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# Oral Retinoid in Combination with Bleomycin, Cyclophosphamide, Prednisone and Transfer Factor in Mycosis Fungoides


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*Abstract.* Oral retinoids seem to have been of great benefit in a non-randomized study on advanced mycosis fungoides using two different chemotherapy regimens, one with retinoid, the other without. Both groups also received a 3-drug chemotherapy with bleomycin, cyclophosphamide and prednisone. Complete remission including all signs of lymph-node involvement was found in 8 of 10 patients of the retinoid treated group, while none went into complete remission in the control group. All in the control group died between 3 and 12 months after therapy, whereas all but one in the retinoid treated group are alive. Other treatment differences between the groups were related to the use of transfer factor, topical treatment, and steroid administration. These differences make a final evaluation of the use of retinoids in mycosis fungoides difficult at the present stage. Further studies are needed.

*Key words:* Retinoids; Transfer factor; Chemotherapy; Bleomycin; Cyclophosphamide; Prednisone; Mycosis fungoides

Vitamin A and its newly developed synthetic analogues have been used within recent years with great success in the treatment of disorders of keratinization. Lately retinoids have also attracted interest as pharmacological anticancer agents (1, 2, 4). We have tried out an oral retinoid RO 10-9359 (Tigason) as adjunct to a 3-drug combination chemotherapy comprising bleomycin, cyclophosphamide and prednisone for advanced mycosis fungoides (MF). Patients from Marselisborg Hospital in Aarhus received this treatment, together with transfer factor (TF), an immune-stimulatory agent, which is undergoing long-term evaluation against MF at this hospital (5), while patients of other participants in the Scandinavian Mycosis Fungoides Study Group (3) received the 3-drug chemotherapy alone. One patient from Aarhus received both the 3-drug chemotherapy and TF but no retinoids.

## MATERIAL AND METHODS

Nine patients with MF in stage IV according to the staging criteria of the Scandinavian Mycosis Fungoides Study Group (3), i.e. with lymph-node involvement, and one patient having a subcutaneous tumour received the 3-drug combination of bleomycin, cyclophosphamide and prednisone (BCP) together with retinoid and TF. Six patients were treated with BCP alone.

All patients were allowed to continue their present topical treatment, which in Aarhus was nitrogen mustard (NM), in the other hospitals oral psoralen combined with long-wave ultraviolet light (PUVA). Both topical treatment schedules were performed according to the procedures of the group (3). Steroids were also administered somewhat differently among the patients. All patients from Aarhus received prednisone 40 mg daily throughout the treatment period, while the other patients received the same prednisone dosage orally only on days 1–7, but repeated every 3 weeks.

Bleomycin was given 5 mg i.m. on day one and day four, repeated every third week. Cyclophosphamide was administered 100 mg/m$^2$ orally each day, but eventually reduced in some patients according to toxicity. RO 10–

Table I. *Responses following treatment with BCP (bleomycin, cyclophosphamide and prednisone) and retinoid in mycosis fungoides*

CR, complete remission; PR, partial remission; PD, progressive disease; TF, transfer factor; and NM, topical nitrogen mustard. Stage IVa represents dermatopathic lymphadenopathy, stage IVb histologically verified mycosis fungoides

| Pat. no. | Age/Sex | Stage | Start of therapy | Initial response | Present state | Additional treatment |
|---|---|---|---|---|---|---|
| 1 | 40/M | IVb | Mar. 1980 | CR | . 1980 | CR |
| TF + NM | | | | | | |
| 2 | 45/M | IVb | May1980 | CR | PR | TF + NM |
| 3 | 43/F | IVa | Oct. 1980 | CR | CR | TF + NM |
| 4 | 64/M | IVb | Jun. 1980 | CR | CR | TF + NM |
| 5 | 68/M | IVb | Oct. 1980 | CR | PR | TF + NM |
| 6 | 60/F | IVb | Sep. 1980 | CR | CR | TF + NM |
| 7 | 76/M | V[a] | Oct. 1980 | CR | CR | TF + NM |
| 8 | 73/M | IVb | Oct. 1980 | CR | Dead[b] | TF + NM |
| 9 | 68/M | IVa | Mar. 1980 | PR | CR | TF + NM |
| 10 | 63/M | IVa | Dec. 1980 | PR | PD | TF + NM |

[a] Died whilst CR in Feb. 1981 due to a pulmonary embolus from a deep vein thrombosis.
[b] The patient in stage V had subcutaneous MF only, with no cutaneous involvement in the present state.

9359 (Tigason) was given 100 mg daily. BCP plus or minus retinoids was planned, given corresponding to six treatment periods of bleomycin and then withdrawn.

## RESULTS

*BCP + retinoid + transfer factor.* Complete remission (CR) was achieved in 8 of 10 patients and partial remission (PR) in 2 patients. The duration of the remissions and the present status of the patients appear in Table I. All except one are alive. The patient who died had a pulmonary embolus while he was in complete remission from MF.

*BCP.* Partial remission (PR) was obtained in 3 of 5 patients, while 2 continued to deteriorate. The one patient who also got TF went into PR. All 6 patients, however, soon continued into progressive disease (PD) and after 3–12 months, all had died, one probably of a cause other than MF (Table II).

The most pronounced side effect seen was haemorrhagic cystitis following cyclophosphamide treatment. This led to discontinuation of BCP in 4 of 5 cases after 12100, 20250, 9800, and 9200 mg of cyclophosphamide respectively. All these 5 also received Tigason. One patient receiving BCP alone got haemorrhagic cystitis. Temporary bone-marrow depression was occasionally found. Tigason gave the well-known side effects such as telogen defluvium, cheilitis, milder desquamation of skin, and pruritus (1). These side effects were never of such a degree as to warrant discontinuation of the drug.

## COMMENTS

This is a non-randomized pilot study using two different regimens of chemotherapy, one with retinoid, the other without. The disease had reached

Table II. *Responses following treatment with BCP in mycosis fungoides*

The abbreviations used are the same as in Table I. PUVA represents treatment with oral psoralens and long-wave ultraviolet light. All patients died between 3 and 12 months following therapy

| Pat. No. | Age/Sex | Stage | Start of therapy | Initial response | Present state | Additional treatment |
|---|---|---|---|---|---|---|
| 1 | 49/M | IVb | June 1979 | PD | Dead | PUVA |
| 2 | 76/M | IVa | Feb. 1980 | PR | Dead[b] | PUVA |
| 3 | 63/M | IVb | Apr. 1980 | PR | Dead | PUVA |
| 4 | 55/F | IVa | Apr. 1980 | PR | Dead | PUVA |
| 5 | 62/F | IVb | June 1980 | PD | Dead | PUVA |
| 6 | 58/M | IVb | May 1980 | PR | Dead | TF+ NM[a] |

[a] Later methotrexate.
[b] This patient died of thrombosis following cancer surgery.

roughly the same extent and stage in the two groups. TF was used in both groups but all in the retinoid group received TF, as against only one in the non-retinoid group. Also the adjunct topical treatment differed, together with the mode of prednisone administration. In spite of these differences, we feel our data should receive attention due to the striking differences in the results of treatment.

Complete remission, including resolution of palpable lymph-nodes, was found in most patients in the retinoid treated group, while only a partial remission was obtained in patients treated with BCP alone, and all of these patients have now succumbed.

Due to the other differences in treatment schedules already mentioned, we dare not at present to attribute the good therapeutic results to retinoids alone. It is our opinion, however, that the addition of retinoids was the most significant difference in treatment between the groups. Our experience has been that PUVA and nitrogen mustard are of equal efficacy (3), and TF has so far shown only insignificant differences in survival rates in MR (6). Further and more easily compared studies on retinoids in MF are necessary.

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# Effect on Oral Leukoplakia of Reducing or Ceasing Tobacco Smoking

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*Abstract.* Oral leukoplakia patients who were smokers were asked to give up their smoking habits. It was found that leukoplakias present in persons with smoking habits might be reversible, when the smoking habit was reduced or given up. Leukoplakias which were not reversible could possibly be of the same idiopathic type as leukoplakias in non-smokers.

*Key words:* Oral; Leukoplakia; Tobacco

Oral leukoplakia is a precancerous lesion (1, 2, 3, 5, 7, 9) which has a statistically significant association with tobacco use, either in the form of tobacco chewing or tobacco use, either in the form of tobacco chewing or tobacco smoking (3, 7, 8). This is indicated by observations showing that there is a larger proportion of tobacco users among patients with oral leukoplakia than in the normal population. Furthermore, by undertaking a multivariate analysis on one such set of data it has been shown that the high male–female ratio for oral leukoplakia is secondary to differences in smoking habits among males and females (7).

It has also been reported that oral leukoplakias were reversible after tobacco smoking had ceased (9, 10), and/or local irritants were removed (1), but the effect of stopping smoking was not examined separately (1, 9, 10). The present study was initiated to examine whether reducing or ceasing to smoke tobacco would by itself result in a decrease in or disappearance of oral leukoplakia.

## MATERIAL AND METHODS

In the present study oral leukoplakia was defined as a white patch, not less than 5 mm across, which could not be removed by rubbing, and which could not be ascribed to any other diagnosable disease. The definition did not carry any histological connotation (5). The definition is compatible with that suggested in 1978 by the WHO Col-