Systemic Polychemotherapy in Patients with Mycosis Fungoides and Lymph Node Involvement: A Follow-up Study of 17 Patients

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Seventeen patients with mycosis fungoides and lymph node involvement were treated with polycytostatic courses consisting of cyclophosphamide, vincristin (Oncovin) and prednisone (COP). A response rate of 76% was found. In 7 patients (41%) a complete remission and in 6 patients (35%) a partial remission was obtained. The actuarial survival rate at 5 years was 64%. This treatment was well-tolerated by most patients and severe side effects were not observed. *Key words: Cutaneous T-cell lymphoma; Combined therapy.* (Received July 24, 1984.)

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Mycosis fungoides (MF) is a T-cell lymphoma, clinically originating in the skin. Although the disease may be limited to the skin for many years, many patients eventually develop lymph node and/or visceral involvement. Once this has happened the survival is markedly shortened (1, 2).

At present there exists no consensus about the optimal treatment for MF. In most centers systemic polychemotherapy is only given to patients with advanced disease, in particular to patients with lymph node and/or visceral involvement. Based on the concept that MF might be a systemic disease from its very outset, other investigators suggested that aggressive polychemotherapy in the early stage of the disease might have a curative effect (3).

Since 1974 patients with MF and lymph node involvement have been treated in our clinic with polycytostatic courses, consisting of cyclophosphamide, vincristin (Oncovin) and prednisone (COP), the results of which will be reported.

PATIENTS AND METHODS

Between 1974 and 1984 17 patients with MF showing skin as well as lymph node involvement were treated with a polychemotherapeutic regimen as described below. This study group comprised 4 females and 13 males. Their median age at the time of lymph node involvement was 64 years (range 45–80 years). The criteria on which the diagnosis was made and the subsequent staging procedure

have been described previously (2). All patients had lymph node involvement, as demonstrated according to the criteria of Scheffer et al. (4), while no other localizations could be found.

All patients were treated with a polycytostatic schema consisting of cyclophosphamide, vincristin (Oncovin) and prednisone (COP). The treatment program consisted of 1.4 mg/m^2 vincristin given i.v. on day 1 (maximum dose 2 mg), 200 mg/m^2/day cyclophosphamide given orally for 5 days and prednisone 40 mg/day orally for 5 days. Courses of COP were repeated every 3 weeks under control of white blood cell and platelet counts. Induction treatment consisted of 8 COP courses.

Ten out of these 17 patients received total-skin electron beam irradiation (35 Gy, 4 MeV) (5, 6) prior to the cytostatic therapy (E+COP). The selection of patients for irradiation treatment was not randomized, but was based on the general health of the patient, availability of the linear accelerator and the extent of skin involvement.

After induction treatment the results were evaluated. In defining complete and partial remission we followed the recommendations of the WHO (7). Progressive disease was defined as the failure to induce a remission.

Patients who achieved a complete remission after induction treatment, but subsequently developed new plaques or tumours, received additional treatment with topical nitrogen mustard or orthovolt X-ray irradiation, respectively. In patients who failed to reach complete remission the 3-weekly COP courses were continued.

The survival rate for all patients was calculated according to actuarial method. The time at risk was taken as the period between the diagnosis of lymph node involvement and the end of the follow-up period.

RESULTS

The results of induction treatment as well as the follow-up data are shown in Table I. The median follow-up period after lymph node involvement was 44 months with a range of 3–77 months.

The response rate for all patients was 76%. At the end of the induction treatment 7 patients (41%) achieved a complete remission, 6 (35%) a partial remission, whereas 4 patients died of progressive disease.

There were more complete remissions in the E+COP group (60%) than in patients treated with COP alone (14%). However, this difference failed to reach statistical significance (p=0.08).

The disease-free interval in the patients with a complete remission ranged between 1 and 52 months (median 5 months). At the end of the follow-up period two of these patients (nos. 3 and 5) were still in complete remission after 52 and 16 months respectively, three patients (nos. 1, 2 and 4) developed only occasional small plaques, whereas one patient (no. 6) was successfully treated with polychemotherapy (COP+adriamycin) because of the development of large inguinal lymph nodes, 63 months after terminating induction treatment. Three of the six patients, who achieved a partial remission, died during the follow-up period, two (nos. 8 and 15) of MF and one (no. 7) of unrelated disease. The other 3 patients continued to develop plaques and tumors during a follow-up period which ranged from 44 to 77 months. For the total group of patients a 5-year survival rate of 64% was found (Fig. 1).

In general polycytostatic therapy was well-tolerated by most patients. Subjective complaints, like nausea and fatigue were only experienced by a few patients. In most patients only a mild myelosuppression (WBC$<3.0\times10^9$/l) occurred.

DISCUSSION

In the present report we have described our experience with a polycytostatic regimen consisting of COP courses with or without previous total-skin electron beam irradiation in 17 patients with mycosis fungoides and lymph node involvement. For the whole group a response rate of 76% was found. A complete remission was achieved in 7 out of the 17

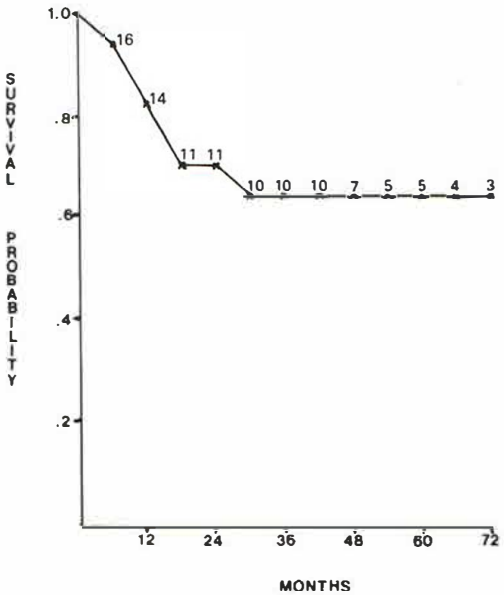

Fig. 1. Actuarial survival for 17 patients with MF and lymph node involvement treated with COP courses. The numbers at each point denote the number of the patients at risk at that time.

Table I. *Results of polychemotherapy and follow-up data in 17 MF patients with histologically proven lymph node involvement*

E = electron beam irradiation; COP = cyclophosphamide, Oncovin and prednisone. CR = complete remission = complete disappearance of all clinical evidence of disease for at least 4 weeks. PR = partial remission = regression of at least 50% of all clinical signs for at least 4 weeks. PD = progressive disease = failure to induce a remission

Pat.	Age/sex	Skin lesion	Initial treatment	Results	Duration of follow-up period[a] (months)	Current status
1	69/M	Plaques	E+COP	CR(1)[b]	76	Occasional small plaques
2	61/M	Plaques	E+COP	CR(3)	75	Infiltration eye lids, occasional small plaques
3	57/M	Plaques	E+COP	CR(52)	52	No skin lesions
4	56/M	Plaques	E+COP	CR(5)	44	Occasional plaques
5	80/M	Plaques + tumours	E+COP	CR(16)	16	No skin lesions
6	60/N	Plaques + tumours	E+COP	CR(1)	66	Plaques and tumours
7	69/M	Plaques + tumours	E+COP	PR	47	†, no MF
8	80/M	Plaques + tumours	E+COP	PR	28	†, MF
9	63/M	Plaques + tumours	E+COP	PD	13	†, MF
10	64/M	Plaques + tumours	E+COP	PD	3	†, MF
11	74/M	Plaques + tumours	COP	CR(38)	53	Small plaques
12	45/M	Plaques	COP	PR	62	Occasional plaques
13	71/F	Plaques	COP	PD	6	†, MF
14	51/F	Plaques + tumours	COP	PR	77	Plaques and tumours
15	75/F	Plaques + tumours	COP	PR	16	†, MF
16	58/F	Erythroderma	COP	PR	44	Plaques and tumours, erythroderma
17	74/M	Erythroderma	COP	PD	6	†, MF

[a] After diagnosis of lymph node involvement.
[b] The numbers between parentheses indicate disease-free interval in months.

patients (41%). The diease-free interval ranged from 1 to more than 48 months (median 5 months). A 5-year survival rate of 64% was found.

A considerable number of single and multiple agent chemotherapeutic regimens, as reviewed by Levi & Wiernik (8) and Minna et al. (9) has already been used in patients with advanced stage MF. Polycytostatic regimens, including COP, were used by the Scandinavian Mycosis Fungoides Study Group (10). However, only short-lived complete remissions could be obtained and many side effects occurred. Grozea et al. (11) treated 12 patients with advanced MF with cyclophosphamide, adriamycin, Oncovin and prednisone (CHOP) or adriamycin, Oncovin and prednisone (HOP), and another 12 patients with COP plus bleomycin. A response rate of 95% was found, while 29% of the patients achieved a complete remission with a median duration of 12 months. The median survival was less than 2 years. However, in patients with complete remissions a maintenance treatment with polychemotherapy was given for 18 months, whereas in our patients, who achieved a complete remission systemic therapy was discontinued.

In recent years two reports on combined modality therapy with electron beam iradiation and polychemotherapy have been published. Bunn et al. (3) treated 25 patients having advanced mycosis fungoides with courses of vinblastine, adriamycin and bleomycin, alternating with courses of cyclophosphamide, methotrexate and prednisone. A response rate of 96% was found, while a complete remission was achieved in 29% of the patients with a median duration of 28 months. The 3-year survival rate was 60%. Griem et al. (12) also used the combined modality treatment. With a regimen, consisting of mitoxin, vincristine, procarbazine and prednisone a 1-year survival of 100% was found. However, their patient group was rather small (9 patients). Moreover 6 of these 9 patients had only cutaneous involvement and 2 patients had concomitant Hodgkin's disease.

Comparison of our results with those of other study groups is rather difficult because of differences in staging procedures, staging criteria and patient selection. One major difference with those studies is the histological evidence of lymph node involvement in all our patients, whereas in any of the aforementioned studies also patients with dermatopathic lymphadenopathy without involvement by MF and even patients without lymph node enlargement have been included. Recent studies (2, 4), however, have demonstrated that the prognosis of patients with enlarged lymph nodes with or without involvement by MF is quite different.

In conclusion, polychemotherapy with COP courses seems a safe, well-tolerated therapy in mycosis fungoides with a significant effect on morbidity. Although definitive proof for a similar effect on survival is lacking, it is evident that the prognosis in these patients is not as poor as has been suggested earlier (1).

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REFERENCES

1. Epstein EH Jr, Levin DL, Croft JB Jr, Lutzner MA. Mycosis fungoides: survival, prognostic features, response to therapy and autopsy findings. Medicine 1972; 15: 61–72.
2. Hamminga L, Hermans J, Noordijk EM, Meijer CJLM, Scheffer E, Van Vloten WA. Cutaneous T-cell lymphoma: clinicopathologic relationships, therapy and survival in 92 patients. Br J Dermatol 1982; 107: 145–155.
3. Bunn PA, Fishman AB, Glatstein F. Staging and treatment of the cutaneous T cell lymphomas (Mycosis fungoides and the Sézary syndrome) at the National Cancer Institute (USA). In: Goos M, Christophers E, eds. Lymphoproliferative diseases of the skin. Berlin, Heidelberg, New York: Springer-Verlag, 1982: 270.

4. Scheffer E, Meijer CJLM, Van Vloten WA. Dermatopathic lymphadenopathy and lymph node involvement in mycosis fungoides. Cancer 1980; 45: 137–148.
5. Fuks ZY, Bagshaw MA, Farber EM. Prognostic signs and the management of mycosis fungoides. Cancer 1973; 32: 1385–1395.
6. Van Vloten WA, Vermey J, De Vroom H. Total skin electron irradiation in mycosis fungoides. Dermatologica 1977; 155: 28–35.
7. WHO Handbook for reporting results of cancer treatment. Geneva, 1979.
8. Levi JA, Wiernik PH. Management of mycosis fungoides—current status and future prospects. Medicine 1975; 54: 73–88.
9. Minna JB, Roenigk HH, Glatstein E. Report of the committee on therapy for mycosis fungoides and Sézary syndrome. Cancer Treatm Rep 1979; 729–736.
10. Thomsen K. Scandinavian mycosis fungoides trial. In: Goos M, Christophers E. eds. Lymphoproliferatie diseases of the skin. Berlin, Heidelberg, New York Springer-Verlag, 1982: 266–269.
11. Grozea PN, Jones SE, McKelvey EM, Coltman CA Jr, Fisher R, Haskins CL. Combination chemotherapy for mycosis fungoides: A southwest oncology group study. Cancer Treatm Rep 1979; 63: 647–653.
12. Griem ML, Tokars RP, Petras V, Variakojis D, Baron JM, Griem SF. Combined therapy for patients with mycosis fungoides. Cancer Treatm Rep 1979; 63: 655–657.