MF patients has required the cooperation of the dermatologist and the oncologist or the hematologist.

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