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Non-Hodgkin's Lymphoma in Saudi Arabia: Prognostic Factors and an Analysis of the Outcome of Combination Chemotherapy Only, for Both Localized and Advanced Disease

EZZELDIN M. IBRAHIM,* MOHAMED B. SATTI,* HASSAN Y. AL-IDRISSI,* FATMA A. AL-MULHIM,* GAMEL H. ABSSOD* and AHMAD ABDEL JABAR†

**College of Medicine and Medical Sciences, King Faisal University, Dammam and †King Abdelaziz Air Base Hospital, Dhahran, Saudi Arabia*

Abstract—*Seventy-eight previously untreated patients with clinical stage (CS) I and II (42 patients) and CS III and IV (36 patients) and non-Hodgkin's lymphoma (NHL) were treated with systemic chemotherapy only. All patients had intermediate or high grade lymphoma. Two different regimens were used: bleomycin, adriamycin, cyclophosphamide, vincristine and prednisone (BACOP); and a combination of methotrexate with folinic acid rescue, epirubicin, cyclophosphamide, vincristine, prednisone and bleomycin (MECOP-B), for 57 and 21 patients respectively. Objective clinical remission was achieved in 90% of the cases, of which 73% were complete. Complete remission (CR) was demonstrated in 90% and 53% of patients with CS I + II and III + IV respectively (P = 0.0008). Two variables, bone marrow and liver involvement, were negatively associated with CR rate in a multivariate analysis. The actuarial overall survival for the entire group was 65%. The median survival for complete responders has not been reached, but a projected 80% relapse-free survival at 3 years is estimated. The Cox proportional hazards model predicted that advanced stage (CS III and IV) and pretreatment lactic dehydrogenase serum level above 400 iu/l (N < 200 iu/l) independently influenced survival adversely. The latter prognostic variables were used to identify several groups with different risk probabilities. Despite an apparent comparability between patients receiving the two regimens, no significant difference in response or survival rates was noted between the two protocols. We conclude that the results of systemic chemotherapy compared favorably with radiation therapy for early stage disease and is an acceptable strategy for developing countries with limited availability of radiotherapy facilities. Based on certain risk factors, therapy should be individualized so that more intense regimens, with or without radiation, should be offered only to those patients in the high risk group at highly specialized centers.*

INTRODUCTION

NON-HODGKIN'S LYMPHOMA (NHL) presents certain interesting features in Saudi Arabia where its occurrence is quite common. The disease represents about 15–20% of all adult cancer sites [1, 2], and about 17% of all pediatric tumors [3]. This high frequency distribution of NHL in hospital-based registries was further confirmed by data retrieved from our newly established computerized regional tumor registry. Secondly, space-clustering of Burkitt's and other NHL in the Southern parts of the Kingdom has been noted [1, 3–5]. The topographic and endemic disease patterns of those Southern areas are very similar to the regions where Burkitt's lymphoma is highly endemic in Africa [6], for they are mountainous, predominantly rural, with considerable rainfall and are also known to be endemic for malaria. Though this space-clustering phenomenon is a preliminary observation, it merits further in-depth investigation. Thirdly, low-grade types have been observed to be rare [5], compared to figures from the U.S.A. and Italy [7].

The effective role of systemic combination chemotherapy in the management of advanced stages of aggressive NHL is well documented [8–12]. However, its effectiveness as the sole treatment

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Correspondence should be addressed to: Ezzeldin M. Ibrahim, King Fahd University Hospital, Al-Khobar, PO Box 40004, Saudi Arabia.

modality in stages I and II has been assessed in only a few reports [13, 14]. The limited availability of radiotherapy facilities in Saudi Arabia has necessitated the use of systemic combination chemotherapy for the management of localized as well as advanced disease in several oncology service satellites. In a recent study we presented preliminary data which showed that combined systemic chemotherapy in Stage II disease compared favorably with radiation therapy [15].

In this study we present data concerning patients with early and advanced stages of NHL, employing combination chemotherapy only in two different regimens. We also critically analyze the various prognostic factors that predict response to therapy and survival probability. The reason for the latter exercise is to identify certain high-risk subgroups that might require more intense chemotherapy regimens, a combination of chemotherapy and radiation, or even an early consideration for autologous bone marrow transplantation in more specialized units.

PATIENTS AND METHODS

Between August 1981 and November 1986, 81 consecutive adult patients with NHL were treated using combination chemotherapy only. The first 57 patients received the BACOP regimen [8], and the subsequent 24 had a modified MACOP-B protocol [12] where doxorubicin was replaced by epirubicin (MECOP-B). Excluded from the study were those who had previously been treated with radiotherapy and/or chemotherapy, or those who were rendered disease-free following biopsy, and those above 70 years of age. Also excluded were those patients with low-grade category based on the Working Formulation Classification [16].

All patients were clinically staged. Staging included complete history and physical examination, routine laboratory studies, chest roentgenogram, bipedal lymphangiogram, CT scan of the chest and/or abdomen and pelvis, bilateral bone marrow aspiration and biopsy and percutaneous liver biopsy if it was suspected to be involved. Liver and spleen scan, bone survey and scan, gallium scan and abdominal ultrasound were done in selected symptomatic patients. Positive studies were observed for response documentation. Laparotomies were not routinely performed for staging or for evaluation of response; however, patients presenting abdominal disease had a diagnostic laparotomy.

The extent of disease was categorized according to Ann Arbor Staging Conference [17]. Patients with bulky nodal disease were those with disease that had a single site of tumor measuring 10 cm or more in diameter, palpable abdominal mass displacing intra-abdominal organs, abdominal mass 10 cm or more in diameter demonstrated radiologically or mediastinal mass. With the exception of some patients with splenic and gastrointestinal tract (GIT) involvement, all extranodal sites of disease were confirmed cytologically and/or histologically. Splenic and GIT disease was also based on clinical, operative, endoscopic or radiological evidence.

BACOP regimen was administered as follows: cyclophosphamide i.v. 650 mg/m^2, doxorubicin i.v. 25 mg/m^2 and vincristine i.v. 1.4 mg/m^2 all given on days 1 and 8. Bleomycin 5 mg/m^2 was given i.v. on days 15 and 22. Oral prednisone 60 mg/m^2 was given on days 15–28. Doses were modified according to blood counts at the time of administration. Blood counts were obtained weekly during therapy. Dosages of doxuribicin and cyclophosphamide were reduced by 50% if the WBC count was 2000–3000/mm^3 or platelet count 50,000–100,000/mm^3; dose was deferred if the WBC count was under 2000/mm^3 or the platelet count under 50,000/mm^3. The vincristine dose was reduced by 50% if moderate neuropathy developed and was discontinued with severe neuropathy. Bleomycin was omitted with any evidence of pulmonary toxicity or with severe mucous membrane or cutaneous reactions.

The dose and schedule of the MECOP-B protocol are shown in Table 1. Methotrexate was given as a 100 mg/m^2 i.v. bolus followed by 300 mg/m^2 i.v. infusion over 4 h. Twenty-four hours later, folinic acid given 15 mg orally every 6 h for six doses to extend to 12 doses if methotrexate-related mucositis had occurred. The doxorubicin dose of 50 mg/m^2 in the original MACOP-B program [12] was replaced with epirubicin 75 mg/m^2. Blood counts were obtained weekly during therapy. The full dose of both cyclophosphamide and epirubicin was given if the absolute granulocytic count (AGC) was >1000/mm^3; 65% of the dose was administered if it was 100–1000/mm^3; and therapy was deferred if it was <100/mm^3. No dose adjustment was made for thrombocytopenia; however, prophylactic platelet transfusions were given if the platelet count dropped below 10,000/mm^3. The methotrexate dose was replaced by bleomycin 10 mg/m^2 if creatinine clearance was <50 ml/min. None of our patients had central nervous system (CNS) disease at presentation and CNS prophylaxis was not considered for patients based on either tumor grade, histologic type or bone marrow involvement.

For the BACOP regimen, all responding patients were scheduled to receive a minimum of six cycles or two cycles following clinical remission. Cycles were repeated every 28 days. For the MECOP-B protocol, therapy was completed in 12 weeks and none of the patients who achieved complete response received any further therapy until relapse. Chemotherapy was stopped if there was clear evidence of

Table 1. *Doses and schedule of the MECOP-B regimen*

Drug	Dose	Route	Timing
Methotrexate	400 mg/m²	i.v.	Weeks 2, 6, 10
Epirubicin	75 mg/m²	i.v.	Weeks 1, 3, 5, 7, 9, 11
Cyclophosphamide	350 mg/m²	i.v.	Weeks 1, 3, 5, 7, 9, 11
Vincristine	1.4 mg/m²	i.v.	Weeks 2, 4, 6, 8, 10, 12
Bleomycin	10 U/m²	i.v.	Weeks 4, 8, 12
Prednisone	75 mg	Oral	Daily for 10 weeks then tapered over 2 more weeks
Co-trimazole	2 tablets	Oral	Twice daily for 12 weeks

progression after 2–3 full cycles of BACOP or 3–4 weeks of MECOP-B therapy. At the end of scheduled therapy the treatment was stopped, and 1 month later each patient was re-staged for evidence of residual disease. Re-staging included physical examination, laboratory and relevant radiological studies, bone marrow aspiration and biopsy and biopsy of any previously involved extranodal site where feasible.

A complete remission (CR) was defined as a full regression of all clinical evidence and normalization of all laboratory and radiological abnormalities related to the disease for a minimum period of 1 month after completion of therapy. A partial remission (PR) was defined as a reduction of 50% or greater in the largest diameter of each site of measurable disease for at least 1 month. Tumor reduction of less than 50%, transient response of less than 1 month or disease progression were considered as treatment failure (TF). Survival duration was calculated from the start of therapy until death or date of last contact using the life table method. Duration of complete remission was dated from the time of its documentation to the first objective evidence of disease relapse. No patient was excluded from the analysis because of major protocol violation, recent entry, insufficient data, incomplete therapy, toxicity or early death.

Data analysis and statistical methods

A computerized database was constructed to include patients' identification, and all relevant clinical, laboratory, and radiological data. Also included were therapy details, response and follow-up. All pretreatment variables were first tested for their unadjusted association with response in a univariate analysis using the chi-square test. For variables where the chi-square test was inappropriate, the Fisher exact test was used in 2 × 2 contingency tables [18] combining PR and TF patients in one group. Variables found significant at the 0.10 level were included in a multivariate regression (all possible subsets regression analysis) to identify the 'best' subset of predictor variables for response. The 'best' subset model was selected using Mallows' C_p (coefficient) criterion [19]. Some parameters were entered both as continuous and dichotomous values by using different cutoffs when appropriate. Survival curves and estimated median survival and disease-free survival were calculated by the method of Kaplan and Meier [20]. The log-rank test of Breslow (generalized Wilcoxon) was used to assess the significance of unadjusted differences in survival for each prognostic factor [21]. Some factors were used both as continuous and dichotomous variables and those found significant at the 0.10 level were examined for their independent prognostic significance on survival with the multivariate regression model of Cox [22]. All data analyses were carried out using the 1L, 2L, 9R and LR programs of the BMDP Statistical Software (University of California, 1985).

RESULTS

Of the 81 patients entered, three could not be evaluated: two were found to have low-grade lymphoma upon review of the pathology material and the third was lost to follow-up after the first 2 weeks of the MECOP-B regimen. The remaining 78 patients could be evaluated and their main clinical characteristics are presented in Table 2. Of all these patients there were 68 Saudi patients (87%), of them 54% were originally residents of the South.

Analysis of response

Of all patients evaluated, objective clinical remission was achieved in 90%, 73% were complete. Twenty-one prognostic variables were evaluated individually for their influence on response. As shown in Table 2, the only statistically significant ($P < 0.05$) unadjusted factors that adversely affected response were: clinical Stage III and IV, bone marrow and liver involvement, and lactic dehydrogenase level (LDH) above 400 iu/l (normal < 200 iu/l). The negative effect of the advanced stage was still evident when the comparison was made among the four different stages in isolation (8, 34, 8 and 28 patients for Stages I, II, III and IV respectively, $P < 0.001$), or when comparing Stage I and II jointly with Stage III and IV ($P = 0.0008$).

Table 2. Clinical characteristics and response of 78 evaluable patients

	Response No. (%)			*P* value
	CR	PR	TF	
All group	57 (73)	13 (17)	8 (10)	
Age in years				
median 38				
range 14–70				
<40	34 (79)	5 (12)	4 (9)	
>40	23 (66)	8 (23)	4 (11)	0.36
Sex				
males	39 (67)	12 (21)	7 (12)	
females	18 (90)	1 (5)	1 (5)	0.14
Performance status*				
0–1	29 (78)	4 (11)	4 (11)	
2–4	28 (68)	9 (22)	2 (10)	0.42
Stage				
I and II	38 (90)	3 (7)	1 (3)	
III and IV	19 (53)	10 (28)	7 (19)	0.0008
B symptoms				
absent	12 (80)	2 (13)	1 (7)	
present	45 (72)	11 (17)	7 (11)	0.79
Grade				
intermediate	29 (78)	4 (11)	4 (11)	
high	28 (68)	9 (22)	4 (10)	0.42
Bulky nodal site(s)				
no	30 (81)	5 (14)	2 (5)	
yes	27 (66)	8 (20)	6 (14)	0.27
No. of bulky nodal site(s)				
0	30 (81)	5 (14)	2 (5)	
1	22 (69)	5 (15.5)	5 (15.5)	
2 or more	5 (56)	3 (33)	1 (11)	0.37
Marrow involvement				
no	56 (77)	9 (12)	8 (11)	
yes	1 (20)	4 (80)	0 (0)	0.02
GIT involvement				
no	22 (82)	2 (7)	3 (11)	
yes	35 (69)	11 (21)	5 (10)	0.28
Liver involvement				
no	52 (81)	9 (14)	3 (5)	
yes	5 (36)	4 (28)	5 (36)	0.0002
Splenic involvement				
no	47 (77)	9 (15)	5 (8)	
yes	10 (59)	4 (23)	3 (18)	0.30
Lung involvement				
no	55 (73)	12 (16)	8 (11)	
yes	2 (67)	1 (33)	0 (0)	0.83
Pleural involvement				
no	57 (75)	13 (17)	6 (8)	
yes	0 (0)	0 (0)	2 (100)	0.20
Bone involvement				
no	56 (76)	11 (15)	7 (9)	
yes	1 (25)	2 (50)	1 (25)	0.08
Other sites				
no	52 (71)	13 (18)		
yes	5 (100)	0 (0)	0 (0)	0.37
WBC (/mm^3)				
<3000	4 (44)	3 (34)	2 (22)	
3000–5000	12 (70)	3 (18)	2 (12)	
>5000	41 (79)	7 (13)	4 (8)	0.06

Table 2. *Cont.*

	Response No. (%)			*P* value
	CR	PR	TF	
AGC(/mm³)†				
<2000	25 (66)	10 (26)	3 (8)	
>2000	32 (80)	3 (7.5)	5 (12.5)	0.08
Lymphocytic count (/mm³)				
<500	23 (80)	3 (10)	3 (10)	
500–1000	24 (75)	4 (12.5)	4 (12.5)	
>1000	10 (59)	6 (35)	1 (6)	0.22
LDH(IU/l)				
<400	44 (81)	7 (13)	3 (6)	
>400	13 (54)	6 (25)	5 (21)	0.02
Therapy				
BACOP	39 (68)	10 (18)	8 (14)	
MECOP-B	18 (86)	3 (14)	0 (0)	0.16

*Performance status according to the ECOG criteria.
†AGC = absolute granulocytic count.

Table 3. *Evaluation of response according to the Working Formulation Classification*

Subclass	Total No.	Response No. CR	PR	TF
Intermediate grade				
Diffuse small, cleaved cell	13	9	2	2
Diffuse mixed, small and large cell	12	11	—	1
Diffuse large cell	12	9	2	1
High grade				
Lymphoblastic	14	10	3	1
Immunoblastic	13	8	4	1
Small non-cleaved cell	14	10	2	2

Probability of achieving CR according to subclass of intermediate and high-grade NHL: *P* value = 0.89 and 0.96 respectively.

We also analyzed patients' response based on their histologic subclassification according to the International Working Formulation. Table 3 shows that the histologic subclasses did not significantly influence the probability of achieving CR.

Variables not predictive of response included age (using different cutoffs), sex, performance status, symptoms, pathologic grade based on the Working Formulation Classification, the absence or presence and number of bulky nodal sites, extranodal involved sites other than liver and bone marrow, and the pretreatment level of WBC, AGC and lymphocytic count.

All unadjusted variables found to be significant ($P < 0.1$) in the univariate analysis were included in a multivariate regression model. The dependent variable was the response to therapy (CR vs. PR + TF), and the independent variables were clinical stage, bone marrow, bone and liver involvement and pretreatment WBC, AGC and LDH levels. Based on the multivariate regression analysis (Table 4), only two characteristics, liver and bone marrow involvement, were negatively associated with the probability of achieving CR.

Survival analysis

Over a median follow-up of 16 months (range 4–64 months) and at the time of the analysis, 62 patients (79.5%) were alive, of whom 51 (65%) were disease-free. Clinical and/or pathological evidence of disease was documented for all deceased. The overall survival for all 78 patients is shown in Fig. 1.

The median survival duration of the entire group has not been reached. The actuarial projections predict that the median survival will be greater than 40 months and that more than 65% will attain this survival.

Table 4. Multivariate regression analysis of response: all possible subset regression

Prognostic variables	Regression coefficient	2 Tail probability	Model mallow's C_p	Model tail probability
First model				
Liver	−0.507	<0.000		
Bone marrow	−0.664	<0.000		
			1.33	<0.0001
Second model				
Liver	−0.507	<0.000		
Bone marrow	−0.664	<0.000		
			0.84	<0.0001

First model: WBC, PMN, LDH were used as continuous variables. Clinical Stage I vs. II vs. III vs. IV. Second model: WBC, PMN, LDH used as dichotomous variables (Table 2). Clinical Stage I and II vs. III and IV.

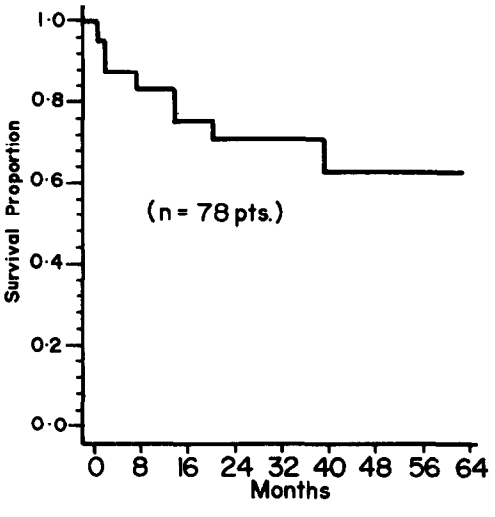

Fig. 1. Survival in months of all 78 evaluable patients.

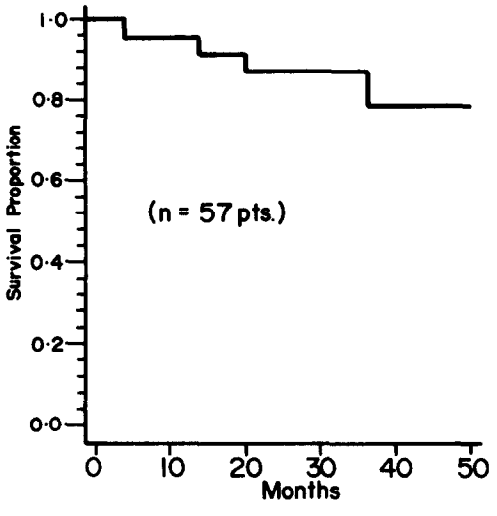

Fig. 2. Disease-free survival of the 57 patients who achieved complete remission.

Of the 57 patients who had a complete response, eight have had relapses (14%) all of whom had the BACOP regimen. Six patients were retreated using methotrexate-containing combinations with or without radiation therapy, and only one patient achieved CR and remained disease-free for more than 12 months after relapse. A second patient is still alive with evidence of disease. The other six patients have died.

Of the 13 patients achieving PR on initial therapy, one (Stage II) achieved CR for 23 months induced by salvage radiation, eight are still alive with evidence of disease (survival range 4–14 months) and the rest (four patients) have died.

The disease-free survival of patients achieving CR is recorded in Fig. 2. Their median duration of relapse-free survival has not been reached. More than 45% of CR patient are alive and have been disease-free for more than 14 months. The projected relapse-free rate of 3 years is approx. 80%.

The same prognostic factors assessed for their influence on response were also tested for that on overall survival. Unadjusted variables found significant at the 0.1 level (Table 5) were tested in a multivariate analysis using the proportional hazards model of Cox. Table 6 shows that advanced clinical stage and high LDH level were the only significant factors which adversely affected survival. Figure 3 demonstrates the survival curves of patients according to their clinical stage and LDH level. The median survival of patients with Stage I and II was not reached; however, an actuarial survival rate of more than 90% is projected at 4 years. This compared favorably to a median survival of 40.4 months for patients with more advanced disease ($P > 0.0001$). For the group with LDH level less than 400 iu/l the median survival was not reached, those patients compared also favorably to those with LDH above 400 iu/l who had a median survival of 20.75 months ($P = 0.0003$).

Alternative models were also explored where response to therapy (CR vs. PR + TF) was entered into the multivariate analysis together with the other variables. Failure to achieve initial CR and advanced clinical stage were significantly associated with increased death rate ($P < 0.001$ and 0.001

Table 5. Significant ($p<0.1$) unadjusted variables predicting survival

Variable	Description	*P* value*
Stage	I vs. II vs. III vs. IV	0.0003
	I and II vs. III and IV	0.0001
Marrow involvement		0.059
Liver involvement		0.0001
Splenic involvement		0.037
Lung involvement	Without pleural disease	0.021
Pleural involvement	Without lung disease	0.02
No. of extranodal sites involved		0.0004
LDH	Cutoff point of 400 iu/l	0.0003

*Log-rank test [21].

Table 6. Proportional hazards regression analysis of variables predicting survival

Prognostic variable	Estimated coefficient	*P* value	Model chi-square	DF	Model *P* value
First model			36.14	2	<0.0001
Stage	1.3787	<0.000			
LDH	0.0006	0.007			
Second model			22.38	2	<0.0001
Stage	0.8822	<0.000			
LDH	1.2622	0.016			

First model: stage I vs. II vs. III vs. IV.
LDH is used as continuous variable.
Second model: Stage I and III vs. III and IV. LDH is used with a cutoff point of 400 iu/l.

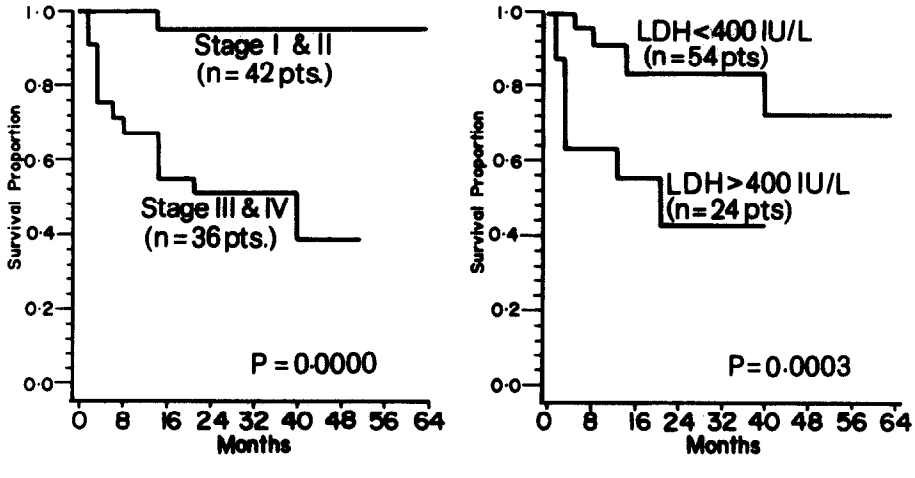

Fig. 3. Survival curves for patients grouped according to their clinical stage (left) and their pretreatment LDH levels (right).

respectively). Advanced CS (clinical stage) remained significant. However, high LDH (>400 iu/l) was the third significant variable ($P = 0.025$) only when tested as a dichotomous variable, but lost its significance when used as a continuous covariate.

Survival analysis of subgroups

Based on the significant factors identified by the Cox model, patients were stratified into different risk groups. Low-risk patients were those with clinical Stage I and II, and normal LDH (<200 iu/l). The high-risk group included patients with clinical Stage III and IV, and LDH more than 400 iu/l. The median survival of the low-risk group (19 patients) was not reached, but a projected long-term 88% survival is estimated. On the other hand, the median survival of the high-risk group (17 patients) was only 13 months. A highly significant difference in survival between the two groups was demonstrated ($P = 0.0001$). Two other groups of intermediate risk were evaluated. The first (seven

patients) included patients with clinical Stage I and II and LDH of more than 400 iu/l. None of the patients in this group died. The second intermediate risk group (19 patients) included those with clinical Stage III and IV and LDH level less than 400 iu/l. Despite two early deaths, the median survival in the later group had not been reached at the of the analysis. The difference in survival between those two intermediate risk groups was not significant ($P = 0.54$).

Analysis of therapy regimens

Although there was a trend for a higher CR rate for MECOP-B compared to BACOP (CR 86% vs. 68%) this difference was not statistically significant ($P = 0.16$). Furthermore, the univariate and the multivariate analyses failed to demonstrate a significant difference between the two regimens on survival. Further evaluation of the subgroups of patients in the two regimens based on the independent risk factors for response and survival was carried out to ascertain the comparability of the two study groups (Table 7). With the exception of a suggested difference indicating that more patients in the BACOP group had liver involvement, no other risk variable showed dominance in either of the two groups. Table 7 also shows the results of analyzing the distribution of intermediate and low-grade NHL among patients receiving BACOP or MECOP-B. The difference was not significant. Furthermore, there was no significant difference in CR rate between BACOP and MECOP-B in any of the histologic subclasses.

Evaluation of toxicity

For the BACOP regimen, leukopenia occurred in 24% of courses, resulting in nadirs below 3000/mm^3. Serious infection was documented in eight patients and was fatal in one. There was no incidence of serious thrombocytopenia-related bleeding episodes. Most patients developed alopecia, and 12 developed mild to moderate neuropathy. In one patient, the neuropathy was severe enough to necessitate discontinuation of vincristine. The expected degree of nausea and vomiting was experienced and was not a significant dose-limiting toxicity. None of the patients developed cardiomyopathy, pulmonary fibrosis or hemorrhagic cystitis. The percentage of patients who received at least 85% of the scheduled full dose for each drug was as follows: bleomycin 100%, doxorubicin 85%, cyclophosphamide 85%, vincristine 80% and prednisone 90%.

For the 21 patients who received MECOP-B, leukopenia, moderate and severe mucositis were the most commonly encountered complications, they occurred in 28%, 42% and 12% of the patients respectively. Non-fatal serious infection developed in one patient and another developed activation of an old pulmonary tuberculosis 2 months after completion of therapy. Severe neuropathy with subsequent withdrawal of vincristine developed in only one patient. Emesis was not a significant toxicity during most weeks of MECOP-B therapy. None of the patients developed treatment-related renal failure, cadiomyopathy, bleomycin lung toxicity or hemorrhagic cystitis. Dose modification, to less than

Table 7. Risk factors and histologic subclassification analysis for patients receiving BACOP vs. MECOP-B regimens

Factor	BACOP No. of patients		MECOP-B No. of patients		*P* value*
Bone marrow (yes vs. no)	3	53	2	20	0.867
Liver (yes vs. no)	13	43	1	21	0.046
Stage (I and II vs. III and IV)	27	29	15	7	0.089
LDH (<400 vs. >400 iu/l)	38	18	17	5	0.29
Grade (intermediate vs. high)	27	30	10	11	0.81

Histologic subclass	Total No./CR BACOP	MECOP-B	*P* value*
Small cleaved cell	11/7	2/2	0.55
Diffuse mixed, small and large cell	9/8	3/3	0.63
Diffuse large cell	7/5	5/4	0.62
Lymphoblastic	11/8	3/2	0.66
Immunoblastic	9/5	4/3	0.55
Small noncleaved cell	10/6	4/4	0.44

*Fisher exact test.

90% of planned full dose, based on bone marrow suppression and/or other non-hematologic complications, particularly mucositis, was necessary in only 10–15% of patients, mainly for methotrexate, doxorubicin and cyclophosphamide.

DISCUSSION

NHL is a common neoplasm in Saudi Arabia. It demonstrates interesting clinical and epidemiological features [1–5]. The space-clustering of the disease in the Southern parts of the country deserves future in-depth examination. In our series, 54% of our patients were from the Southern region which constitutes less than one-fifth of the area and is inhabited by less than one-fifth of the population of Saudi Arabia [4].

In our study, the efficacy of systemic combination chemotherapy in the evaluation of 78 patients with intermediate and low grade disease was evident. An objective remission rate of 90%, of which 73% was complete, was demonstrated. Extensive analysis of various prognostic variables has shown that liver and bone marrow involvement were negatively associated with the probability of achieving CR. On the other hand, the previously reported adverse effects of high LDH level [23], low performance status score [23] and B symptomatology [24] on CR rate were not reproduced in our study. Those differences might be due to different study populations and to the fact that more than half of our patients had early stage disease. Furthermore, we cannot rule out the potential significant of other explanatory variables due to the small number of patients in each subgroup such as the histologic subclass based on the Working Formulation Classification (type II error).

Earlier chemotherapy regimens used in the management of advanced stages of large-cell NHL, demonstrated a CR rate of 40–50% with a large proportion of patients achieving long relapse-free survival [8, 25, 26]. More intensive protocols have resulted in higher remission rates of 55–85% and more than 75% relapse-free survival [9–12]. Traditionally, patients with localized disease have been treated with radiation therapy alone, resulting in 5-year survival rates of 60% and 25–40% for Stage I and Stage II disease respectively [27]. The limitation of radiation therapy as the primary modality in early-stage disease was recently alluded to in a study where most patients who had relapses had them in extralymphatic sites, and most relapses occurred outside the radiation fields [28]. These findings support the rationale of managing those patients primarily with cytotoxic therapy. However, the role of systemic chemotherapy as the sole treatment for these patients had not been frequently evaluated [13–15]. The lack of access to modern radiotherapy facilities in the developing countries, supported by previous evidence [13–15], justified the employment of systemic chemotherapy only as the initial therapeutic modality for localized as well as for advanced disease. This strategy was preliminary tested in a pilot study at our institution for Stage II disease [15]. Longer follow-up on a larger number of patients of Stage I and II in the current analysis has shown that the achieved CR rate of 90% and the projected 90% long-term survival rate are superior to those of radiation therapy.

Survival analysis showed that at the time of evaluation, about 80% of patients were still alive of whom 65% of all patients were disease-free. The median survival of the entire group was greater than 40 months and it is projected that 65% of them will attain such survival. The median duration of relapse-free survival has not been reached, but, the freedom from relapse rate after 3 years was approx. 80%.

The discrete analysis of unadjusted risk variables affecting survival has shown that advanced stage, high LDH level above 400 iu/l, increased number of extranodal sites and bone marrow, liver, splenic, lung and pleural involvement were associated with a high death probability. However, on the multivariate analysis, advanced stage, i.e. Stage III and IV and high LDH, were the only variables that remained significant. These results confirmed previous reports on the adverse influence of advanced stage, and the high level of LDH on survival [29–32]. It is interesting to observe that LDH was an accurate objective measure for tumor burden, more significant—perhaps—than clinical or radiologic criteria for bulky disease. On the other hand, using an alternative multivariate analysis model showed that achieving CR is one of the significant independent variables, in addition to advanced stage and high LDH level, that predict survival. However, we acknowledge that survival analysis based on achieving CR might be invalid and seriously misleading [33].

The Cox multivariate analysis has aided the identification of several groups of patients with varying degrees of risk factors that might determine the therapeutic strategy and individualization of therapy. In this respect, patients in the low risk group having early stage disease and normal LDH level can perhaps be cured by less intense regimens, which can be administered safely at various oncology satellites. However, the third generation, more intense protocols with potentially higher iatrogenic morbidity and mortality rates, should only be given to those patients in the high risk group who might also need a combination of chemotherapy and radiation therapy or even an early consideration for autologous bone marrow transplantation. Those therapeutic alternatives should be administered

only at more specialized units equipped with modern radiation facilities.

In our study we have not been able yet to observe a significant difference in remission or survival rates between BACOP and MECOP-B despite the apparent comparability of patients in the two groups regarding risk criteria, and the lack of a significant difference in dose modification between the two regimens. However, our data cannot rule out the potential superiority of MECOP-B over BACOP; in particular a longer follow-up is needed to compare the durability of the achieved CR rates. Current randomized studies are investigating the efficacy of the more intense regimens against older combination therapy with appropriate stratification for risk variables [34]. The results are still not available.

Analysis of CR rates based on histological subclasses did not reveal any significant difference between BACOP and MECOP-B. However, the relatively small number of patients in each subclass could be a factor that explains the lack of any significant difference.

The employment of epirubicin in our MECOP-B protocol did not compromise the efficacy of MACOP-B [12]; however, it confirmed its previously tested potential benefit in the management of NHL [35]. However, its presumed less bone marrow and GIT toxicity, compared to that of doxorubicin reported in the MACOP-B trial, was not evident in our study. The considerable high incidence of mild and moderate mucositis encountered among patients receiving the MECOP-B and MACOP-B protocols has been one of the most frequently encountered side-effects. Giving co-trimoxazole on a daily basis for 12 weeks probably affected the renal clearance of methotrexate and increased its toxicity [36].

CONCLUSION

We conclude that systemic combination chemotherapy is as effective in the management of early stage disease as it is for advanced stage. This approach of treating early stage disease with systemic chemotherapy is also safe and not associated with significant morbidity or life threatening complications. Longer follow-up is needed to confirm its favorable effect on survival compared to conventional radiation therapy. Analysis of various variables has identified certain risk factors that adversely affected response and survival. The identified risk variables could be different based on the trial methodology and the study population. However, knowing these factors would assist in the recognition of several subgroups of patients with different risk probabilities. In developing countries like Saudi Arabia, therapy should be individualized so that low-risk patients could be treated effectively in various oncology satellites using less intense regimens such as BACOP. More aggressive chemotherapy combination should only be offered to high-risk groups at more specialized centers, well-equipped with radiotherapy facilities, where radiation therapy could be also combined with chemotherapy if indicated.

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