chemotherapy. Whatever the case, both treatments increase the well-being of the patients by reducing the discomfort of the cutaneous lesions.

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Advanced Mycosis Fungoides: Chemotherapy with Etoposide, Methotrexate, Bleomycin, and Prednimustine

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We assessed the efficacy and toxicity of a chemotherapeutic regimen in patients with stage II–IV mycosis fungoides. Eleven previously treated outpatients received etoposide and methotrexate p.o. and bleomycin i.v. every 3 weeks. There was 1 complete remission for 2 months and 7 partial remissions with a median duration of 6 months (range 2–16 months). Three patients showed stable disease lasting 1–5 months (median 2 months). In 4 patients, remissions were maintained with prednimustine after 10 courses of induction chemotherapy. Mild nausea occurred in all patients and severe leukocytopenia and thrombocytopenia in 1 patient. Toxicity of the treatment regimen was acceptable and response rates comparable to those seen by others with more toxic single-agent or combination chemotherapies.

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Mycosis fungoides is an uncommon cutaneous T-cell lymphoma with monoclonal proliferation of helper T-cells. Besides impressive skin tumours, patients frequently develop diffuse lymphadenopathy and visceral organ involvement. Extracutaneous disease may require systemic therapy. Approaches with single-agent or combination chemotherapies are associated with high response rates of approximately 60–80%. However, median duration of remission is 6 months only (1). Moreover, there are no reports of cures using chemotherapy alone in advanced stages of disease. The purpose of this study was to induce remissions with a combination chemotherapy regimen of moderate toxicity even in pretreated patients with poor performance status and to prolong response with maintenance chemotherapy.

MATERIAL AND METHODS

Eleven patients with clinical and histological evidence of mycosis fungoides were studied (Table I). All patients had

Table I. *Characteristics of patients and clinical results*

Pat. no.	Age/ Sex (yr)	Duration of MF before entering study (mo)	Disease stage/T N M	Previous therapy	Performance status (WHO)	Response	Duration of response (mo)	Survival (mo)
1	73/F	10	IVA/T3 N2 M0	UV, local irradiation	2	CR	2	38
2	75/F	2	IIB/T3 N1 M0	Local irradiation	1	PR	16	41
3	82/F	18	III/T4 N1 M0	Local irradiation, CP, CM	3	SD	1	4
4	63/M	67	IIB/T3 N1 M0	PUVA, local irradiation, total irradiation, CP	1	PR	12	25
5	68/M	40	IIB/T3 N0 M0 (+ lung cancer)	UV, local irradiation, total irradiation	1	PR	10	10
6	69/M	11	IVA/T3 N2 M0	Total irradiation, COP, COPP	1	PR	6	10
7	59/M	60	III/T4 N0 M0	Topical steroid, PUVA, local irradiation, total irradiation	1	PR	3	32
8	45/M	14	IIB/T3 N1 M0	Topical steroid, UV, PUVA, local irradiation	1	PR	3	18
9	52/M	24	IIB/T3 N1 M0	PUVA, local irradiation, CP	2	PR	2	26
10	51/M	59	IVB/T4 N1 M1 (lung)	PUVA, total irradiation, COMP	2	SD	5	9
11	30/M	36	III/T4 N1 M0	PUVA, local irradiation, total irradiation	1	SD	2	19

UV = ultraviolet phototherapy; PUVA = psoralens, ultraviolet A light; CP = chlorambucil, prednisone; CM = cyclophosphamide, methotrexate; COP = cyclophosphamide, vincristine, prednisone; COMP = cyclophosphamide, vincristine, methotrexate, prednisone; COPP = cyclophosphamide, vincristine, procarbazine, prednisone

progressive disease and clearly measurable lesions to serve as indicators of response to therapy. They were pretreated with topical corticosteroids, ultraviolet phototherapy, photochemotherapy, local radiotherapy, total skin electron beam irradiation, and/or cytostatic chemotherapy.

The following investigations were carried out before starting treatment and at regular follow-ups: history, physical examination, assessment of WHO performance status (2), complete blood counts, biochemical profile, bone marrow aspiration and biopsy, electrocardiogram, sonography or computed tomography of the abdomen, chest X-ray, nuclear bone scan, skin biopsies, and biopsies of suspected lymph nodes. Disease were staged according to the system of the Mycosis Fungoides Cooperative Group (3).

Treatment comprised induction chemotherapy using 3-weekly courses of etoposide (100 mg/m^2 p.o., days 1–5), methotrexate (5 mg/m^2 p.o., days 1–3), and bleomycin (15 mg i.v., day 1, concomitantly prednisone 50 mg i.v. to reduce toxicity). Patients achieving a response and receiving a minimum of 10 courses were subsequently given prednimustine (40 mg p.o., days 1–14) every 4 weeks as maintenance therapy. Treatment was continued until tumour progression or WHO grade 4 toxicity (4).

Evaluation for tumour response was performed at 3-weekly intervals for 6 months, at 6-weekly intervals for the subsequent 3 months, and quarterly thereafter. Complete remission (CR) was defined as disappearance of all lesions for a minimum period of 1 month. Partial remission (PR) was classified as $\geq 50\%$ decrease in measurable lesions lasting at least 1 month. Stable disease (SD) was defined as $< 50\%$ decrease or $< 25\%$ increase in the size of measurable lesions. Progressive disease (PD) involved $\geq 25\%$ increase of any tumour manifestation or the appearance of new lesions. Response duration was dated from confirmation of CR and from start of therapy until tumour progression for PR. Survival was calculated from the beginning of our treatment schedule until death.

RESULTS

All patients were eligible. Table I outlines the therapeutic results. There were 8 objective responses (73%). Remission occurred after a median of 2 courses (range 1–8 courses). One patient (patient 1) with stage IVA had a histologically unproved CR lasting for 2 months. Seven patients achieved a PR with a median duration of 6 months (range 2–16 months). Patient 5 with an unclassified bronchogenic carcinoma 3 years after initial diagnosis of mycosis fungoides had been treated with irradiation to the chest prior to chemotherapy. PR of skin lesions and lymphadenopathy could be noted until death due to

brain metastases. Four patients with response (patients 2, 4, 5, and 6) received intermittent prednimustine for 2–10 months (median 5 months). Three patients demonstrated SD lasting 1, 2, and 5 months. Generalized erythroderma (T4), organ involvement (M1), and prior chemotherapy seemed to be unfavourable prognostic factors for response to our treatment schedule. In patient 4 with a good partial remission, preceding chemotherapy dated back 5 years. Median survival after diagnosis of mycosis fungoides was 50 months (range 21–92 months). Survival from the time of initiation of chemotherapy was 4–38 months (median 19 months).

All patients complained of mild nausea. Two patients developed transient mucositis. Patient 3, a 82-year-old female with WHO performance status 3, being heavily pretreated with cytostatics, showed a leukocytopenia and thrombocytopenia corresponding to WHO grade 3 after the fourth course. She died one month later due to a refractory pulmonary infection. In the other patients, hematologic toxicity did not exceed WHO grade 2, normalizing until the next treatment course was scheduled.

DISCUSSION

The regimen outlined above was found to induce clinical remission rapidly and frequently (73%). Although this is not a randomized study and the number of patients was limited, the response rate is as good as in trials with highly toxic single-agent and combination chemotherapies (1). The precise role of maintenance therapy could not be defined as there was no significant prolongation of the interval until relapse occurred in the group treated with prednimustine. The overall administration was convenient (predominantly on an outpatient basis) and the results were achieved with minimal and tolerable toxic reactions. Only the oldest patient, being heavily pretreated, developed severe therapy-related bone marrow suppression.

We conclude that our treatment regimen is active in advanced mycosis fungoides, affording symptomatic improvement for most patients. Nevertheless, remission and survival could not be prolonged. New therapeutic approaches, especially with interferons (5), have been made in advanced stages of disease. However, the response rates and remission durations in patients treated with interferon alpha are similar to those observed after chemotherapy (5). Several in vitro and in vivo studies have suggested an additive and, in some cases, a synergistic antitumour effect of the combination of cytotoxic drugs and interferon alpha (6). Therefore, further clinical studies should determine efficacy and toxicity of cytotoxic drugs in combination with cytokines.

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