Anti-Cancer Drugs, 2, pp. 383–388

Risk factors in intermediate and high-grade non-Hodgkin's lymphomas of adults: a need for a new staging system

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This study included 120 adult patients of intermediate and high-grade non-Hodgkin's lymphoma (NHL) in clinical stages II, III and IV. They were treated at Kasr El-Aini Center of Oncology and Nuclear Medicine (NEMROCK) during the period 1984–1987, inclusive. All patients were prospectively treated using four different chemotherapy regimens: MEVP (31 patients), COPP/M (23 patients), COPP/A-V (26 patients) and CHOP (40 patients). The clinical characteristics and prognostic factors in the four groups were comparable. Fifty percent (59 patients) of the whole study group attained complete remission (CR). The highest CR was achieved with the CHOP regimen (58%) and the lowest was with MEVP (39%); the difference was statistically insignificant ($p > 0.05$). One third of CR relapsed during the follow-up period and two thirds remained disease-free for a median of 5 years and a range of 2 to 6 years. Eleven possible risk factors were tested for their correlation with survival. Five factors were identified as affecting survival significantly. When these five factors were subjected to stepwise regression analysis, only the quality of initial response and performance status sustained their prognostic significance. These factors were used to classify patients into three risk groups (low, intermediate, and high); the 5-year survivals were 79%, 36%, 17% respectively. When the Ann-Arbor staging system was used, no significant difference in 5-year survival was detected between stages II, III, and IV. The significance of the Ann-Arbor staging system as a prognostic indicator is questioned in G_2 and G_3 NHL. A new staging system is proposed.

Key words: Ann-Arbor staging system, non-Hodgkin's lymphomas, risk factors.

Introduction

Intermediate and high-grade non-Hodgkin's lymphomas (NHL) are aggressive forms of neoplasms; however, they are potentially curable by recent chemotherapeutic protocols. Treatment programs for these types of lymphoma have progressed to the point where more than 60% of patients with an advanced stage of the disease are now being cured.[1,2] The outcome of treatment has been found to be affected by several prognostic factors that are basically indicators of tumor load rather than the anatomic extent of the disease. Most of these factors are not explicitly recognized by the Ann-Arbor classification.[3]

In the present study, treatment results were evaluated for four different treatment protocols (MEVP, COPP/M, COPP/A-V and CHOP) (Table 1). An attempt was made to identify various prognostic factors that could have a significant impact on prognosis in a trial to find a better predicting staging system.

Patients and methods

The eligibility criteria for this study included all adult (more than 15 years old) patients who presented to NEMROCK from January 1984 to December 1987 with the following specifications: pathologically proven G_2 or G_3 NHL, no previous specific treatment, age range between 15 and 72 years, adequate hepato-renal functions and no cardiac contra-indications for adriamycin, and clinically stage II, III, or IV (Ann-Arbor system).[4] All patients were subjected to full staging work-up. In addition, tumor diameter, number of sites affected and performance status were recorded.

During the earlier period of the study all patients (31 cases) had received the MEVP regimen; during the second part of the study patients were postoperatively randomized to receive either the COPP/M, COPP/A-V or CHOP regimen. Radiation therapy was given to sites involved originally by bulk tumor (≥ 5 cm in diameter) in a dose range of 20–40 Gy over 2–5 weeks at a rate of 1.8–2.0 Gy perforation, 5 fractions per week.

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Table 1. Chemotherapy regimes used in the present study

MEV-P				
Methotrexate	20 mg/m^2	D3	i.v.	Recycle D15 for
Endoxan	800 mg/m^2	D1	i.v.	5 cycles and maintain
Vincristine	1.4 mg/m^2	D4	i.v.	every 21 days till
Prednisone	40 mg/m^2	D1 – 4	p.o.	CR or progression
COPP/M				
Cyclophosphamide	650 mg/m^2	D1 + 8	i.v.	
Oncovine	1.4 mg/m^2	D1 + 8	i.v.	
Procarbazine	100 mg/m^2	D1 – 14	p.o.	
Prednisone	40 mg/m^2	D1 – 14	p.o.	
Methotrexate	120 mg/m^2	D21 i.v. infusion (4 h)		Starting 24 h
Leucoverine rescue	12.5 mg i.m.	6-hourly for 4 doses		after methotrexate
CHOP				
Cyclophosphamide	750 mg/m^2	D1	i.v.	
Adriamycin	50 mg/m^2	D1	i.v.	Recycle D21 for 6
Oncovin	1.4 mg/m^2	D1	i.v.	cycles
Prednisone	100 mg/m^2	D1 – 5	p.o.	
COPP/A-V				
Cyclophosphamide	650 mg/m^2	D1	i.v.	
Oncovine	1.4 mg/m^2	D1	i.v.	
Procarbazine	100 mg/m^2	D1 – 14	p.o.	Recycle at D28 for
Prednisone	40 mg/m^2	D1 – 14	p.o.	6 cycles
Ara-c	200 mg/m^2	D8 6 h infusion		
Vepside	120 mg/m^2	D8 50 min infusion		

Details of the chemotherapy regimens are shown in Table 1.

Patients were considered to show complete remission (CR) when all symptoms, clinical, laboratory and radiologic signs of disease had disappeared for at least one month from the end of primary treatment. Patients showing 50% regression or more were considered to show partial remission (PR). Patients with tumor regression less than 50% or with disease progression were considered non-responders (NR).

Actuarial survival was calculated by the life table method,[5] starting from the date of diagnosis. Eleven variables were analysed to identify factors that would affect relapse-free survival: age, sex, site (nodal or extranodal), stage (Ann-Arbor), pathologic grade, performance status, constitutional symptoms, bulk of disease (less or more than 10 cm), number of sites involved, chemotherapy regimen used and response to treatment. Multiple correlation and stepwise regression analysis were used. The identified significant risk variables were used to subdivide cases into three risk groups and survival curves were plotted for each of these three risk categories.

Results

One hundred and twenty consecutive cases of G_2 and G_3 NHL in clinical stages II, III and IV were included in this study. The clinical characteristics of the whole group are shown in Table 2. There was no difference in these characteristics among the four therapeutic groups. The mean age was 42 years $\pm$ 15 with a male-to-female ratio of 1.8:1. Nodal presentation was recorded in 72.5% and extranodal in 27.5% of cases. The majority of cases had G_2 NHL (71%). Forty-three percent had B-symptoms. The mean tumor diameter was 8.3 cm $\pm$ 4.9 and the mean number of sites affected was four.

At the end of primary treatment 58% of cases (23/40) of the CHOP group attained CR; the corresponding rates were 54% (14/26) for COPP/A-V, 43% (10/23) for COPP/M, and 39% (12/31) for MEV-P. The difference in CR rates between the four regimens was statistically insignificant. Among the 59 CR patients, 20 (34%) had relapsed during the follow-up period. Seventy-five percent of relapses (15 cases) occurred during the first two years, but relapses were recorded as late as 6 years

Table 2. Clinico-pathological characteristics of 120 cases of NHL

Male:female ratio	1.8:1
Mean age in years ± S.D.	42 ± 15
Range of age	17–72
Nodal site	87 (72.5%)
Extranodal sites	
Stage II	33 (27.5%)
Stage III	
Stage IV	
Consitutional symptoms	
Absent	68 (57%)
Present	52 (43%)
Mean tumor diameter in cm ± S.D.	8.3 ± 4.9
Mean number of sites ± S.D.	4.1 ± 2.3

Table 3. Comparison of treatment results of four chemotherapy regimes

Regimes	No. of cases	CR[a]		Relapse[b]		DF[b]	
		No.	%	No.	%	No.	%
CHOP	40	23	58	8	35	15	37.5
COPP/A-V	26	14	54	2	14	10	38.5
COPP/M	23	10	43	3	30	7	30.4
MEV-P	31	12	39	7	58	5	16.0
TOTAL	120	59	49	20	34	37	31

[a] $p > 0.05$ insignificant.
[b] 75% of relapses occurred during the first two years.
One case in MEVP regimen relapsed in the sixth year of follow-up.

(Table 3). The highest relapse rate was observed among CR of the MEV-P group (58% of CR). The 5-year actuarial survival was 44%, 37%, 34% and 17% for the CHOP, COPP/A-V, COPP/M and MEV-P groups respectively with a significant difference between the CHOP and MEV-P groups (Figure 1).

Five factors have been identified to correlate significantly with survival: quality of response, number of sites affected, B-symptoms, tumor bulk, and performance status. Complete responders fared much better than PR or NR with 5-year survival rates of 67%, 8%, 0% respectively (Figure 2). Table 4 summarizes the influence of the other four risk factors that affected significantly the 5-year survival rate. Accordingly, patients were classified into three risk groups depending on the number of risk factors present. Group I (low risk) was those patients who had no risk factors. Group II (intermediate risk) had 1–2 risk factors, and group III (high risk) had more than two risk factors (Figure 3). The corresponding 5-year survival rates were 79%, 36% and 17% respectively and the differences were highly significant (Figure 4). When the same group of patients was subdivided according to the Ann-Arbor system, no significant difference was observed at 5 years (Figure 5).

Using stepwise regression analysis, the quality of response, and to a much lesser extent the performance status, have maintained their significant impact on survival (Table 5).

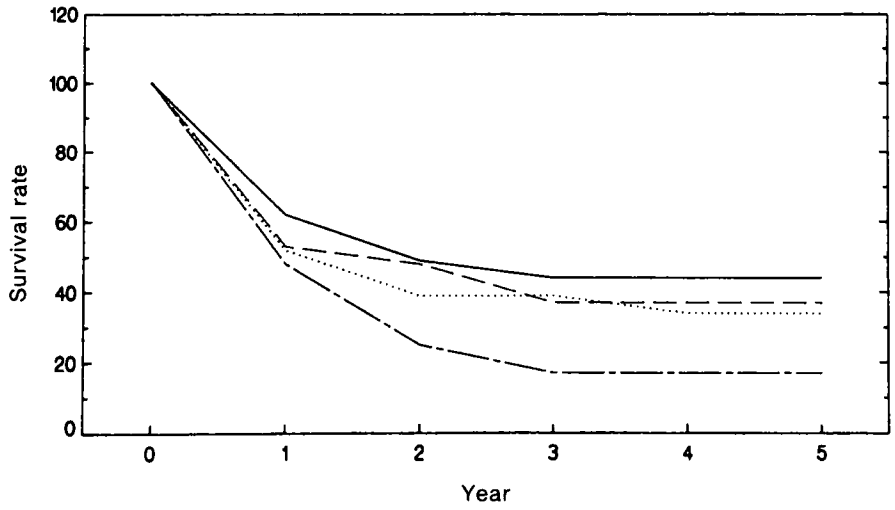

Figure 1. Five-year actuarial survival according to chemotherapy regimen. (—) CHOP; (— — —) COPP/A-V; (····) COPP/M; (— - —) MEVP.

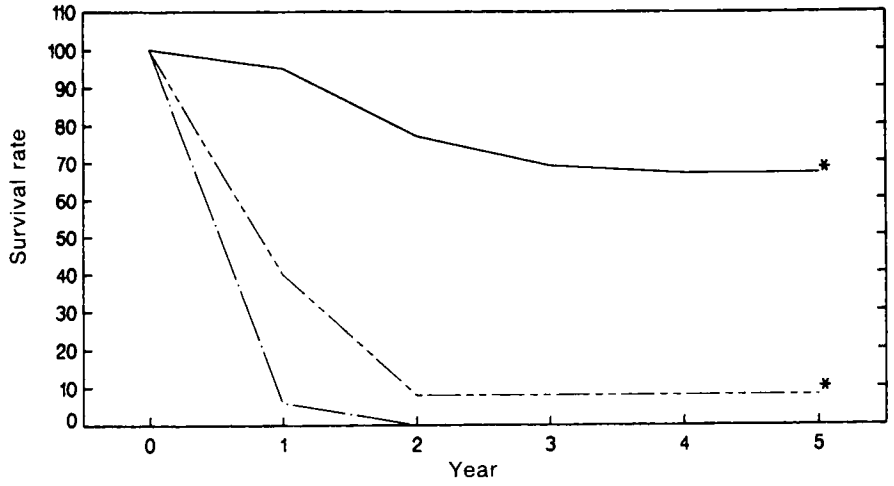

Figure 2. Five-year actuarial survival according to the response to treatment. (—) CR; (— — —) PR; (—·—) NR. *$p < 0.001$.

Table 4. Five-year actuarial survival according to significant risk factors identified

Risk factor	Five-year survival	*p* value
Number of sites:		
<5	43%	<0.001
⩾5	17%	
Constitutional symptoms:		
Absent	50%	<0.001
Present	24%	
Tumor bulk:		
<10 cm	55%	<0.001
⩾10 cm	15%	
Performance status:		
0–1	60%	<0.001
>2	24%	

Discussion

In spite of the marked improvement achieved, no one chemotherapy regimen is entirely satisfactory in the treatment of advanced G_2, G_3 NHL. All newer regimens are associated with major toxicities and fail to cure at least a portion of patients. Searching for better treatment of this disease, we have tried four chemotherapy regimens using different rationales. With MEV-P and COPP/M, the aim was a cheap simple combination and inclusion of methotrexate in low and medium doses; however, results were modest. Best CR was achieved with CHOP (58%) and COPP/A-V (54%).

If we consider that over 80% of the study patients

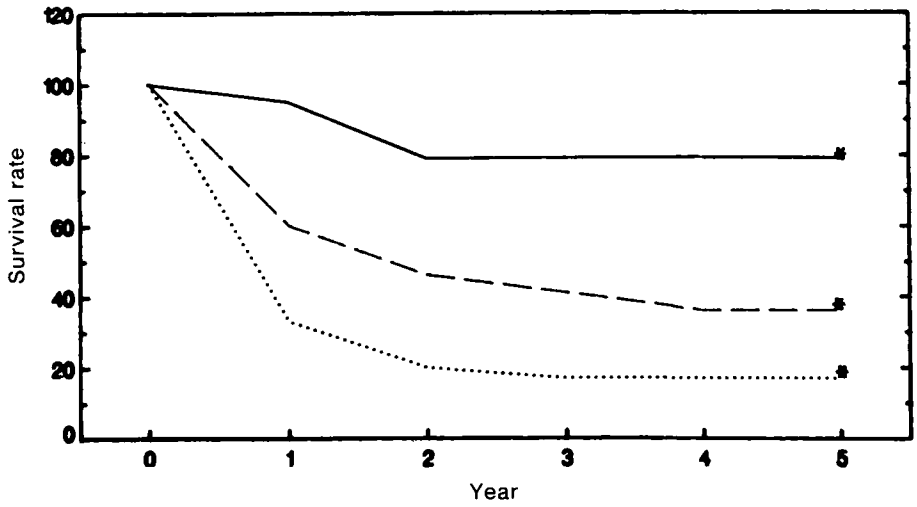

Figure 3. Five-year actuarial survival according to the number of risk factors (NEMROCK 1984–87). (—) no risk factors; (— — —) up to 2; (····) more than 2. *$p < 0.001$.

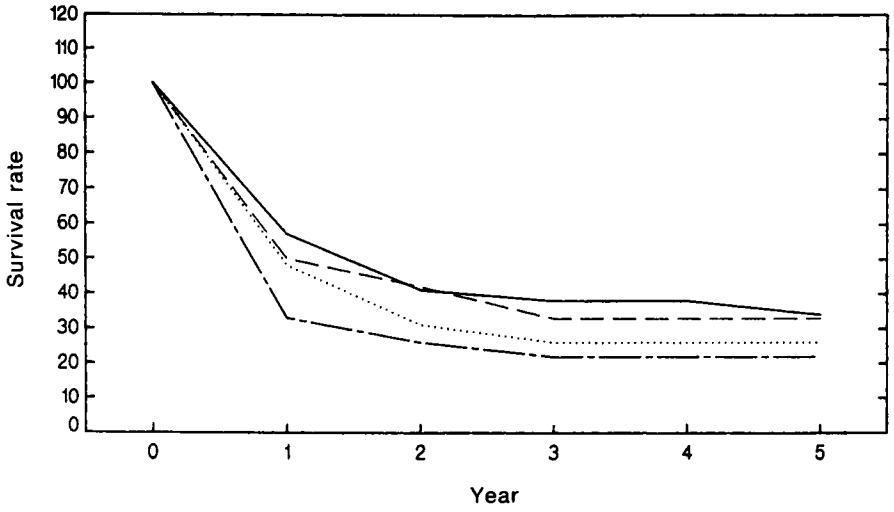

Figure 4. Disease-free actuarial survival at 5 years according to chemotherapy regimen. (—) CHOP; (— — —) COPP/A-V; (····) COPP/M; (— - —) MEVP. $p > 0.05$.

had one or more poor prognostic factors, these results will be comparable with other recent protocols.[2] The inclusion of adriamycin (one of the most active single agents in NHL) in the CHOP group, and the use of six active drugs with early exposure of malignant cells to non-cross-resistant drugs in the COPP/A-V group may explain their better results. It is worth noting that, in spite of relatively good initial CR with CHOP, it showed a high rate of relapse (35%) compared to COPP/A-V (14%). This points to the possibility that the non-cross-resistant combination technique is useful in sustaining longer remission. We therefore combined both principles in our third-generation regimen for high risk G_2, G_3 NHL. In this new protocol we have alternated CHOP with COPP/A-V, hoping to improve the initial CR as well as decreasing relapses. Initial results are very encouraging, with CR in the region of 80%. The 5-year actuarial disease-free survival rates achieved with CHOP and COPP/A-V in the present study are nearly 30% (Figure 2). These results have been reproduced by other workers.[6,7]

Since patients in the four therapeutic groups had similar general characters, all of them (120 cases) were grouped together for risk analysis. Signif-

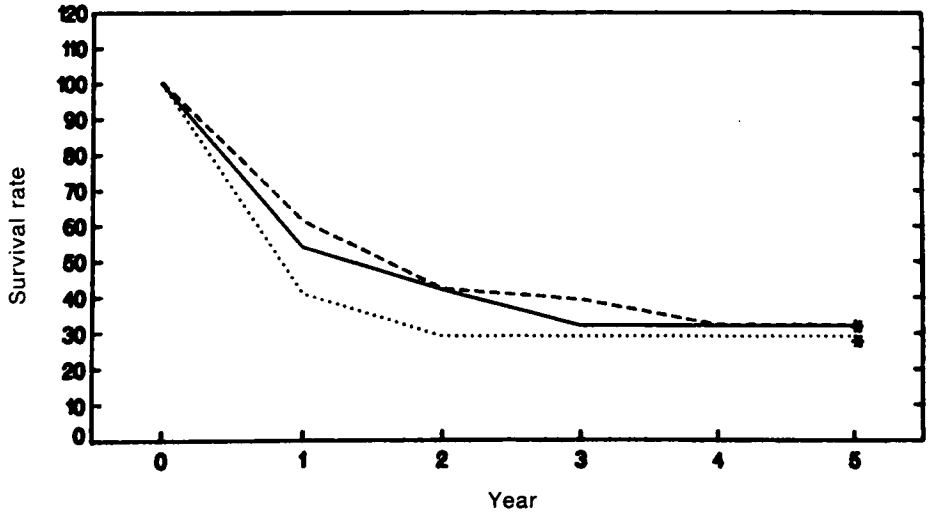

Figure 5. Five-year actuarial survival according to the Ann-Arbor staging system. (—) stage II; (— — —) stage III; (····) stage IV. *$p > 0.05$ (insignificant).

Table 5. Results of stepwise regression analysis

Variable	Regression coefficient	Probability	Partial r^2
Performance	−3.2550	0.1781	0.0474
Quality of response	−20.4774	0.0000	0.5201

icantly identified patient-risk factors were used to subdivide patients into three prognostically different subgroups. Group I (the low-risk group) comprised patients who had no B-symptoms, with good performance (0–1), with less than five sites affected and with a maximum tumor diameter less than 10 cm. The group's 5-year actuarial survival was very high (79%). This was significantly higher than the rates of 37% and 17% for groups II and III, who had 1–2 or more than 2 risk factors respectively.

There is currently considerable uncertainty as to whether classifying patients according to the Ann-Arbor system is as prognostically significant as it is with Hodgkin's disease. Velasquez *et al.*[2] have proposed a newer staging system based on tumor burden assessment and LDH level. A similar approach was suggested by Devita *et al.*[2] Our proposed risk factors, identified in the present study, can be used as the basis of a new staging system for NHL if they are reproduced in a larger study. They also can serve the purpose of selection of chemotherapy regimens. A less aggressive combination can be used for low-risk patients (group I) while more intensive regimens are kept for intermediate and high-risk patients (groups II and III).

In conclusion, the pre-treatment recognition of risk factors that adversely influence results of treatment will help greatly in the choice of an appropriate regimen with the highest CR and can help to predict the 5-year disease-free survival for an individual patient.

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(Received 14 May 1991; accepted 6 June 1991)