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TUMOUR STAGE OF MYCOSIS FUNGOIDES TREATED WITH BLEOMYCIN AND METHOTREXATE: REPORT FROM THE SCANDINAVIAN MYCOSIS FUNGOIDES STUDY GROUP

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Abstract. The Scandinavian Mycosis Fungoides Study Group have treated 19 patients with mycosis fungoides in tumour stage by systemic chemotherapy. Nine patients were treated with Bleomycin 15 mg i.m. twice weekly for 7 weeks and 10 patients with the same dose of Bleomycin in combination with Methotrexate 15 mg i.m. per m^2 body surface each week for 7 weeks. No maintenance treatment was given. The immediate therapeutic effect of Bleomycin alone was considered good in half of the patients. Bleomycin and Methotrexate together produced a better initial effect. In both treatment series the remission was short-lived in the absence of maintenance therapy. The mortality rate was high, especially in combination treatment. Lethal complications occurred in 6 patients during the treatment, 3 of which were thromboembolic, one pancytopenia, one lung fibrosis with pulmonary insufficiency, and one bronchopneumonia. The conclusion is that these two forms of therapy cannot be recommended.

Key words: Mycosis fungoides; Treatment; Bleomycin; Methotrexate; Complications

Mycosis fungoides is a condition that is rare in Scandinavia as in other parts of the world. In Denmark and Sweden only about 20 new cases are reported each year to the national cancer registers. A multicentre study was therefore started, using uniform principles for diagnosis and treatment (3) in order to assess the effects of early active topical therapy in the pretumour stage and of systemic chemotherapy in the tumour stage, and their significance with regard to long-term prognosis.

The clinical classification of mycosis fungoides used (Table I) is a modification of that given by van Scott & Kalmanson (6).

We now present our experience of the treatment of 19 patients with tumour-stage mycosis fungoides during the first 2 years of the project. Half of the patients were treated with Bleomycin and half with a combination of Bleomycin and Methotrexate. The immediate therapeutic effect of Bleomycin alone was considered good in half of the patients. Bleomycin and Methotrexate together apparently produced a better initial effect, but in both series the remission was short-lived in the absence of maintenance therapy, and complications were severe.

MATERIAL AND METHODS

Patients

During the period July 1974 to June 1976 19 patients aged 42–85 years with tumour-stage mycosis fungoides were reported to the present investigation (Table II). Eight had previously received chemotherapy, 3 systemic and 5 topical (extensive mustard-gas painting), but with insufficient effect or relapse.

In 4 of the 19 patients the mycosis fungoides had not been present for more than 12 months before starting treatment. In 11 the condition had been present for 5 years or more.

Clinical picture

Five forms of the condition can be distinguished.

1. The 'classical' or Alibert-Bazin form, in which there are dry, erythematous patches with slight scaling and some degree of infiltration. This condition was seen in 6 patients. The first symptoms had appeared 6–25 years earlier, the degree of infiltration had shown steady increase, and the first tumours had been observed 1–6 years before starting treatment. Three patients were at stage III and 3 at stage IV.

Table I. *Clinical classification of mycosis fungoides*

Stage	Skin lesions	Histological findings in skin	Lymph nodes[a]	Internal organs[b]
I	Erythematous plaques	0	0	0
II	Erythematous plaques	MF	0	0
III	Erythematous plaques Tumour ulceration	MF	0	0
IV	Erythematous plaques	MF	MF	0
V	Erythematous plaques	MF	MF	MF

[a] Confirmed histologically.
[b] Confirmed histologically or by X-ray.
MF Mycosis fungoides.

2. The follicular form (5) was seen in 6 other patients in whom the onset of symptoms had occurred 6 months to 13 years earlier, and who had had tumours for 2 months to 2 years. Two patients were at stage III and 4 at stage IV.

3. Erythrodermia occurred in 2 patients who had shown tumours for 3 months and 2 years, respectively.

4. The *d'emblée-form* (Vidal, Brocq) was present in 2 patients in whom the condition presented with tumours. In one, erythrodermia and infiltrations developed nearly 2 years after the tumours, i.e., the condition showed a course which was the reverse of the classical form (4).

5. Three patients had had tumours for only 1–2 months, but had previously shown poikiloderma atrophicans vasculare (Jacobi) (1) for 30, 17 and 1 years respectively.

Histopathology

Darier-Pautrier abscesses were present on the epidermis. There was a mixed cellular infiltrate extending deep into the dermis, with abnormal histiocytes and lymphocytes, and plasma cells and eosinophils. Sternberg-Reed cells were not seen.

Investigations

All patients were examined clinically and histopathologically by means of multiple skin biopsy. Lymph-node biopsy was done in all with palpable lymph nodes. Bone-marrow biopsy was performed in 11 patients, liver biopsy in 5, and lymphography in 11. Chest X-ray was done in all cases.

Laboratory investigations included erythrocyte sedimentation rate (ESR), haemoglobin concentration (Hb), erythrocyte count, leukocyte count, differential leukocyte count, thrombocyte count, serum-aspartate-aminotransferase (s-ASAT, s-GOT), serum-alanine-aminotransferase (s-ALAT, s-GPT), serum alkaline phosphatase, prothrombin, serum bilirubin, serum creatinine and serum uric acid, and were performed in all patients before treatment.

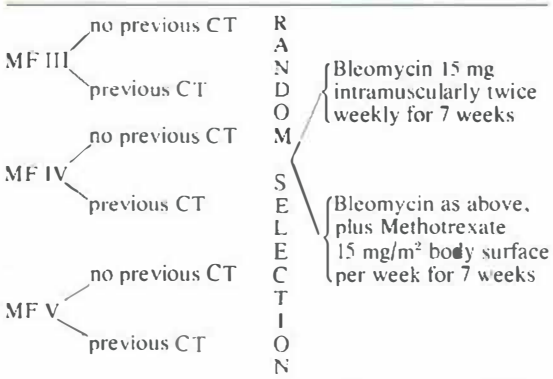
Chest X-ray examination and the above laboratory tests were repeated during and after treatment.

Immunological investigations were carried out before

Table II. *Clinical pattern, histopathology as reported by the hospital pathologists and treatment in 19 patients with tumour-stage mycosis fungoides*

Case no.	Age	Sex	MF stage	Form	Histopathology of Mycosis fungoides	Previous chemotherapy	Duration of illness	Duration of tumour stage
Bleomycin treated								
10	69	M	III	Classical	Compatible	+	14 yrs	1 yr
33	65	F	III	Classical	Obvious	+	22 yrs	5 yrs
12	74	M	III	Follicular	Obvious	−	2 yrs	2 mo.
4	57	F	III	*d'Emblée*	Obvious	−	2 yrs	2 yrs
20	83	M	III	Poikiloderma	Obvious	−	17 yrs	2 mo.
5	59	F	IV	Classical	Obvious	+	7 yrs	4 yrs
1	58	M	IV	Follicular	Compatible	−	5 yrs	3 mo.
21	65	M	IV	Follicular	Compatible	+	13 yrs	9 yrs
24	71	F	IV	Poikiloderma	Obvious	−	1 yr	9 mo.
Bleomycin+Methotrexate treated								
11	58	M	III	Classical	Compatible	−	20 yrs	2 yrs
13	75	M	III	Follicular	Compatible	−	2 yrs	3 mo.
27	63	M	III	Erythrodermia	Compatible	−	Not known	Not known
3	64	F	III	Poikiloderma	Compatible	−	30 yrs	2 mo.
16	42	F	IV	Classical	Obvious	+	10 yrs	1 yr
23	45	F	IV	Classical	Obvious	+	15 yrs	6 yrs
25	42	F	IV	Follicular	Obvious	+	1 yr	10 mo.
41	54	M	IV	Follicular	Obvious	−	6 mo.	4 mo.
6	85	F	IV	Erythrodermia	Obvious	+	6 yrs	5 yrs
22	85	F	V	*d'Emblée*	Obvious	−	3 mo.	2 mo.

Table III. *Standard treatment of mycosis fungoides (stages III, IV and V) with reference to previous chemotherapy (CT)*



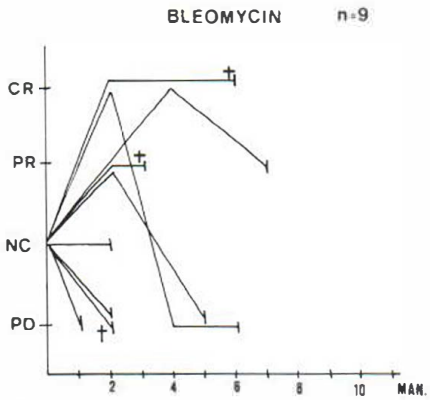


Fig. 1. Survival in patients with mycosis fungoides in tumour stage treated with Bleomycin ($n=9$).

treatment in 11 of the 19 patients, and included tests with tuberculin PPD with 2, 5, or 10 TU intracutaneously, and dinitrochlorobenzene sensitization epicutaneously with induction (DNCB 1 mg applied to the lateral aspect of the upper arm) with challenge after 2–3 weeks. Immunoglobulins, including IgE, were also determined.

Treatment

Patients were treated with Bleomycin alone or in combination with Methotrexate (Table III). They were selected at random with regard to stage of the disease and previous chemotherapy, and placed in one of these two groups. No other treatment was given, except for irradiation of tumours of the face in a few cases. All patients were admitted to a dermatological clinic for treatment. No maintenance chemotherapy was given.

A 7-week course of treatment was given, after which all patients were examined regularly for at least one year or until relapse occurred, when other forms of treatment were instituted.

RESULTS

Eleven patients completed the course of treatment in accordance with Table III, whereas the dose was reduced in 2 cases, and treatment was discontinued in 6 (Table IV).

Table IV. *Therapeutic effect in relation to dosage*

CR=complete remission, PR=partial remission, NC=no change, PD=progressive disease

	Bleomycin		Bleomycin+ Methotrexate		
Treatment	CR+PR	NC+PD	CR+PR	NC+PD	Total
Completed	3	4	4	–	11
Reduced	1	–	1	–	2
Stopped	1	–	4	1	6
Total	5	4	9	1	19

Five of 9 patients treated with Bleomycin alone showed remission which was complete in 3 and partial ('more than 50% regression') in 2 (Fig. 1). Two patients showed rapid deterioration within 2 and 3 months respectively, and another showed slow deterioration after 6 months. Three of the 9 deteriorated, and one remained unchanged despite treatment.

Treatment with Bleomycin and Methotrexate produced remission in 9 of 10 patients (Fig. 2). Only one was resistant to treatment, which had to be modified owing to side effects, however. Two patients who showed partial remission deteriorated again after 7 and 9 months.

We were unable to demonstrate any relationship between effect of treatment and the following factors:

Sex
Age at time of treatment
Interval between onset of clinical signs and start of treatment
Number and size of tumours and ulcers
Lymph-node involvement
Clinical form of mycosis fungoides
Histopathological findings
Immunological status
Earlier treatment.

COMPLICATIONS DURING TREATMENT

Several serious complications developed during or in connection with treatment, causing death in 6 cases.

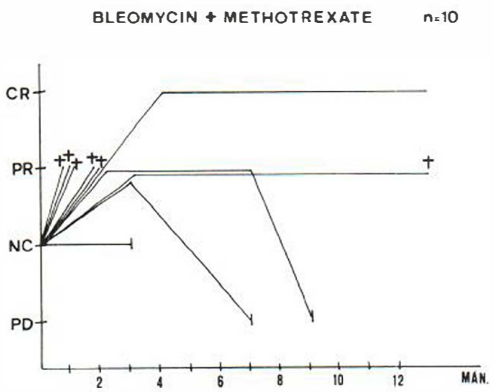


Fig. 2. Survival in patients treated with Bleomycin + Methotrexate ($n=10$).

Case no. 3. The patient was a woman of 64 years in good general condition. Two months before the start of treatment she had presented with stage-III mycosis fungoides, after a 30 years' history of poikiloderma atrophicans vasculare. She showed widespread skin lesions, mostly of infiltrative type, with some ulceration. During treatment with Bleomycin and Methotrexate the infiltrates showed rapid breakdown, leaving large epithelial defects. After 3 weeks' treatment the patient developed rigors and pyrexia, and chest X-ray disclosed shadowing of the right lung indicating pulmonary emboli. Altogether 120 mg of Bleomycin was given. Three days later an arterial embolus appeared in the right leg. Amputation was carried out owing to progressive gangrene, but the patient died the following day. The immediate cause of death was pulmonary emboli with secondary infection.

Case no. 13. a man of 75 years suffering from stage-III mycosis fungoides diagnosed 7 months earlier and showing small, isolated tumours and ulcers for 2–3 months. The patient showed auricular fibrillation and moderate cardiac decompensation at the start of treatment of the mycosis fungoides. He had been treated 6 years earlier for thrombosis of the calf, 7 years earlier for a cerebral vascular insult, and 3 years earlier for cardiac infarct. This patient received Bleomycin and Methotrexate. Owing to pyrexia and aphthous ulcers of the oral mucosa the dose of Methotrexate was halved after 3 weeks. After 6 weeks' therapy the patient developed respiratory distress and died the following day. He had received altogether 180 mg of Bleomycin. Post-mortem examination disclosed widespread arterial thrombosis, chiefly in the carotids, and cerebral infarct, myocardial infarct, pulmonary emboli, and also pulmonary fibrosis.

Case no. 33. a woman of 64 years with a 15-year history of mycosis fungoides and a 5-year history of tumours. This patient had previously received many courses of systemic chemotherapy. For the past year she had been treated with Methotrexate. Owing to deterioration the Methotrexate was replaced by Bleomycin, with good effect. During treatment pulmonary fibrosis developed, with respiratory distress. Despite systemic steroid therapy the lung lesions progressed, and 3 weeks after discontinuing the Bleomycin the patient died. Altogether she received 210 mg of Bleomycin. Post-mortem examination disclosed widespread thrombosis of the inferior vena cava and iliac and femoral veins, many pulmonary emboli and infarcts, and severe pulmonary fibrosis.

Case no. 41. a 54-year-old man with a 6-month history of mycosis fungoides, who had shown tumours and widespread lymph-node involvement for 4 months. He was treated with Bleomycin and Methotrexate, but the tumours continued to progress. Pulmonary fibrosis developed, and the Bleomycin was therefore discontinued after 6 weeks. The total dose of Bleomycin was 180 mg. The pulmonary fibrosis advanced, and the patient died of respiratory failure 6 weeks later. Post-mortem examination disclosed extensive pulmonary fibrosis.

Case no. 6. a woman of 85 years with an 18-month history of mycosis fungoides, and showing erythrodermia and scattered ulcers. She had previously shown cutaneous tumours. She was treated with Bleomycin and Methotrexate. She developed massive right-sided bronchopneumonia, and died 4 weeks after the start of treatment. Post-mortem examination showed no signs of pulmonary or thromboemboli.

Case no. 25. The patient was a woman of 42 years with an 8-year history of Cushing's disease. Mycosis fungoides had been present for 10 months, with tumours for 2 months. She was treated with Bleomycin and Methotrexate, and the tumours showed complete remission. Three weeks after starting treatment the patient developed rapidly progressive pancytopenia, and she died one week later. She received in all 75 mg of Bleomycin and 62.5 mg of Methotrexate. Post-mortem examination showed marked toxic changes in the bone marrow.

Troublesome remittent pyrexia has been reported after injections of Bleomycin in 5 patients. Pulmonary fibrosis has been reported in 2 others, and marked but reversible bone-marrow involvement in a further 2 treated with Bleomycin and Methotrexate.

DISCUSSION

Bleomycin treatment of tumour-stage mycosis fungoides in the doses used in this investigation has caused an initial regression of the disease which was total or more than 50% in more than half of the patients. The remaining patients showed little improvement, and some even became worse. The effect of therapy has been largely in accordance with other reports (2), but seems slightly better than that obtained by van Vloten & Polano (7). Even though many of our patients were suffering from advanced mycosis fungoides with ulcerating tumours and extracutaneous lesions the results cannot be regarded as satisfactory.

With Bleomycin and Methotrexate in combina-

tion a much better initial therapeutic effect was achieved: improvement took place in 9 of 10 cases. Nevertheless, relapse occurred within 6 months of discontinuing the treatment in half of the survivors. This suggests that some form of maintenance therapy is required. Five patients died.

The effect of highly active therapy must always be set off against any complications ascribable to the drug or drugs used. Pulmonary fibrosis is a complication of Bleomycin therapy that has been described previously, but which is believed to depend on the dose. In our series of 19 patients the total quantity given in a 7-week period was 210 mg, which is a moderate figure. Nevertheless, 5 patients developed pulmonary fibrosis: in 2 this regressed, but in the other 3 condition became worse despite withdrawal of the drug. The pulmonary fibrosis probably contributed to the fatal outcome in these 3 patients, 2 of whom also received Methotrexate. Thromboembolism has not previously been reported as a complication of Bleomycin and/or Methotrexate therapy. Even though the phenomenon is not uncommon in patients with advanced malignant disease, it cannot be excluded that it was associated with the treatment in these 3 patients. The suppression of bone-marrow activity that occurred in one patient and the progressive bronchopneumonia in another are also complications that could be ascribed to the drugs, and probably contributed to the patients' early deaths. The risk of complications is a factor of the greatest importance in assessing the value of the drugs, even though the skin lesions showed initial improvement.

In this series of patients with advanced, tumour-stage mycosis fungoides Bleomycin alone has not proved effective except in a few cases. Even though Bleomycin in combination with Methotrexate produced initial improvement in the skin lesions, deterioration supervened fairly soon. Combination treatment should therefore be followed by maintenance therapy doses in order to keep the patient in satisfactory condition and to prolong life. The mortality has been high, however, especially with combination treatment, and many important complications have occurred that must be ascribed to or suspected to be due to the drugs. There is no reason to believe that modification of the dosage would significantly change the effect on the patient's illness, general condition, or survival.

We can therefore only conclude that the two forms of treatment we have tested are not to be recommended in the first place, but that other paths should be explored. Patients included in this series in whom treatment was unsatisfactory, and also others with mycosis fungoides, who have been treated with psoralens and ultra-violet irradiation have so far shown an encouraging response, and we intend to publish a report on them later.

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