Eur J Cancer Clin Oncol, Vol. 24, No. 10, pp. 1617–1622, 1988.
Printed in Great Britain

0277-5379/88$3.00 + 0.00

Prognostic Factors in Stage I and II High and Intermediate Grade Non-Hodgkin's Lymphoma

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Abstract—*Between* 1975 *and* 1986, *the Manchester Lymphoma Group treated* 127 *patients with localized (Stages* I/II) *high and intermediate grade non-Hodgkin's lymphoma (NHL) on one of three protocols of combined involved field radiotherapy and chemotherapy. The study included patients with widespread bulky abdominal disease providing there was no apparent spread outside the abdomen and the liver was not involved with metastatic disease. The median duration of follow-up was* 70 *months. The complete response rate was* 86% *and the overall* 5*-year survival was* 70%. *The* 5*-year relapse-free survival of the complete responders was* 80%. *Cox model multivariate analysis showed that bulk disease* (>5 cm), *low serum albumin and gut involvement were the pretreatment factors associated with shorter survival. When remission status was included in the model the attainment of a complete response was the major determinant of long-term survival but bulk disease and gut involvement were still significant adverse predictors for survival. These factors need to be assessed when analysing results of therapy in NHL and in the design of future treatment strategies.*

INTRODUCTION

Localized (Stage I and II) high grade non-Hodgkin's lymphoma (NHL) is relatively rare comprising only 10–20% of all presentations [1]. Pathologic staging is not commonly performed in NHL and for clinically staged I and II patients the 5-year relapse-free survival following localized irradiation (RT) alone is less than 50% [2–4]. Early systemic chemotherapy (CT) either as initial therapy [5, 6] or as adjuvant treatment after RT [7–10] has improved the relapse-free survival.

Several factors such as age [11, 12], stage (I vs. II) [13], tumour bulk [14] and primary site [15, 16] have been shown to be of prognostic importance in patients treated with RT alone. The aims of this study were, firstly, to review the results of combined CT and RT in a large group of patients with localized NHL treated in a single centre using defined protocols and, secondly, to determine the most important prognostic factors in this group.

MATERIALS AND METHODS

In this retrospective analysis 127 patients with previously untreated, localized, high and intermediate grade NHL were studied. These patients were treated by members of the Manchester Lymphoma Group between 1975 and 1986. All patients had a biopsy-proven diagnosis of high or intermediate grade NHL. The Kiel classification was known in 119 patients (Table 1), all of whose histological specimens were reviewed by one of the authors (M.H.) prior to this analysis. The other eight patients were included as they had definite, previously reviewed high grade histology according to their original Rappaport classification at our institution although pathologic specimens were not available for re-analysis. The Rappaport classification is given for only 98 patients (Table 3) as we no longer routinely use this classification.

All patients were staged according to the Ann Arbor classification [17]. Clinical staging included a full history and physical examination, full blood count and ESR, biochemical profile including liver function tests and serum lactate dehydrogenase (LDH), unilateral bone marrow aspirate with trephine biopsy, chest X-ray and an abdominopelvic CT scan. Patients who remained clinical stage (CS) IA, IB or IIB (all ± E) after staging were included in the study except those with CS IAE disease of Waldeyer's ring who all received RT alone. Patients with pathological stages (PS) I and II primary gastro-intestinal tract (GIT) NHL were also

Accepted 26 May 1988.
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Table 1. Histological classification (Kiel)

Intermediate grade	
Follicular* and diffuse CC/CB	5
Centrocytic (CC)	7
Diffuse CC/CB†	9
High grade	
Centroblastic	25
Lymphoblastic (LB)	13
Immunoblastic (IB)	22
Unclassified (U)	25
True histiocytic	9
Other	4
Total	119

*Originally classified as diffuse in previous review.
†CC/CB—centrocytic/centroblastic.

Table 2. Patient characteristics

Total No.		127
Age (years)	median	51
	range	18–72
Sex	male	65
	female	62
Primary site	nodal	98
	extranodal	29
		(GIT 26)
Stage	I	40
	II	87
Karnofsky performance	≥90	66
	80	40
	70	14
	≤60	7
Bulk disease	>5cm	55
	>7cm	30

included. Bulk disease was defined as measuring greater than 5 cm in greatest diameter at commencement of therapy. In accordance with the Ann Arbor system patients with bulk abdominal disease (either primary GIT or nodal) were included in this analysis. Patient characteristics are outlined in Table 2. On completion of therapy, a full restaging evaluation was performed including repeat of all previously abnormal investigations.

Sixty-five patients (regimen A) received initial involved field RT (30 Gy fractionated over 3 weeks) followed by a randomization to one of two types of adjuvant chemotherapy as previously described by Wagstaff *et al.* [10]. Thirty-three patients (regimen B) received initial chemotherapy with vincristine, adriamycin and prednisolone (VAP) over 6 weeks followed by localized RT and then oral maintenance chemotherapy with cyclophosphamide, 6-mercaptopurine and methotrexate as described by Steward *et al.* [18]. Twenty-nine patients (regimen C) have been treated on our latest protocol with initial VAP, localized RT and then alternating cycles of adriamycin/cyclophosphamide and ifosfamide/etoposide.

Response status was assessed by standard World Health Organization (WHO) criteria [19]. Survival was calculated from the date of starting treatment. Length of survival was analysed in two ways, firstly by taking the event of interest as a death from any

Table 3. Univariate survival analysis

Variable		No.	*P* value
Age	<50	58	0.54
	≥50	69	
Sex	male	65	0.25
	female	62	
Stage	I	40	0.10
	II	87	
Karnofsky performance	≥90	66	0.08
	<90	61	
Bulk (>5cm)	present	55	0.002
	absent	72	
Bulk (>7cm)	present	30	0.002
	absent	97	
Bulk/abdominal	present	18	0.003
	bulk (not abdominal)	37	
	no bulk	72	
No. of involved sites	1	41	0.87
	2	55	
	3+	31	
B symptoms	present	24	0.009
	absent	103	

Table 3. *Contd.*

Variable		No.	*P* value
GIT disease	present	26	0.037
	absent	101	
Extranodal disease	present	29	0.028
	absent	98	
Treatment regimen	A	65	0.73
	B	33	
	C	29	
Remission status	CR	109	<0.0001
	PR	10	
	NR	8	
Histology—Kiel	CC/CB	14	0.07
	CC	7	
	CB	25	
	LB	13	
	IB	22	
	U	25	
	other	13	
Histology—Rappaport	DPDL	27	0.53
	DM	8	
	DH	54	
	other	9	
Histology (grade)	high	97	0.99
	intermediate	22	
Haemoglobin (g/dl)	<12	19	0.04
	≥12	108	
Lymphocyte count ($\times 10^9$/l)	<1.0	25	0.22
	1.0–1.9	54	
	≥2.0	47	
ESR (mm/h)	<20	59	0.0004
	20–39	29	
	≥40	15	
Albumin (g/l)	<40	41	0.04
	≥40	85	
Sodium (mmol/l)	<140	47	0.17
	≥140	53	
Bilirubin (μmol/l)	<6	38	0.21
	≥6	87	
Alkaline phosphatase (iu/l)	<100	97	0.21
	≥100	29	
Aspartate transaminase (iu/l)	<40	112	0.85
	≥40	11	
Gamma GT (iu/l)	<25	52	0.19
	≥25	39	
LDH (iu/l)	<500	74	0.19
	≥500	10	

cause and secondly, as a death from progressive NHL. Relapse-free survival was measured from the time of confirmed establishment of complete remission. The influence of 26 potential prognostic variables on survival (Table 3) was assessed by plotting Kaplan–Meier survival curves [20] which were compared using the log-rank test [21]. The simultaneous effects of the variables on prognosis were explored using Cox's proportional hazards model [22]. The data from continuous variables were examined to ensure that there was a linear relationship between the absolute value of the variable and prognosis. Continuous variables relating to biochemical measurements were transformed by taking logarithms; missing covariate data were handled by the introduction of a dummy variable to indicate the presence or absence of information on a particular variable. Informed consent was

obtained for each protocol according to the institutional ethics committee.

RESULTS

The median duration of follow-up was 70 months. Overall 109 patients (86%) achieved complete remission (CR) and 10 patients (8%) a partial response (PR). Eight patients (6%) did not respond to therapy (NR). Response rates did not vary significantly between treatment regimens ($P = 0.10$). The overall 2- and 5-year survivals were 84% and 70% respectively (Fig. 1). Survival corrected for intercurrent deaths was 86% at 2 years and 76% at 5 years. The 5-year relapse-free survival was 80% (Fig. 1).

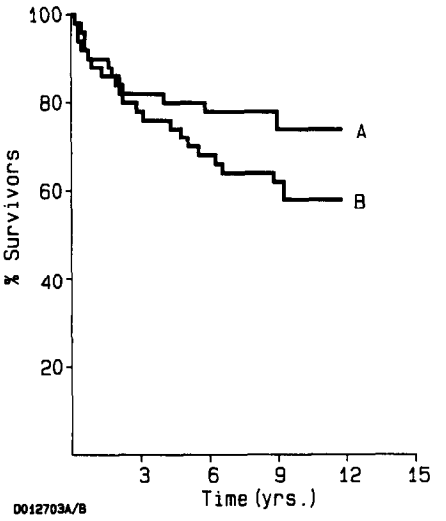

Fig. 1. Relapse-free survival (A) n = 109 and overall survival (B) n = 127 of patient group.

Eighty-three patients remain alive and in CR and seven are alive with disease. There have been 37 deaths, 29 from NHL and eight intercurrent deaths. All non-responders have died from progressive NHL with a median survival of 7 months. Four partial responders have died from NHL and six remain alive with disease. Twenty-one (19%) of the complete responders have relapsed, 11 within 12 month and 15 within 2 years of initial treatment. Fourteen of the 18 patients not achieving CR had bulk disease, including nine with bulk abdominal disease.

Univariate analyses showed that pre-treatment variables associated with shorter survival were the presence of bulk disease, high ESR, B symptoms, extranodal or primary GIT involvement, low serum albumin and a low haemoglobin (Table 3). Cox model multivariate analysis showed that the only pre-treatment factors which proved independently predictive of poor survival were the presence of bulk disease, a low serum albumin and GIT involvement (Table 4). When the Cox analyses were repeated with subsequent response to treatment included, this became the major determinant of survival although GIT and bulk were still significant (Table 4). When the multivariate survival analysis was corrected for intercurrent deaths, bulk disease ($P = 0.0013$) and GIT involvement ($P = 0.0036$) were again the most significant adverse predictors of survival, apart from remission status.

To date no patient has developed secondary leukaemia, however there have been three non-haematological second malignancies. One patient developed an operable rectal carcinoma 5 years from initial diagosis and is alive with no evidence of recurrence; a second developed a parietal astrocytoma whilst on maintenance CT (regimen A) and died from this with no evidence of lymphoma at post-mortem; the third patient developed malignant melanoma 4 years after completion of therapy and died of metastatic melanoma.

DISCUSSION

Localized RT alone has been shown to be inadequate therapy for patients with clinical stage I and II high grade NHL [2–4]. Three prospective randomized trials [7–9] have shown superiority for combined RT and CT. The results in this study are also superior to those reported using RT alone and are comparable to other series using combination therapy, further supporting the role of systemic CT in this disease. In our series approximately half the patients received initial VAP chemotherapy followed by RT and in half the CT followed initial RT. There were no differences in response rates or survival between protocols and the optimal timing of systemic CT in localized NHL awaits appropriate controlled trials.

Factors related to the survival of patients from the start of treatments are important for the clinical

Table 4. Cox's multivariate survival analysis

Variable	*P* value	Favourable feature
Remission status	0.000004	CR
GIT involvement	0.022	Absent
Bulk disease (>5cm)	0.033	Absent
Excluding remission status		
Bulk disease (>5cm)	0.0023	Absent
Albumin	0.0024	High value
GIT involvement	0.021	Absent

management of individual patients and for stratification in clinical trials. Factors predictive for survival in advanced high grade NHL have been well documented [23–25]. Prognostic factors in localized high grade NHL have not been as well studied probably because of the relative rarity of this disease. In previous reports where prognostic features have been identified, patients have usually been treated with RT alone. Bitran *et al.* [26] found that relapse-free survival was related to the number of sites of involvement in 20 patients with PS I and II disease. The latter was not supported by the study of Kushlan *et al.* [14] which found tumour size to be the only significant prognostic factor. Cabanillas and Burke [27] have also identified tumour bulk as a poor prognostic factor. Other factors reported to be of prognostic significance include age [11, 12] and primary site of involvement [15, 16]. The purpose of this study was to identify the major prognostic determinants in a large group of patients with localized NHL treated 'optimally' with combination therapy.

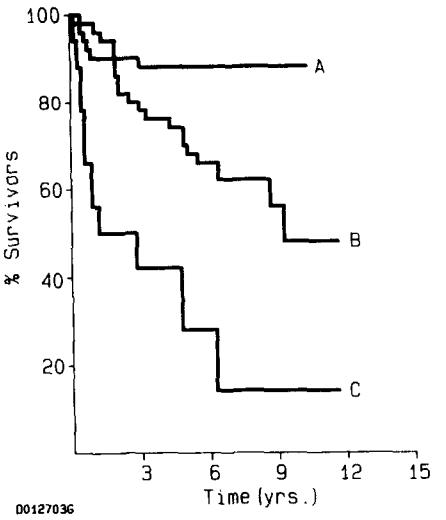

Fig. 2. Survival related to number of favourable features present. (A) Three favourable features (n = 47); *(B) two favourable features* (n = 61); *(C) less than two favourable features* (n = 18).

As for advanced high grade NHL the attainment of CR was the single most important predictor of long-term survival. However, when allowance was made for this, bulk disease and GIT involvement were still significant adverse factors. Bulk disease was also the major adverse prognostic feature ($P = 0.00047$) for relapse-free survival of the complete responders.

Remission status, although the single most important factor, is obviously not known at the commencement of therapy at which time bulk disease, serum albumin and GIT involvement were the major determinants of survival. One possible use of this model is to group the patients according to the number of favourable features (Fig. 2). This divides the patients into good, intermediate and poor risk groups with 88%, 71% and 29% 5-year survival rates respectively for patients with all three, two or less than two favourable features. For patients with bulk GIT lymphoma maximal surgical debulking should be performed prior to other therapy as previously recommended by our group [17, 28]. Our results also suggest that surgical debulking may be indicated for patients with bulk nodal disease. Subsequently alternate treatment strategies, possibly employing weekly systemic CT followed by RT to areas of previous bulk disease, need to be considered for these high risk patients.

Histological subtype was not a significant predictor of relapse-free or overall survival, nor was there a significant survival difference between high and intermediate grade tumours (Table 3). The latter supports the inclusion of intermediate grade NHL in this analysis. Other factors which proved not to be of significance included age, sex, clinical stage and number of involved sites. Most relapses occurred within the first 2 years although isolated relapses continued to be seen several years after initial therapy (Fig. 1), indicating that long-term follow-up of these patients is necessary.

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