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## TREATMENT OF DIFFUSE HISTIOCYTIC AND DIFFUSE MIXED NON-HODGKIN LYMPHOMAS WITH CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE AND PREDNISONE (CHOP)

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### Abstract

During 1977 to 1985 90 patients with large-cell non-Hodgkin lymphoma (diffuse histiocytic or diffuse mixed according to Rappaport classification) were treated by the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) with a mean follow-up of 41 months. Thirty-four patients were treated with radiation therapy as well. The mean number of CHOP cycles to achieve complete response was 4.0 and the mean total number of cycles was 6.6. For 78 patients it was possible to calculate relative dose intensity (RDI) for each drug and the average RDI. Sixty-four patients (71%) achieved CR. The actuarial 5-year survival rate of all patients was 52%. The median RDI for cyclophosphamide was 0.72, for doxorubicin 0.70, for vincristine 0.69 and the median average RDI was 0.69. The following favorable prognostic factors were found to be of statistical significance: female sex and stages I-III as compared to stage IV. The 5-year survival rate for stage I & II patients treated by CHOP plus radiotherapy was 70% as compared to 55% for those treated by CHOP only; this difference was not statistically significant.

*Key words:* Non-Hodgkin lymphoma, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), results, prognostic factors.

Since the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) was introduced in 1976 by McKelvey et al. (11), it has become widely used, and the treatment of choice for large-cell non-Hodgkin lymphomas (1, 8). It has been found to give a high response rate and prolonged survival compared to previous combinations (5), it is easy to administer, has acceptable toxicity and may cure some patients definitively. When the CHOP regimen was published and doxorubicin became available to us, we started to use this protocol and have continued to use it for about 8 years. We used CHOP with some modifications up to the time when regimens like M-BACOD (16) PROMACE-MOPP (6) and MACOP-B (3)

were introduced and seemed superior to CHOP. In this report our accumulated experience of CHOP treatment of large-cell non-Hodgkin lymphoma is presented.

### Material and Methods

Ninety evaluable patients with large-cell non-Hodgkin lymphoma (diffuse histiocytic and diffuse mixed according to Rappaport classification (13), referred to the Northern Israel Oncology Centre (15) from March 1977 to March 1985, and treated by CHOP (11) with or without irradiation, are included in this report. Each patient underwent a physical examination, blood counts, liver and renal function tests, and chest radiography. Lymphography was performed when indicated and possible. In some patients CT of the abdomen or ultrasonography were performed in the initial evaluation. Each new patient underwent bone marrow biopsy. Routine staging laparotomy was not performed. Liver biopsy was performed in 25 patients. The patients were staged according to the recommendations from the Ann Arbor committee (2). Histologic slides, when available, were reviewed and classified according to the Rappaport classification (13). Fifty-six of the slides were re-examined and re-classified according to the international working formulation (12). If the histologic slides could not be obtained for review, treatment decision was based on the original diagnosis from the referring hospital.

CHOP was given as described by McKelvey et al. (11): cyclophosphamide 750 mg/m<sup>2</sup> i.v. day 1; doxorubicin 50 mg/m<sup>2</sup> day 1; vincristine 1.4 mg/m<sup>2</sup> day 1 (total dose not exceeding 2.0 mg) and prednisone 100 mg p.o. days 1-5.

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**Table 1**

*Clinical characteristics of 90 patients with DH or DM non-Hodgkin lymphomas treated by CHOP with or without irradiation*

Male:female	45:45	
Age	56 (range 16-79) years	
Median age	60 years	
Performance status (Karnofsky)	77 (range 20-100)	
Histology	No.	%
Diffuse histiocytic	71	79
Diffuse mixed	19	21
Stage		
I	16	18
II	24	27
III	23	25
IV	27	30
Total	90	100
Constitutional symptoms		
A	55	61
B	35	39
Bulky disease	45	50
No bulky disease	45	50
Previous radiation	7	5

Mean time from diagnosis to CHOP 1.7 months

Mean follow-up time from start of CHOP 41 months

Treatment cycles were repeated once in 3 to 4 weeks. Patients were evaluated after each cycle by clinical examination. Previously positive x-ray films and biopsies were repeated when the patient appeared to be in complete remission on physical examination. The treatment policy for stages I or II was to give 6 cycles of CHOP plus radiation therapy, 40 Gy in 4 weeks to involved or extended field. Some patients received chemotherapy only. Patients with stage III or IV received CHOP cycles until complete remission (CR) was achieved, followed by 2-3 additional courses or continued treatment up to the maximal tolerated dose of doxorubicin (450-550 mg/m<sup>2</sup>). Seventeen patients received COP (cyclophosphamide, vincristine and prednisone) as maintenance therapy.

Statistical analysis: Data were computerized and analyzed by an interactive report generator developed by one of us (Y.C.) (4). Differences between the mean of values of the various groups were evaluated by the Student's t-test. Qualitative differences were assessed with the  $\chi^2$ -test. For survival analysis, the Kaplan-Meier method (9) was used. Dose intensity was calculated according to Hryniuk et al. (7).

### Results

Patient characteristics are shown in Table 1. The mean age was 56 years. Twenty-five patients were over 70 years. Most patients had good performance status. The high proportion of stages I and II can probably be attribut-

**Table 2**

*Treatment parameters for 90 patients with DH or DM non-Hodgkin lymphomas treated by CHOP with or without irradiation*

Treatment modality		
CHOP (No. of patients)	56 (62%)	
CHOP and radiotherapy	34 (38%)	
No. of CHOP cycles for CR	4	
Mean No. of CHOP cycles	6.6 (range 1-12)	
Median (range) relative dose intensity (RDI)		
Cyclophosphamide	0.72	(0.24-1.10)
Doxorubicin	0.70	(0.24-1.07)
Vincristine	0.69	(0.20-1.04)
Median average RDI	0.69	(0.23-1.08)
Routine radiation dose	40 Gy	

**Table 3**

*Results of treatment of 90 patients by CHOP chemotherapy with or without radiation therapy*

	No.	%	p value
Complete remission (CR)	64	71	
5-year actuarial survival rates			
All patients	90	52	
Complete responders	64	73	
Relapse free survival	64	68	
Stage I	16	64	
Stage II	24	60	stages I, II and III vs. stage IV p<0.05
Stage III	23	59	
Stage IV	27	32	
Age			
<60 years	43	61	
>60 years	47	42	NS* (p<0.1)
Sex			
Male	45	39	
Female	45	65	p<0.02
Constitutional symptoms			
A	55	49	
B	35	56	NS
Bulky disease			
No	45	43	
Yes	45	62	NS
Extranodal disease			
No	37	53	
Yes	53	52	NS
CHOP only	56	52	
CHOP and radiotherapy	34	53	NS

\*NS not statistically significant

ed to understaging, as staging laparotomy was not performed and only 25 patients underwent liver biopsy. Bulky disease, defined as masses above 7 cm, was found in 50% of the patients. Only 7 patients (5%) were treated by radiation therapy as a first line treatment. Table 2 shows treatment parameters. Fifty-six patients received

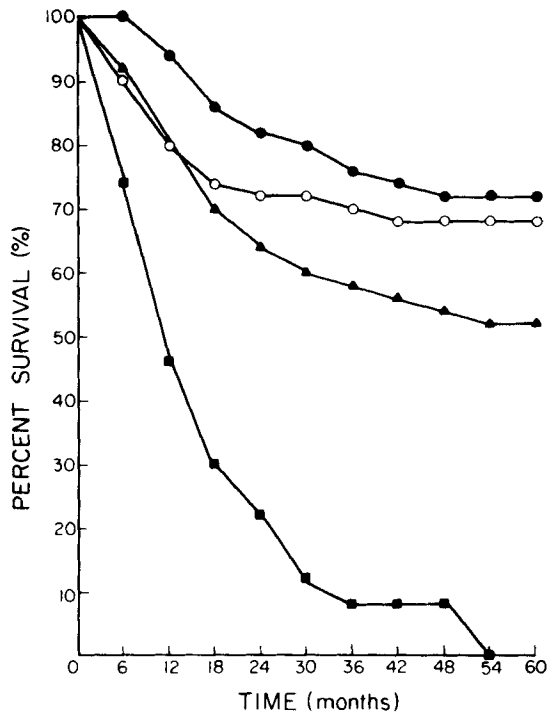


Fig. 1. Actuarial survival curves for 90 patients with non-Hodgkin lymphoma (DH and DM) treated by CHOP chemotherapy with or without radiation therapy.  $\blacktriangle$ - $\blacktriangle$  all patients (n=90);  $\bullet$ - $\bullet$  complete responders (n=64);  $\blacksquare$ - $\blacksquare$  non complete responders;  $\circ$ - $\circ$  relapse free survival.

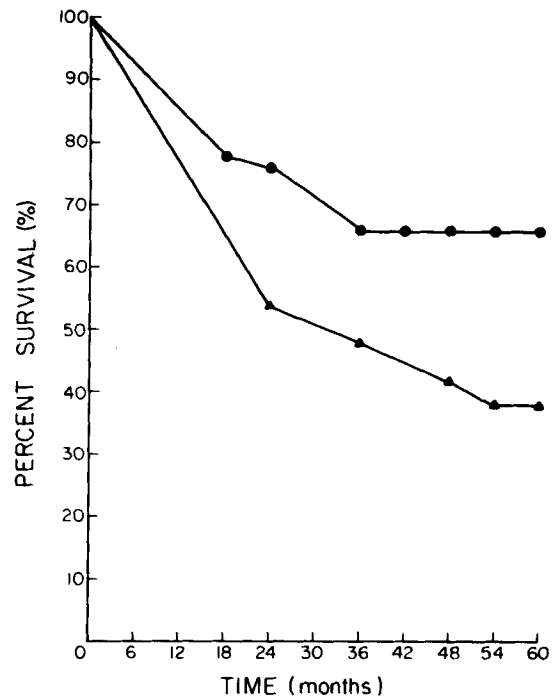


Fig. 3. Actuarial survival curves according to sex.  $\blacktriangle$  males;  $\bullet$  females.  $p < 0.02$ .

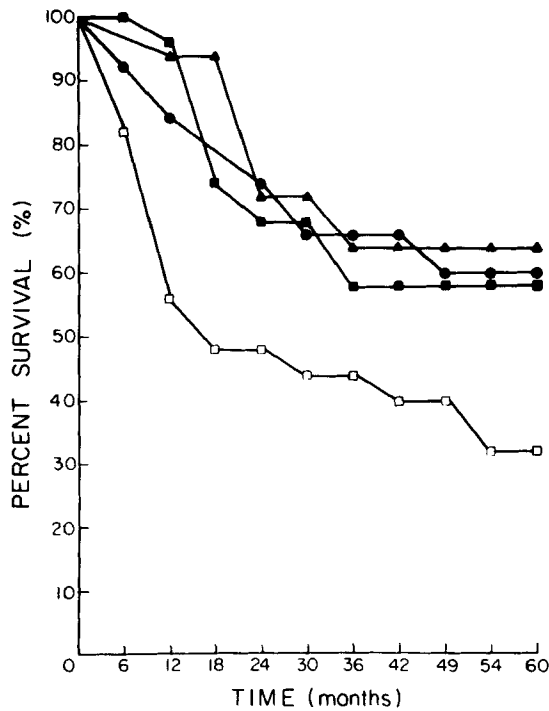


Fig. 2. Actuarial survival curves according to stage.  $\blacktriangle$  stage I;  $\bullet$  stage II;  $\blacksquare$  stage III;  $\square$  stage IV.

chemotherapy only with a mean number of CHOP cycles of 6.6 (median 6). Thirty-four patients were treated by chemotherapy and radiotherapy and their mean number of CHOP cycles was 6.6. In the 1970s most patients received radiation therapy prior to chemotherapy while in the 1980s, radiation therapy as a rule was added after chemotherapy. In some stage III or IV patients with bulky disease radiation therapy was added to involved or extended fields. The treatment was well tolerated with no treatment related death. The median average RDI of the 3 drugs, cyclophosphamide, doxorubicin and vincristine was 0.69 of the scheduled dose. Twenty-five of the 34 patients (73%) who received both chemo- and radiotherapy were in stage I or II, while only 15 of the 56 patients (27%) who received chemotherapy alone were in these stages. Patients who received both chemo- and radiotherapy and patients who received chemotherapy only had similar survival curves. For stage I and II patients receiving combined radio- and chemotherapy the 5-year survival rate was 70% as compared to 55% for those treated by CHOP alone. However, this difference was not statistically significant. The results of treatment are shown in Table 3. Seventy-one percent of all patients achieved complete remission. The relapse-free 5-year survival rate of patients achieving complete remission was 68%. Thirteen (65%) of the relapses occurred within the first year and 4 (15%) within the second year. Late relapses occurred in 3 patients at 30, 41 and 70 months after achieving complete

remission. The 5-year survival rate in the total material was 52%. None of the patients who had not achieved complete remission survived at 5 years. The survival curves had a demarcation line between stage III and stage IV and patients with stages I, II and III had quite similar survival (Fig. 2). Female sex (Fig. 3) was positively correlated in our single-factor analysis while several other parameters had no significant prognostic association. Patients with age below 60 survived longer as compared to patients whose age was above 60, however, the difference was not statistically significant (Fig. 4). Relative dose intensity of  $>0.70$  versus  $<0.70$  of cyclophosphamide, doxorubicin and vincristine, for all patients, and for those who achieved a complete remission, was not associated to survival in a statistically significant way. For stage III and IV patients who achieved complete remission, the relative dose intensity did not influence survival sufficiently enough to reach statistical significance.

### Discussion

Our experience confirms the favorable features of CHOP mentioned in the introduction. We obtained a complete remission rate of 71%, and a 5-year survival rate of 52% in all the treated patients, with acceptable toxicity. However, although we initially hoped that prolonged relapse-free survival would be compatible with cure, we have encountered 3 patients who relapsed at 30, 41 and 70 months after attaining a complete remission. This phenomenon of late recurrence has previously been described (14).

Our study was non-randomized and in some cases the histopathology could not be re-examined. Conclusions should thus be drawn cautiously. The similar survival curves for stages I, II and III may reflect understaging but it might also indicate that aggressive staging in large-cell non-Hodgkin lymphomas is not essential. The important question concerning the place of radiation therapy in the initial treatment cannot be answered by the present study. In the total series survival curves for patients who received and did not receive radiotherapy were quite similar. In the subgroup of patients with stage I or II the radiation treated patients had a higher 5-year survival rate than those treated by chemotherapy only; however, the difference was not statistically significant. Another important question is whether doxorubicin should be pushed to the highest acceptable dose. In our series no significant difference in survival was observed between patients with relative dose intensity below and above 0.7. This might indicate that pushing the doxorubicin dose to sub-toxic level is not necessary. Again, this conclusion should be regarded with caution as the study was retrospective and not randomized. The conclusion is, however, supported by the work of Lee et al. (10). They looked at long-term results after CHOP-Bleo in regular and high-dose in dif-

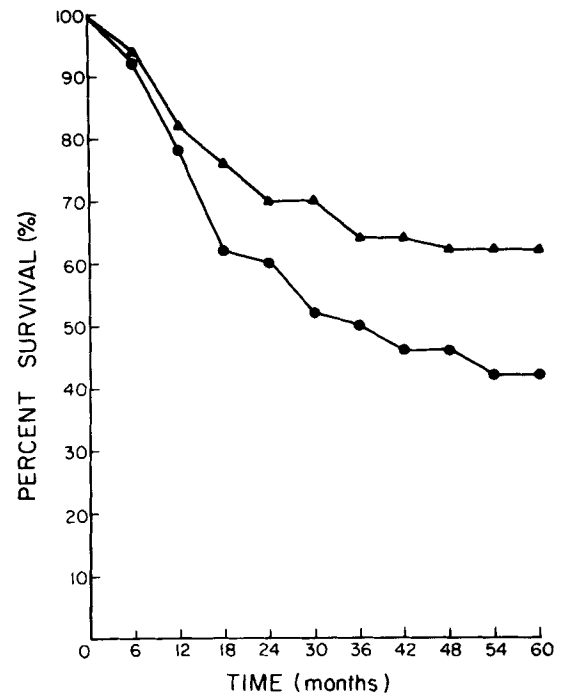


Fig. 4. Actuarial survival curves according to age below and above 60 years. ▲ <60 years; ● >60 years.  $p < 0.1$ .

fuse large-cell non-Hodgkin lymphomas. The high-dose CHOP-Bleo did not result in any advantage judging from long-term follow-up. We have used maintenance therapy of COP (11) in 18 patients for a mean treatment time of 6 months. Our survival curves do not suggest that this maintenance therapy was of benefit. A question of interest is if CHOP is as effective in intermediate grade as in high grade large-cell lymphoma. We have as yet reviewed only 56 cases according to the international working formulation (12), but so far the 5-year survival rates of intermediate and high grade are similar.

In conclusion CHOP has represented a very valuable tool for treatment of non-Hodgkin lymphomas with unfavorable histology. We now hope that new chemotherapy regimens, perhaps with CHOP as base, will further improve the treatment results.

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