



Low dose interferon- α 2b combined with PUVA is an effective treatment of early stage mycosis fungoides: results of a multicenter study

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ABSTRACT

Background and Objective. The early stages of mycosis fungoides (MF) can be treated but not cured by photochemotherapy (PUVA) alone; some recent studies of the effect of a combination of human interferon- α (IFN α) and PUVA reported a high degree of response. The aim of our study was to evaluate the activity of a low dose of IFN- α 2b combined with PUVA.

Design and Methods. Twenty-five patients were included: 16 men and 9 women aged between 23-80 years; 19 patients had stage I and 6 stage II disease. In the induction phase, the dose of IFN α was gradually raised over 6-8 weeks to the target dose of 18 MU/week; in the maintenance phase, the combination with PUVA allowed IFN α to be reduced to a maximum dose of 6 MU/week; in this way the cumulative administration of IFN α and PUVA was considerably lower than in similar combination protocols. Treatment success was analyzed in terms of freedom from treatment failure (FFTF).

Results. After the induction phase 9/25 patients (36%) achieved complete remission (CR) and 15/25 (56%) achieved partial remission (PR). One to five months from the beginning of the maintenance phase, a CR was recorded in 19/25 patients (76%) and a PR in 5/25 patients (20%) accounting for an overall response rate of 96%. The median of FFTF was not reached; probability of FFTF was 82% at 12 months and 62% at 24 months. Disease free survival projected to 48 months was 75%.

Interpretation and Conclusions. Even with low doses of IFN α plus PUVA it is possible to achieve excellent clinical responses, many of which are long-lasting, in patients with early MF.

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Key words: mycosis fungoides, early stages, interferon α 2b, PUVA

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Mycosis fungoides (MF) is an uncommon indolent T-cell lymphoma that may progress from a premycotic stage to more advanced stages characterized by the presence of infiltrated plaques, cutaneous tumors and dissemination to visceral sites, lymph nodes and peripheral blood.

Treatment planning depends on disease stage and biological aggressiveness. Only early-stage patients are currently believed to have the potential to be cured. Several studies have demonstrated the effectiveness of psoralen and UVA (PUVA) therapy for clearing early-stage MF and for extending response duration.¹

Recently various cytokines including interferons have been tested in patients suffering from MF. As single-agent therapy, recombinant interferon- α (IFN α) proved to be a relative effective agent in the treatment of MF, producing responses in about half of the patients.² The only known predictive parameter of the clinical response to interferon treatment is the stage of disease, with higher response rates in the early stages.³ However, while some patients respond to relatively low-dose regimens, the higher doses required by most patients entail significant side-effects and are associated with poor compliance.

Some authors have investigated the feasibility and efficacy of combining PUVA with variable doses of systemically administered IFN α to reduce the number of PUVA treatments and IFN α doses required to produce remission.⁴⁻⁶ Even though this combination proved to be more effective than IFN α monotherapy in all MF stages, its still considerable toxicity prompted the development of alternative regimens, e.g. lower IFN α doses, shorter PUVA applications, different maintenance therapy.

This study reports on the application of a protocol consisting of a two-phase regimen of low-dose IFN α monotherapy combined with PUVA in the second phase. Our efforts focused on both relieving symptoms and achieving durable remission while limiting toxicity and costs.

Design and Methods

Patients' characteristics

Between October, 1993 and November, 1997, we enrolled 25 patients with MF. There were 16 males and 9 females, aged 23 to 80 years (median 57 years), (3 from Clinica di Ematologia, Ancona, 9 from Unità Operativa di Dermatologia I.N.R.C.A.-IRCCS Ancona, 3 from Unità Operativa di Dermatologia, Macerata, 5 from Divisione di Dermatologia, lesi, 2 from Divisione di Dermatologia, Ancona, and 3 from Clinica di Dermatologia, Ancona, Italy).

The characteristics, stage of disease and history of prior therapy of the 25 patients are listed in Table 1. Previous treatments included topical steroids in 10 patients, PUVA in 4 patients, UVA in 1 patient, RT in 1 patient, IFN α in 3 patients. Six patients had not received any prior therapy. The median time from the onset of symptoms to diagnosis was 48 months (range 1-252). Disease duration, defined as the interval between the first diagnostic cutaneous biopsy and enrollment in our trial, ranged from 1 to 240 months (median 4 months).

Treatment plan

During the induction phase, IFN α 2b (Intron-A, Schering-Plough) was administered at a dose of 1.5 MU/day sc or im during the first week and increased up to 3MU/day s.c. or i.m. in the second week. Combination of IFN α 2b and PUVA was started from the third week: IFN α 2b was administered at a dose of 6 MU three times a week and PUVA was applied three times a week. This combination was planned to be continued until complete remission (CR) was achieved or for a maximum of 2 months.

After the induction phase, combination therapy was discontinued in patients with evidence of stable or progressive disease; patients who achieved a CR or partial remission (PR) received maintenance therapy.

The maintenance phase consisted of IFN α 2b therapy combined with PUVA at gradually reduced doses every two months and applied for an overall period of 12 months.

More in detail, our treatment plan for the maintenance phase was as follows:

- months 1-2: IFN α 2b (3 MU) and PUVA three times a week;
- months 3-4: IFN α 2b (3 MU) and PUVA twice a week;
- months 5-6: IFN α 2b (3 MU) twice a week and PUVA once a week;
- months 7-8: IFN α 2b (3 MU) twice a week and PUVA once every 2 weeks;
- months 9-12: IFN α 2b (3 MU) twice a week and PUVA once a month.

The standard PUVA regimen consisted of the ingestion of 0.6 mg/kg 8-methoxypsoralen 2 hours before UVA irradiation. The initial dose of 1.5-3 J/cm² was increased by 0.5 J/cm² each time on the basis of indi-

vidual pigmentation and photosensitivity. In the period of combination therapy IFN α 2b was administered one day prior to PUVA treatment.

Response parameters and follow-up

Before starting the combination therapy, patients were examined for evidence of significant palpable lymph nodes and hepatosplenomegaly; furthermore comprehensive staging tests including a complete blood count, chemistry panel, immunophenotyping of peripheral blood mononuclear cells, chest roentgenogram, computerized tomography of the chest and abdomen, examination of blood for circulating Sézary cells and bone marrow were performed. Disease was staged according to the Committee on Staging and Classification of MF.⁷

Blood counts and chemistry panel were monitored every two weeks during the induction phase and monthly thereafter. Response to treatment was considered as CR, PR, NR (no response) or PD (progressive disease) based on measurements of skin lesions performed at 2-monthly intervals:

CR: complete disappearance of all lesions;

PR: \geq 50% reduction in the size of all lesions;

NR: no improvement or worsening of skin lesions;

PD: increase in lesion size and/or appearance of new lesions.

CR or PR had to last at least for 4 weeks and were assessed by two independent observers, blind to each other's evaluation. Toxicity was graded according to WHO toxicity criteria.

Study design and statistical methods

This is a prospective, multicenter phase II study performed to assess the feasibility and activity of a two-phase IFN α 2b plus PUVA regimen. Inclusion criteria: no previous treatment or an interval of at least 4 weeks since the last topical therapy and 4 months since the last systemic treatment; age <70 years (or 75 if performance status = 100%); performance status >60%; histologic diagnosis of MF with CD4⁺ phenotype; no unilesional localization; no significant underlying hepatic, renal, respiratory, cardiac or thyroid diseases; no previous or concomitant autoimmune disease; no psychiatric condition; no clear contraindication to UVA/PUVA therapy; no ongoing pregnancy.

We carried out an intention to treat analysis to evaluate the response rate. Freedom from treatment failure (FFTF) was calculated from treatment initiation to the date of permanent abandoning of treatment for any reason (refusal without adequate reason, lack of efficacy or toxicity of therapy). Like Dixon *et al.*,⁸ we did not consider unrelated deaths as a cause of treatment failure. Disease free survival (DFS) was calculated from CR to relapse or to the last follow-up. FFTF and DFS were analyzed by the Kaplan-Meier method.⁹

Results

After the induction phase, 9/25 patients (36%) achieved a CR and 15/25 (56%) achieved PR; two

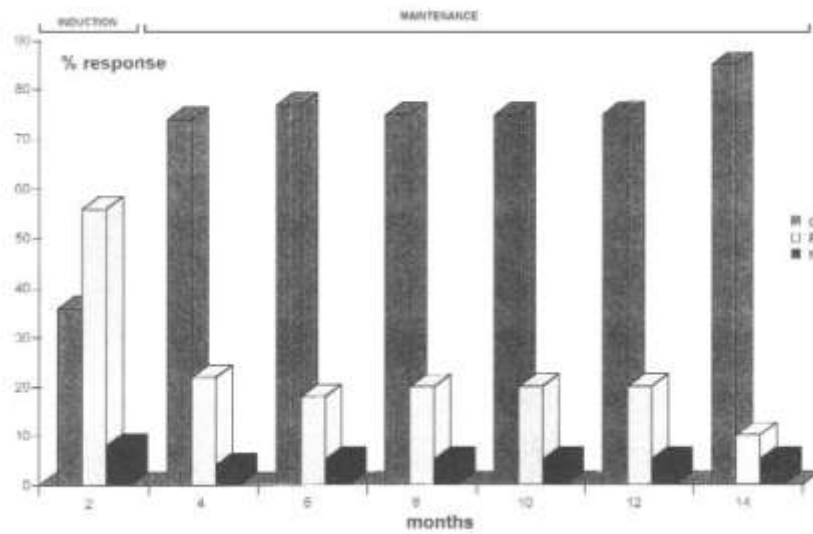


Figure 1. Complete remission (CR) increased from 36% after induction phase to 80% after 6 months of maintenance therapy.

patients (8%) were unresponsive (one of them suffered from previous acute myeloid leukemia) (Figure 1). One to five months from the beginning of the maintenance phase, CR was observed in 19/25 patients (76%, histopathologically confirmed in 14) and a PR in 5/25 patients (20%) producing an overall response rate of 96%.

Follow-up data from the start of the combination therapy were available for 23 patients. The median follow-up time for evaluable patients was 33 months.

Our results showed that the median FTF was not reached; after 12 months of treatment 82% of patients were still event-free, this percentage decreasing to 77% after 18 months (Figure 2). In more detail, 3 patients relapsed after 14, 19 and 25 months of treatment; one of these patients obtained a second CR and another achieved a good PR with minimal skin disease once maintenance treatment was recommenced. Two patients interrupted the therapy after 2 and 4 months due to intolerance (itching), whereas in 1 patient the treatment was stopped after 22

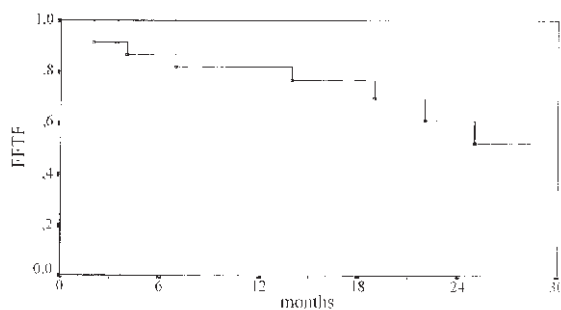


Figure 2. Kaplan-Meier probability of freedom from treatment failure (FTF). Our protocol produces a FTF of 82% at 12 months and 62% at 24 months.

months because of documented immunologic abnormalities (lupus anticoagulant, rheumatoid factor); furthermore 2 patients refused to continue the treatment after 2 and 7 months, although they were in CR.

Figure 3 shows that the median DFS was not reached; DFS projected to 48 months was 75%.

Two patients decreased the programmed dose of IFN α ; one patient had his IFN α dose increased over a 2-month period. Mild gastrointestinal side effects (grade I) and flu-like syndrome were observed in 9 and 5 patients, respectively; nausea and vomiting (grade II) occurred in one patient; itching was recorded in 2 patients, reversible depression was observed in 1 patient; 1 patient had mild leukopenia (grade I) and another showed immunologic abnormalities (lupus anticoagulant, rheumatoid factor). Routine monitoring of laboratory parameters showed no significant alterations of renal and liver functions.

PUVA was well tolerated with occasional nausea following 8-methoxypsoralen administration. An ery-

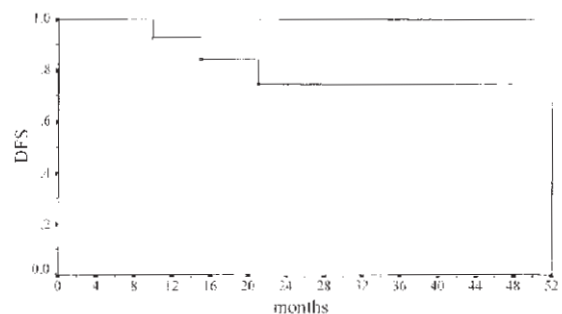


Figure 3. Kaplan-Meier probability of disease free survival (DFS). Our protocol produces a DFS of 75% projected to 48 months.

thematous reaction after PUVA-therapy sometimes necessitated administration of a lower dose in order to avoid skin burning. One patient developed nail melanosis and one cataract after PUVA treatment, so only IFN α 2b monotherapy was continued in these two patients. A median of 111 joules of UV-A was required to achieve complete clearing of skin lesions (range 22-276). A median of 469.5 joules of UV-A was administered in an entire treatment course (range 170-1,010).

Discussion

Treatment for early-stage MF includes topical chemotherapy, electron beam and other ionizing radiation, PUVA and systemic therapy.

Topical mechlorethamine is of value only in the treatment of limited cutaneous disease (60% of CR, as a whole); in spite of the high percentage of CR and long event-free survival, most patients relapse.^{10,11}

Traditional radiotherapy, used since the last century, was legitimized by the marked radiosensitivity of lymphocytes. It has now been completely replaced by electron beam radiation which produces extremely high percentages of CR (97%).¹² Unfortunately, due to considerable rates of acute and late complications, only a few centers with experience can deliver this radiation treatment.

Beneficial effects have been reported in several clinical trials using PUVA.¹³⁻¹⁵ However, complete clearance of lesions and prolongation of remission usually require maintenance therapy, and long-term UVA/PUVA exposure is associated with high incidences of cutaneous carcinomas and/or cataract. Moreover the fact that neoplastic cells may be detected at distant sites also in clinically localized disease¹⁶ supports the concept that PUVA alone is unable to prevent systemic spread.

Among systemic therapies, IFN α is of proven efficacy against MF even in heavily pretreated patients; nevertheless the overall response rate has been reported to be 55% (17% CR) and the duration of response is generally short.² The response rate is higher in early-stage and in less heavily pretreated patients; in the early stages of the disease low-dose IFN α (3MU daily or 3MU three times a week) seems to have a similar efficacy to that of higher doses.³

Retinoids have been demonstrated to have antitumor activity, but oral retinoids alone produced an overall response of 50% with a CR rate of 19%, which is comparable to that of IFN α as single therapy.^{2,17}

Several reports have suggested that the combination of IFN α with PUVA or with retinoids enhances therapeutic efficacy, a hypothesis supported by the achievement of CR among patients who had failed to respond to individual therapies.^{4-6,18}

Recently a prospective randomized multicenter clinical trial was conducted to compare the combination of IFN α plus PUVA with that of IFN α plus acitretin.¹⁹ IFN α plus PUVA was superior to IFN α plus

acitretin (CR 70% vs 38.1%); furthermore the interval of time to achieve a response was significantly shorter with the combination IFN α plus PUVA.

In terms of responses, our results (76%CR, 20%PR) were similar to those reported by Kuzel in patients with early and advanced diseases (62%CR, 28%PR).⁶ However, Kuzel's results were associated with more marked toxicity since IFN α was continued for two years, the maximum dose was 12 MU/m² three times per week, and PUVA was maintained indefinitely after skin clearing.

In our study, we favored the strategy of treating early MF as soon as possible in order to optimize response and reduce the hazard of more severe therapies. Taking into account Mostow's study⁵ we applied a new schedule to lessen the toxicity of the treatment program. In the induction phase, the dose of IFN α was raised over 6-8 weeks to the target dose of 18 MU/week; in the maintenance phase, the combination with PUVA allowed IFN α to be reduced to a maximum-tolerated dose of 6 MU/week; in this way the cumulative administration of IFN α was considerably lower than in otherwise similar combination protocols.

We agree with other authors²⁰ that overall survival and DFS are not appropriate outcome measures in patients with early stage MF (median survival longer than 10 years); FFTF,^{21,22} defined as the time from the start of treatment to the time of permanent withdrawal from therapy, is preferable for evaluation of patient compliance, treatment success and long-term results. Unfortunately, no data concerning FFTF were available in any of the above mentioned studies with combined regimens and therefore we were not able to make comparisons.

Our experience suggests that the combination of low dose IFN α with PUVA should be sufficient to maintain antitumor activity especially if continued for a reasonable period of time; moreover it seems important to decrease the dosage of IFN α and PUVA very slowly to prevent recurrence.

The efficacy of the combination therapy suggests that immunoregulatory biological mechanisms are involved in antitumor activity. As previously reported,^{23,24} immunophenotypic studies of skin lesions of patients with MF have revealed a complex interaction between malignant T clone and non-malignant tumor-infiltrating T cells (TILs); the malignant cells produce Th2 cytokines (IL4, IL5, IL10) whereas non-malignant TILs release Th1 cytokines (INF γ , TNF).^{24,25} In the early stages of MF when the density of malignant cells is low, the quantity of INF γ produced by TILs may counteract many of the biological effects of the IL4 produced by the neoplastic cells.²⁴ IFN α may produce its beneficial effects (at least in part) by modifying the balance between Th1 and Th2 thus improving immunosurveillance both locally and systemically.

PUVA presumably acts by inhibiting DNA and RNA synthesis; in this way malignant cells may be killed or,

alternatively made more immunogenic. Furthermore PUVA alone or, better, in combination with IFN α , may alter epidermal cytokine synthesis or TILs that control the malignant clone growth.

Based on these findings and our encouraging data, we believe that the combination of low-dose IFN α with PUVA may exert a profound negative effect on proliferation of the malignant clone. However, given the financial costs associated with combination therapy, a multicenter study randomly comparing IFN α plus PUVA and PUVA alone will be required.

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Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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