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CHOP vs MEV for the Treatment of non-Hodgkin's Lymphoma of Unfavourable Histopathology: a Randomized Clinical Trial

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Abstract—*The Swedish Lymphoma Study Group has compared the results of treatment with a CHOP regimen (cyclophosphamide, adriamycin, vincristine and prednisone) with those of treatment with a MEV regimen (methotrexate, cyclophosphamide and vincristine) in patients suffering from generalized non-Hodgkin's lymphoma (NHL) of unfavourable histopathology in a prospective randomized trial. The complete remission rate for 67 evaluable patients receiving CHOP was higher (61%) than for 74 patients receiving MEV (24%) (P < 0.001). The relapse rate was 18/41 (44%) in the CHOP group and 11/18 (61%) in the MEV group (difference not significant). At follow-up the number of patients alive in a first complete remission was thus 23/67 in the CHOP group but only 7/74 (9%) in the MEV group. This difference is highly significant (P < 0.001). However, there is still no significant difference in overall survival between the two treatment groups. This is probably due to the more efficient rescue treatment (mainly CHOP) found in the patients who primarily received MEV than in those who primarily received CHOP. It is concluded that the CHOP regimen is superior to the MEV regimen in NHL patients with unfavourable histopathology.*

INTRODUCTION

ADVANCES in chemotherapy have made it possible to achieve prolonged relapse-free survival in patients with generalized non-Hodgkin's lymphoma (NHL) of unfavourable histology. Most patients with a lymphoma of unfavourable histology who are free from relapse 2 yr after the end of treatment are cured, as first demonstrated in 1975 by De Vita and associates [1] using the MOPP regimen (nitrogen mustard, vincristine, procarbazine and prednisone). This observation has since been confirmed after treatment with several other combinations of chemotherapy [2–6]. In these studies complete remissions have been achieved in approximately 40–60% of the patients, and 75–80% of these were long-term survivors free from relapse. There have been only a few clinical trials in which the effects of different regimens have been compared prospectively. In 1979 we therefore initiated the present study to compare the curative potential of the CHOP regimen (cyclophosphamide, adriamycin, vincristine and prednisone) as described by McKelvey *et al.* [2] with that of a slightly modified MEV regimen (cyclophosphamide, vincristine and methotrexate) as proposed by Lauria *et al.* [4].

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MATERIALS AND METHODS

Patient characteristics

Between January 1979 and December 1981, 145 untreated adult patients with generalized NHL of

unfavourable histology entered the study. Generalized disease was defined as stages III and IV or a systemic relapse after local radiotherapy for patients in stages I and II. The patients were from 14 departments of medicine or oncology, participating in a national co-operative lymphoma study. The histopathological criterion for entering the study was that the patients should have an unfavourable histology, which was classified as diffuse histiocytic (DH), nodular histiocytic (NH) or diffuse mixed (DM) according to Rappaport's classification [7]. In six patients the histology was only termed unfavourable and could not be subdivided according to Rappaport's system.

Besides the 145 patients included in the study, eight patients were randomized (six patients randomly allocated for CHOP therapy and two randomly allocated for MEV) but excluded since they did not fulfil the criteria for inclusion in the study. Thus the diagnosis was changed to Ewing's sarcoma in one patient, to small-cell lung cancer in one patient and to undifferentiated cancer in two patients. Three previously untreated patients were in stages I and II, and received only local radiotherapy. One patient had received chemotherapy before randomization.

The characteristics of the 145 patients included in the study (73 men and 72 women) are presented in Table 1. The median ages of the patients in the CHOP and MEV groups were 65 yr (range 23–80 yr) and 63 yr (range 33–81 yr) respectively. The diagnosis was based on the result of biopsy of a lymph node or other organ. Since all patients had generalized disease, the intensity of the staging procedure varied. However, in all patients a complete history was taken and physical examination, bone marrow biopsy and X-ray of the lungs were performed. Investigation for abdominal involvement comprised one or more of the following procedures: computerized tomography, ultrasonography, lymphography and, in a few patients, diagnostic laparotomy. Laboratory tests included complete cell counts, measurements of the erythrocyte sedimentation rate and liver enzymes, and serum and urine electrophoresis. The Ann Arbor staging classification was used [8].

Table 1. Patient characteristics

Histopathology	CHOP ($n=70$)	MEV ($n=75$)
Diffuse histiocytic	47	49
Diffuse mixed	16	20
Nodular histiocytic	3	4
Unclassified	4	2
Stage		
III	16	14
IV	44	52
Systemic relapse after primary radiotherapy	10	9
B*-symptoms	32	32
Bone marrow involvement	13	16
Gastrointestinal involvement	8	8

*Fever, night sweats of weight loss according to the Ann Arbor staging classification.

Complete remission was defined as disappearance of all clinically detectable tumour masses and resolution of all radiographic and laboratory evidence suggesting active disease. The remission was ascertained by repeating the staging procedures (except laparotomy). The patients were not reassessed before the fifth course of treatment.

Chemotherapy

The CHOP and MEV chemotherapy regimens used are described in Table 2. The doses were reduced in accordance with the leukocyte and/or platelet counts (Table 3). If vincristine (Oncovin) caused neurotoxicity, this was replaced by vinblastine (Velbe), 5 mg/m². The patients received at least nine courses of chemotherapy unless the disease showed progression. Patients with progressive disease and those in whom a relapse occurred after a first complete remission were treated individually.

Table 2. CHOP and MEV regimens

	Drugs	Drugs and Schedule
CHOP	cyclophosphamide	750 mg/m²/day, 1, i.v.
	adriamycin	50 mg/m²/day, day 1, i.v.
	vincristine	1.4 mg/m²/day, day 1, i.v.
	prednisone	50 mg/m²/day, days 1–5, p.o.
	repeated every third week	
MEV	cyclophosphamide	800 mg/m²/day, day 1, i.v.
	methotrexate	20 mg/m²/day, day 3, i.m.
	vincristine	1.4 mg/m²/day, day 4, i.v.
	repeated every third week	

Statistical methods

Survival time was calculated from the start of therapy until death or the time of follow-up, i.e. February 1983. Relapse-free survival was calculated from the day of reassessment until objective evidence of relapse was observed or until follow-up. Survival curves were produced by the life-table method and the log-rank test was used for statistical analyses [9].

RESULTS

Of the 145 patients, 141 could be assessed with regard to remission, and of the other four patients,

Table 3. Dose attenuation for chemotherapy

Leucocyte count (10^9/l)	
<4.0	100% all drugs
3.9-3.0	100% prednisone and vincristine 75% doxorubicin 50% cyclophosphamide and methotrexate
2.9-2.0	100% prednisone and vincristine 50% doxorubicin 25% cyclophosphamide and methotrexate
<1.9	No treatment. New peripheral blood counts after a week.
Platelet count (10^9/l)	
<125	100% all drugs
125-100	100% prednisone and vincristine 75% doxorubicin, cyclophosphamide and methotrexate
99-75	100% prednisone and vincristine 50% doxorubicin 25% cyclophosphamide and methotrexate
<74	no treatment. New peripheral blood counts after a week.

two (one in the CHOP group and one in the MEV group) refused treatment and two (both in the CHOP group) died before the first course of cytostatics. The rate of complete remission is given in Table 4. In the CHOP group 41/67 patients (61%) achieved complete remission and in the MEV group 18/74 (24%) ($P < 0.001$). The same difference was also found when the remission rates were compared only in the patients who received treatment without dose reduction. These rates were 19/37 (58%) in the CHOP group and 10/37 (27%) in the MEV group ($P < 0.05$). Patients initially in stages I and II who received chemotherapy after a systemic relapse had a lower complete remission rate than the other patients (Table 4).

Twenty-eight patients who relapsed or did not achieve complete remission with the MEV regimen received CHOP as 'second-line' treatment. Among these patients, eight (29%) then achieved complete remission, and three of these were still free from disease 6, 12 and 13 months respectively after termination of treatment. Eleven patients in the CHOP group who did not achieve complete remission or relapsed received MEV as 'second-line' treatment; none of them subsequently achieved complete remission.

Table 4

	Stages III and IV	Stages I and II with systemic relapse	Total
	(a) Complete remission rates		
CHOP	38/57 (66%)	3/10 (30%)	41/67 (61%)
	($P < 0.001$)	(n.s.)	($P < 0.001$)
MEV	16/65 (25%)	2/9 (22%)	18/74 (24%)
	(b) *Patients still alive in their first complete remission*		
CHOP	22/57 (39%)	1/10 (10%)	23/67 (34%)
	($P < 0.001$)	(n.s.)	($P < 0.001$)
MEV	6/65 (9%)	1/9 (11%)	7/74 (9%)

The overall survival among patients in each treatment group is shown in Fig. 1. A slightly better survival time was observed in the CHOP group than in the MEV group, but the difference is not significant on a 5% level.

Of the 18 patients in the MEV group who achieved complete remission, 11 have relapsed (61%). The corresponding number of relapses in the CHOP group is 18 out of 41 (44%). The difference in duration of the relapse-free survival between the two groups is not significant ($P = 0.2$) (Fig. 2). Thus at follow-up only 7/74 (9%) patients in the MEV group were still alive in the first complete remission, while the corresponding number in the CHOP group was 23/67 (34%) ($P < 0.001$) (Table 4).

The dose was reduced (by >5%) in 34 patients (51%) on the CHOP regimen and in 37 patients (50%) on the MEV regimen. The reduction was moderate (<25%), however, in 22/34 of the patients in the CHOP group and in 18/37 of those in the MEV group (Table 5a). The frequency of patients with prolonged intervals betwen the courses was higher in the CHOP group than in the MEV group (Table 5b).

DISCUSSION

This study clearly shows that the CHOP regimen is superior to the MEV regimen for patients with generalized NHL of unfavourable histology. Compared with MEV, treatment with CHOP resulted in a significantly higher rate of

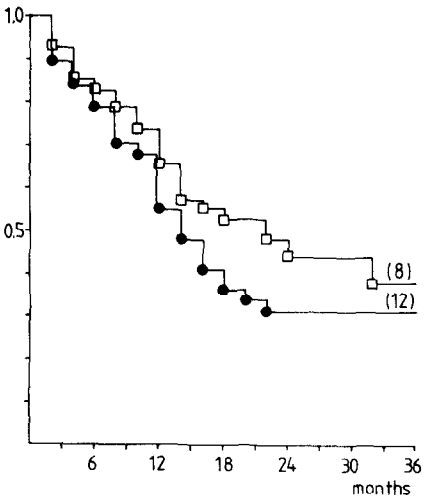

Fig. 1. Actuarial survival of patients treated with CHOP (□ n = 70) and MEV (○ n = 75). The numbers of patients surviving after 36 months are given in parentheses.

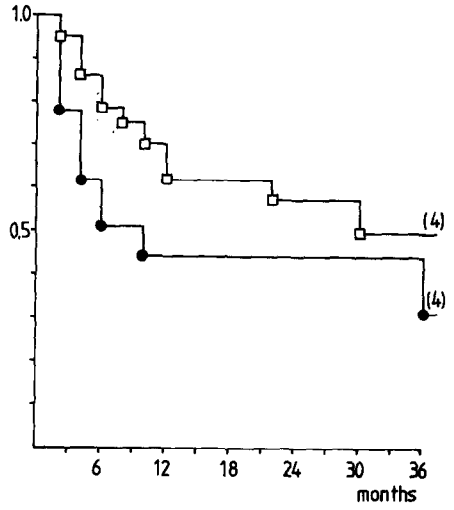

Fig. 2. Relapse-free survival of patients treated to complete remission with CHOP (□ n = 41) *and MEV* (○ n = 18). *The numbers of relapse-free patients after* 36 months *are given in parentheses.*

Table 5. *(a) Dosage of the cytostatics (% of the planned dose)*

Dosage %	No. of patients CHOP	MEV
100-95	33 (49%)	37 (50%)
94-75	23 (34%)	19 (26%)
74-50	8 (12%)	15 (20%)
<49	3 (4%)	3 (4%)

(b) Prolongation of intervals between the courses, in % of the planned interval

Prolongation %	No. of patients CHOP	MEV
<5	48 (72%)	66 (89%)
5-25	6 (9%)	5 (7%)
26-50	10 (15%)	3 (4%)
>51	3 (4%)	0

complete remission and a larger number of patients alive in their first complete remission. However, the difference in overall survival did not reach statistical significance. This may be due to a greater efficacy of the CHOP regimen in salvaging some of the failures in the MEV group than the reverse. To date, however, there are more patients in the MEV group than in the CHOP group who are not free from disease. This makes it probable that with a longer follow-up a significant difference between the two treatment groups will emerge.

The complete remission rate of 61% among the patients treated with CHOP is similar to that previously reported [2, 5, 10]. The complete remission rate of only 24% among patients treated with MEV is inferior to the results reported by Lauria *et al.* [4], who found that 15 of 19 patients (79%) with histiocytic lymphoma of stages III and IV achieved complete remission. Furthermore, in the latter series only four (27%) of the 15 patients treated to complete remission relapsed, while the corresponding number in our study was 11/18 (61%). The observation time in the two studies is similar. Our MEV regimen differed slightly from theirs in two respects. Lauria *et al.* [4] used an interval of 19 days between the first days of two cycles while we used 21 days, and they administered only 5-6 cycles compared with at least nine in the present study. In our MEV group a dose reduction was necessary in 37 (50%) of the patients. This number was considerably greater than among the patients of Lauria *et al.* [4], none of whom received lower doses than planned. In most of our patients, however, the dose reduction was less than 25%. It is unlikely that these differences account for the poor result of MEV in this study, as the complete remission rate was also low in those who received full-dose treatment.

The superior outcome for the patients treated with the CHOP regimen cannot be due to a randomly occurring excess of bad prognostic signs in the MEV group. Accepted predictors of a poor prognosis such as earlier radiation treatment, B-symptoms, bone marrow pathology and gastrointestinal involvement were well comparable between the two treatment groups. The superiority of the CHOP regimen is also evident from the results of 'second-line' treatment.

While this study was in progress new and more extensive combinations of cytostatics were developed. Recently, Fisher *et al.* [11] reported a complete remission rate of 90% in patients with unfavourable histology treated with etoposide in addition to adriamycin, cyclophosphamide, vincristine and prednisone as induction therapy (ProMACE). Another combination, M-BACOD [12], containing high-dose methotrexate with leucovorin rescue in addition to bleomycin, adriamycin, cyclophosphamide, vincristine and prednisone, has also given promising results. However, these regimens have not yet been compared with CHOP in randomized trials.

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