High-grade Non-Hodgkin's Lymphoma Treated in Northern Norway

Treatment, Outcome, and Prognostic Factors

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Acta Oncologica Vol. 38, No. 1, pp. 117–124, 1999

In an unselected group of patients with high-grade non-Hodgkin's lymphoma (HG-NHL) treated at our institution during a 10-year period (1986–1995), we studied treatment outcome and influence of possible prognostic factors. 187 HG-NHL patients were analysed retrospectively with regard to personal, treatment and disease-specific characteristics. Median age was 65 years and the male : female ratio was 1.2 : 1. Over a median follow-up of 57 months the overall response rate was 87% (complete response 72%, partial response 15%). The 2- and 5-year cumulative disease-specific survival rates were 64 ± 4% (mean ± SEM) and 48 ± 5%, respectively. In a univariate analysis, the following variables were associated with prognosis in terms of survival: Patient age, clinical stage, performance status, bone-marrow infiltration, haemoglobin, erythrocyte sedimentation rate, lactate dehydrogenase (LDH), and serum albumin. In multivariate analyses, patient age, performance status, LDH, and haemoglobin came out as independent prognostic factors for survival.

Received 14 May 1998
Accepted 1 October 1998

During the last few decades, major advances have been achieved in the classification, staging, and treatment of non-Hodgkin's lymphoma (NHL). World-wide, a variety of histological classification systems have been applied. In Europe, the Kiel classification system (1) has been widely accepted, whereas in the US the Lukes and Collins classification (2) and the Working Formulation (3) are the most commonly applied systems. The various classification systems can lead to problems in interpreting and comparing results from different treatment centres. There is a significant difference concerning prognosis between the two major subgroups characterized morphologically as low grade (LG-NHL) and high-grade (HG-NHL) according to the Kiel classification (4–6).

The introduction of the first-generation anthracycline-based combination chemotherapy regimens in the late 1970s, e.g. CHOP, has been one of the major successes in the treatment of NHL. Twenty-five years ago few patients survived more than 2 years after diagnosis, whereas today 30–35% of the patients are cured (7–10). During the 1980s, emerging third-generation regimens (MACOP-B, mBACOD, Pro-MACE-CytaBOM), increasing the number of antineoplastic drugs and dose intensity, were reported to give higher complete remission (78–84%) and survival rates (55–65%) in non-randomized studies (11–13). A subsequent phase III study has, however, shown that the CHOP regimen gave similar remission and survival rates, but lower risk of treatment-related mortality when compared to the third-generation regimens (10). Thus, CHOP is still considered the golden standard in treatment of HG-NHL.

Most publications on treatment and prognosis in NHL are based on selected patient groups (9, 10, 14, 15); trials with strict inclusion criteria or selected treatment groups where patients above the age of 70 have been excluded. Approximately 50% of patients with NHL are over 65 years of age (16). Elderly patients with HG-NHL usually have concomitant diseases and reduced performance status compared with younger patients. Consequently, elderly patients usually receive suboptimal treatment, and thus have a poorer prognosis compared to their younger counterparts (17). The exclusion of NHL patients above the age of 70 will lead to a significant selection of any population of lymphoma patients.

All adult patients with HG-NHL in the northern region of Norway have been diagnosed and/or treated at the Department of Oncology, University Hospital of Tromsø since 1986. In a 10-year period from 1986 we have regis-

 ISSN 0284-186X

tered 187 patients with HG-NHL in our region. The present study is based on this unselected clinical material, in which we have evaluated the patient population and investigated treatment results and possible prognostic factors.

MATERIAL AND METHODS

Patients

A retrospective analysis was carried out on all patients diagnosed with and/or treated for HG-NHL in our department during the 10-year period from 1986 to 1995. This material included only patients above 15 years of age. All clinical records were collected for registration and analyses of data. On completion of data registration in November 1996, 187 patients with HG-NHL were registered, with a median follow-up of 57 months (range 11–130 months). Of these, 23 patients were excluded from the study owing to: (i) concomitant component of low-grade lymphoma (LG-NHL, n = 19); (ii) concomitant component of Hodgkin's lymphoma (n = 2); and (iii) uncompleted initial treatment (refusal because of side effects, n = 2). Thus, 164 patients were included in the study. Of these, seven patients had lymphoblastic lymphoma (n = 4) or Burkitt's lymphoma (n = 3).

Median age was 65 years (range 15–86 years). There were 89 (54%) males and 75 (46%) females, yielding a male : female ratio of 1.2 : 1. Further patient characteristics are presented in Table 1. The median size of the largest tumours was 5 cm (range 1–20 cm). At our institution the histologic classification as LG or HG lymphomas was carried out according to the original Kiel classification system (1). In our material, subgroup classification could not be performed in 40 (24%) patients. These patients were histologically diagnosed mainly during the first years of the study period. Revision of the histology has not been performed retrospectively. Subclassification according to B- and T-cell lymphoma was initiated during the early 1990s and is thus missing in 62 (38%) patients. Whereas staging was performed according to the Ann Arbor classification (18), affection of the Waldeyer's ring was categorized as extranodal manifestation. For patients where the clinical stage was not explicitly registered in the hospital records, staging was performed retrospectively based on data at the time of diagnosis. The criteria for systemic symptoms (B-symptoms) were: (i) fever > 38°C; (ii) profuse night sweat; and (iii) weight loss > 10% from baseline.

Diagnosis and treatment

All patients underwent a full physical examination, complete blood cell count, renal and liver function tests, erythrocyte sedimentation rate (ESR), albumin, and immune electrophoresis. Furthermore, a biopsy of the lesion was performed including a CT scan of the area of local manifestation. For staging procedures, routine radiological examinations with chest roentgenograms and CT scans of the abdomen and pelvis and a unilateral bone-marrow needle biopsy from the iliac crest were carried out. The histological diagnosis was confirmed by a pathologist with lymphoma classification experience.

All patients were uniformly treated according to mainly unaltered national guidelines during the period. Stage I patients were administered 6 courses of chemotherapy (CHOP = cyclophosphamide, adriamycin, vincristine and prednisolone/CNOP = cyclophosphamide, mitroxantrone, vincristine and prednisolone) at 3-week intervals, usually followed by radiotherapy (40–41.4 Gy) with 'involved field' technique (not GI (n = 9) and testis (n = 5) NHL). Stages II–IV patients received 8 courses of CHOP/CNOP

Table 1

Patient characteristics

		n	(%)
No. of patients		164	
Age (years)	< 60	71	43
	≥ 60	93	57
Sex	Men	89	54
	Women	75	46
Histology	Centroblastic	93	57
	Immunoblastic	13	8
	Large cell/anaplastic	11	7
	Lymphoblastic	4	2
	Burkitt's	3	2
	Unclassifiable	40	24
	Missing	0	
Stage	I	45	28
	II	38	23
	III	20	13
	IV	57	36
	Missing	4	
Systemic symptoms	A: Absent	108	66
	B: Present	54	34
	Missing	2	
ECOG PS[1]	0: Full activity	85	53
	1: Ambulatory	49	30
	2: Bedridden < 50%	12	7
	3: Bedridden ≥ 50%	12	7
	4: Completely bedridden	4	3
	Missing	2	
Largest tumour	≥ 5 cm	71	65
	< 5 cm	38	35
	Missing	55	
Bone marrow	Positive	21	13
	Negative	143	87
	Missing	0	
Extranodal lesion	Yes	89	55
	No	75	45
	Missing	0	

[1] WHO performance status according to the Eastern Cooperative Oncology Group.

or a 12-week treatment with MACOP-B. The latter combination regimen was used in a clinical phase III trial for a short period in the early 1990s (n = 10). Elderly patients who were medically unfit for IV combination chemotherapy were administered oral trophosphamide (n = 9, each $\geq$ 80 years). In stages II–IV patients with bulky disease, chemotherapy treatment was followed by radiotherapy (40–41.4 Gy) of the initial bulky tumour volume ('involved field'). In total, 51 patients received radiotherapy in the primary setting either due to stage I disease (n = 26) or 'bulky' tumour (n = 25). Patients with affection of the Waldeyer's ring or bone-marrow infiltration were administered 12 mg methotrexate (MTX) intrathecally (6 doses, n = 27). In the first part of the period patients with lymphoblastic or Burkitt's lymphoma received courses of high-dose MTX in the interval between the CHOP/CNOP courses. In the last part of the period these patients received induction and consolidation treatment similar to ALL treatment protocols.

If relapse occurred after completed treatment or progression during initial therapy, combination chemotherapy with MIME or ENAP or single agent therapy with oral Ixoten (trophosphamide) was used (n = 62). Third-line chemotherapy was administered to 26 patients, mainly as oral Ixoten (trophosphamide). In second remission, patients below the age of 60 (in the last part of the period) were candidates for ABMT/high-dose therapy with stem cell support (n = 11).

Response criteria and survival

All patients underwent repeated staging at evaluations during and after therapy. Evaluations included physical examination, biochemistry, radiologic examinations, and possible bone-marrow biopsy (when positive at diagnosis). During the entire study period, evaluations were carried out using CT scanning. Response criteria followed the WHO recommendations (19). Complete response (CR) is defined as disappearance of all lesions for a minimum of 4 weeks; partial response (PR) as $\geq$ 50% reduction in the sum of the products of the largest perpendicular diameters of all measurable tumour masses in the absence of new lesions, lasting at least 4 weeks; stable disease (SD) as $<$ 50% decrease or $\leq$ 25% increase in one or all measurable lesions; progressive disease (PD) as appearance of new lesions or a $>$ 25% increase of pre-existing lesions. Survival was calculated from the date of diagnosis to the end of follow-up or to death. Survival was presented as overall survival (crude) when all deaths were taken into account. When survival was defined as disease-specific, deaths from clearly documented causes unassociated with lymphoma were excluded (n = 16). Deaths from possible treatment-related causes, e.g. infections, postoperative complications, or from other diseases where the lymphoma contributed to the deterioration, were considered as death from lymphoma. Disease-free survival (DFS) was defined from the time of first CR to first relapse, last follow-up or death.

Statistics

Comparative statistics were mainly done by univariate analysis of variance (SPSS®, SPSS Inc., Chicago, IL, USA). Patients with missing data were excluded from analysis of that variable. Survival analysis was carried out using the Kaplan–Meyer method (20), and differences in survival rates were analysed using the logrank test (21). Multivariate analysis was performed by Cox's proportional hazards method (22) to identify subsets of independent prognostic factors for disease-specific survival. Variables reaching statistical significance ($p < 0.05$) at the univariate level were included in the multivariate analysis. The following eight variables were entered at step 1: age, clinical stage, performance status, bone-marrow infiltration, haemoglobin, lactate dehydrogenase (LDH), ESR, and albumin. Probability for stepwise entry and removal were set at 0.05 and 0.10, respectively.

RESULTS

Clinical characteristics

Patient characteristics are presented in Table 1. At diagnosis, 51% of patients had stage I/II disease, whereas 36% of patients were in stage IV. Bone-marrow infiltration was found in 13% of the patients, while 55% had extranodal manifestations. Systemic symptoms such as fever, night sweats, and weight loss were reported by 34% of the patients. Performance status was relatively good with 90% of the patients classified as ECOG 0-2 and only 10% as ECOG 3-4. With regard to morphology, centroblastic lymphoma dominated as it was demonstrated in 57% while subclassification was missing for 24% of the patients. The largest tumour size was $\geq$ 5 cm and $\geq$ 10 cm (bulky disease) in 65% and 24% of the patients, respectively. Biochemical characteristics for the patient are recorded in Table 2. Approximately 50% of the patients were anaemic at the time of diagnosis. The ESR was elevated in 52% of patients, while 53% of the patients had elevated LDH. The serum albumin levels were subnormal in 29% of patients.

Response rates

At completion of the lymphoma treatment, 72% (n = 118) had achieved CR, while 15% (n = 25) were in PR. The overall response rate (CR + PR) was 87%. Of patients achieving CR, 39% (n = 46) had relapsed, 20% of them (n = 9) progressing on second-line treatment. In univariate analyses the following clinical variables correlated negatively to treatment response: advanced stage $\geq$ 3 ($p < 0.03$), reduced performance status (ECOG $\geq$ 2, $p < 0.001$), anaemia ($p < 0.001$), elevated LDH ($p < 0.001$), low serum albumin ($p < 0.001$) and age above 60 years ($p < 0.02$).

Table 2

Biochemical parameters at time of diagnosis. Number and percentage of patients in each group

	Value	n	(%)
Haemoglobin (g/dl)			
Females	<11.5	29	41
	≥11.5	41	59
	Missing	5	
Males	<13.5	47	53
	≥13.5	41	47
	Missing	1	
Serum LDH[1] (U/l)	≤450	70	47
	>450	79	53
	Missing	15	
ESR[2] (mm/h)	≤20	70	48
	>20	75	52
	Missing	19	
Serum albumin (g/l)	<35	44	29
	≥35	106	71
	Missing	14	

[1] Lactate dehydrogenase.
[2] Erythrocyte sedimentation rate.

Survival

By November 1996 (median observation 57 months), 54% (89/164) of the patients had died; treatment-related complications were the cause of death in 3 patients (2%). Median overall survival was 3.8 years, and calculated 5- and 10-year overall survival rates were $44 \pm 4\%$ (mean $\pm$ SEM) and $25 \pm 7\%$, respectively (see Fig. 1). In 16 of the deceased patients (18%), the cause of death was not associated with their malignant lymphoma. Consequently, the disease-specific survival was somewhat higher than the crude survival. The 2-year disease-specific survival was $64 \pm 4\%$, whereas the 5- and 10-year disease-specific survival rates were $48 \pm 5\%$ and $38 \pm 6\%$, respectively. The median disease-specific survival was 4.8 years.

There were significant differences in disease-specific survival according to stage ($p < 0.002$, Fig. 2). While median disease-specific survival rates for stages II, stage III, and stage IV disease were 4.8 years, 2.7 years, and 1.7 years, respectively, the median survival for stage I patients was not reached during the observation period (69% 5-year survival). Moreover, survival analyses showed a significantly better outcome in patients below the age of 60 years

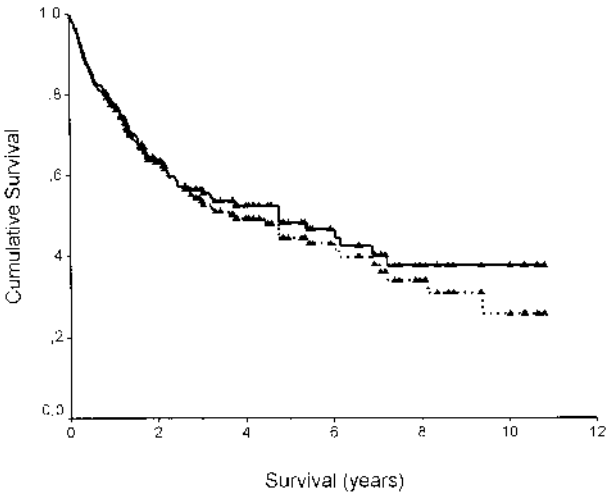

Fig. 1. Crude and disease-specific survival for patients with high-grade non-Hodgkin's lymphoma ($p = 0.53$). Crude survival is delineated by the dotted line ($n = 164$). Disease-specific survival was calculated after exclusion of 16 deaths, not associated with the malignant disease (solid line, $n = 148$). Censored cases are denoted by filled triangles.

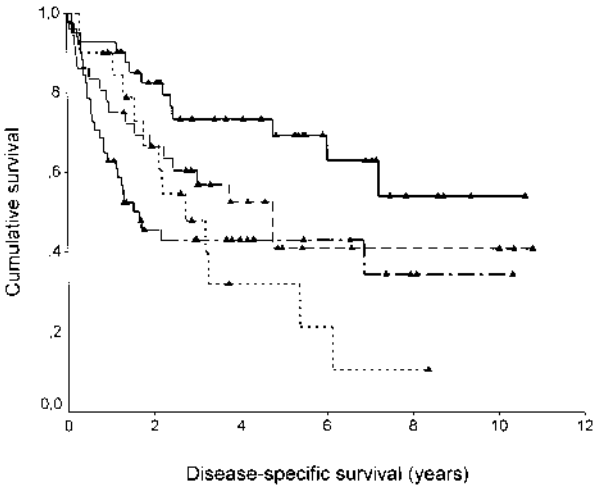

Fig. 2. Disease-specific survival for patients with high-grade non-Hodgkin's lymphoma according to clinical stage ($p < 0.02$). Stage I (solid line) $n = 41$; stage II (broken line) $n = 36$; stage III (dotted line) $n = 20$; stage IV (dot-dash-dot line) $n = 51$. Censored cases are denoted by filled triangles.

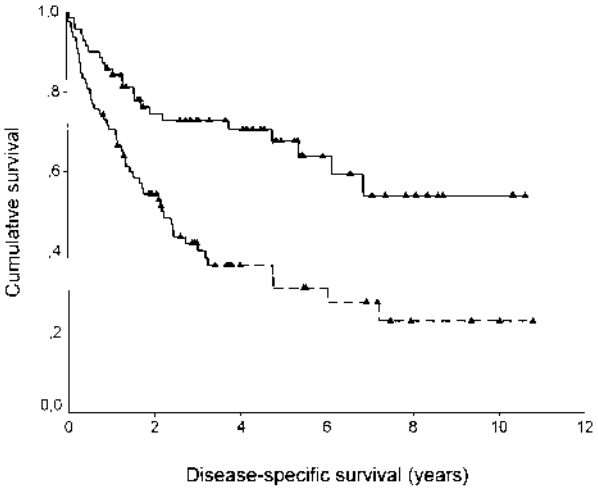

Fig. 3. Disease-specific survival for patients with high-grade non-Hodgkin's lymphomas according to age ($p < 0.0003$). Age < 60 years (solid line) $n = 70$; ≥ 60 years (broken line) $n = 78$. Censored cases are denoted by filled triangles.

when compared with those above 60 ($p < 0.0003$, Fig. 3). Chemotherapy dose intensity according to age is, however, unknown as possible dose reductions were not registered. In patients with a poor performance status (ECOG 2-4), disease-specific survival was significantly lower than in those with a better status (ECOG 0 and 1, $p < 0.0001$), with 2-year survival at 18% versus 60% and 80%, respectively. Furthermore, cause-specific survival was significantly lower in patients with elevated LDH ($p < 0.0002$) and ESR ($p < 0.006$) compared with those with values within the normal range. Large tumour burden (≥ 10 cm) tended towards a reduced survival ($p = 0.08$), but this did not reach a statistically significant level.

Survival data demonstrate the importance of achieving CR during treatment of HG-NHL. Median disease-specific survival in patients who did not achieve CR was 0.6 years, whereas median survival in those with CR was not reached during the observation period ($p < 0.0001$). In patients with CR, 5- and 10-year disease-specific survival rates were 65% and 53%, respectively. In comparison, only 12% and 0% of patients who did not reach CR were alive after 2.5 years and 5.5 years, respectively. The median DFS was 6.9 ± 4.3 years.

Prognostic factors

To estimate the prognostic value of the various pretreatment clinical and biochemical variables, these data were investigated by univariate and multivariate analyses. The results of the univariate analyses can be found in Table 3. Gender, systemic symptoms, extranodal manifestations, and bulky disease (largest tumour ≥ 10 cm) did not reach significant levels. However, bulky disease (tumour ≥ 10 cm) tended to influence prognosis although the number of patients was low.

In a multivariate analysis the following pretreatment factors were included: patient age, clinical stage, bone-marrow infiltration, performance status, haemoglobin, serum LDH, serum albumin, and ESR. After stepwise exclusion and inclusion, patient age, performance status, serum LDH and anaemia came out as independent prognostic factors for survival (Table 4). Clinical stage tended toward, but did not reach statistical significance ($p = 0.089$).

Table 3

Pretreatment variables predicting survival by univariate analyses. Deaths which were not associated with non-Hodgkin's lymphoma have been excluded (see Material and methods)

	n	5-year survival (%)	p-value
Age (years)			
<60	70	69	<0.0003
≥60	78	31	
Sex			
Male	81	45	0.758
Female	67	43	
Stage			
I, II	77	58	<0.002
III, IV	71	39	
Systemic symptoms			
A	97	49	0.129
B	49	37	
ECOG PS[1]			
0, 1,	122	48	<0.0001
2, 3, 4	24	19	
Extranodal			
No	68	49	0.460
Yes	80	38	
Bulky disease (≥10 cm)			
No	75	50	0.08
Yes	24	32	
Bone-marrow infiltration			
No	129	48	<0.01
Yes	18	0	
Anaemia			
No	64	57	<0.007
Yes	71	32	
Serum LDH[2] >450 U/l			
No	60	69	<0.0002
Yes	74	34	
ESR >20 mm/h			
No	64	63	<0.02
Yes	69	37	
Serum albumin <35 g/l			
No	94	51	<0.004
Yes	43	31	

[1] ECOG performance status according to the WHO.
[2] Lactate dehydrogenase.

DISCUSSION

The University Hospital of Tromsø covers the northern region of Norway (population 460000. To our knowledge, all adult patients with high-grade non-Hodgkin's disease diagnosed since 1986 have been referred to our department. The registered number of patients is also consistent with NHL national incidence rates published by the Cancer Registry of Norway (23). Consequently, our study should represent an unselected clinical material. This is also supported by a higher median age than in most clinical studies (10, 24, 25), and a higher proportion of patients with poor performance status (10% ECOG 3 and 4) compared with a recent meta-analysis (24). Our material is relatively homogeneous as only HG-NHL patients, classified histopathologically according to the Kiel classification (1), were included in this retrospective study. Furthermore, our national guidelines for treatment of NHL have remained principally unaltered during the time period studied.

The remission rates in our material are superior to the findings in a number of other clinical studies. While 72% of our patients achieved CR, this was found retrospectively in 53% of high-grade NHL patients in northern Sweden (26). In a meta-analysis of 2031 patients published by the International Non-Hodgkin's Lymphoma Prognostic Factor Project in 1993 (24), the CR rate was 53% although the median age was approximately 10 years lower than in our study. In a relatively small Spanish study where the median age was considerably lower than in our patient group, Llanos and co-workers (27) presented remission data similar to our study (CR 71%, PR 16%). Assessment of response rates is less reliable than survival data, as it depends on high-quality examinations and skilled professionals. However, it continues to be an important endpoint and prognostic factor in the treatment of malignant lymphoma.

For survival analysis, we chose to focus primarily on cause-specific instead of crude survival. Crude survival is more prone to being biased by different age distributions in patient populations. When using disease-specific survival, there will always be a judgement on whether or not a death has been caused by the lymphoma. In the present study, we considered death as being caused by lymphoma also when the cause of death was a complication of the treatment or the malignant disease itself. In four patients who were lost to follow-up, the cause of death could not be established and was consequently classified as associated with lymphoma. The achievement of CR is considered a prerequisite for long-term survival. Accordingly, the 5-year survival in patients attaining CR was 66% compared with 4% in patients which did not achieve CR. The overall and disease-specific survival in our material is similar to the findings in a British study presented by Leonard and co-workers (25), but the median age (50 years) was significantly lower in the British study. In addition, in a Canadian study (16) of 145 high-grade NHL patients with an age average similar to that of our patient group, the overall survival was significantly lower.

Clinical stage appeared to influence overall and disease-specific survival. In accordance with several other investigators (24, 26, 28), we found a significantly poorer survival rate in stage III/IV compared with that in stage I/II. The unexpected intersection of survival plots for stage III and stage IV may be explained by the lower number of patients in stage III ($n = 10$ after three years). Survival rates in stage I patients are consistent with a recent Swedish study on high-grade NHL stage I patients diagnosed between 1985 and 1990 (29).

NHL constitutes a heterogeneous mixture of lymphatic disorders. In addition to separating the entity into LG- and HG-NHL, it is important to know the relevant prognostic factors within each of these groups. Several investigators acknowledge the importance of prognostic pretreatment indicators in high-grade NHL (26, 29–32). An accurate pretreatment prognostic assessment of patients could improve the physician's selection of appropriate anticancer treatment, e.g. distinguishing between patients requiring intensive treatment such as high-dose therapy with stem cell support in first remission and those who should be treated with standard regimens. In this context, an International Prognostic Index for patients with high-grade NHL has been introduced (24, 32).

The prognostic factors identified by univariate analyses in our material have been identified in previous studies (26, 31). Of these prognostic factors, clinical stage, bone marrow infiltration, ESR, and serum albumin were not identified as independent prognostic factors in multivariate analyses, probably because these factors correlate with other pretreatment variables. Studies have shown that, for example, low serum albumin correlates with the presence of systemic symptoms, weight loss, or poor performance status (31). In previous studies, clinical stage has been shown to have important prognostic implications (18) or no significance at all (33). In Cox regression analyses, clinical stage did not qualify as an independent prognostic variable in our study. The finding of age, performance status, LDH and haemoglobin as independent prognostic factors for survival of HG-NHL is principally in accordance with previous investigations (10, 24–26, 29, 32, 34).

The prognostic impact of age has been frequently focused for different malignant diseases. Impaired survival in elderly patients with HG-NHL has been demonstrated in several studies (28, 32, 35–37). In some studies, however, it

Table 4

Prognostic pretreatment variables. Results of Cox's multivariate analysis

Covariate	Relative risk	95% CI[1]		
		Lower	Upper	p-value
Age (≥ 60 vs. <60)	3.3676	2.0044	5.6577	<0.0001
Performance status (2–4 vs. 0–1)	2.8071	1.6231	4.8549	<0.0006
LDH[2] (>450 vs. ≤ 450)	1.9318	1.2200	3.0587	<0.005
Haemoglobin (<11.0 vs. ≥ 11.0)	1.7619	1.0766	2.8835	<0.03

[1] Confidence interval.
[2] Lactate dehydrogenase.

has been demonstrated that the survival differences between elderly patients and patients under 60 years of age can be largely eliminated by censoring patients that died of causes other than lymphoma or of treatment-related toxicity (38, 39). In our study though, age was the principal prognostic factor for disease-specific survival, i.e. when other causes of death had been excluded. On the other hand, higher prevalences of concomitant diseases and lower performance status in elderly patients could result in suboptimal cancer treatment in the elderly and thus represent an external factor with a possible detrimental effect on survival in this patient group. Consistently, nine elderly patients in our study received monotherapy with oral trophosphamide as first-line therapy instead of more intensive treatment with IV combination chemotherapy. Each of these patients was over 80 years of age. Whether or not administered chemotherapy doses and possible dose reductions had any impact on the impaired survival in the elderly patients cannot be answered in this study, since these variables were not registered.

Consistent with our data, serum LDH has previously been shown to be one of the strongest predictors of prognosis along with age (31, 40). Elevated LDH levels in lymphoma have been considered a manifestation of high growth rate or bulky disease (16). In recognition of LDH as an independent prognostic factor in NHL, Swan and co-workers (41) incorporated LDH into the staging system used at the M. D. Anderson Hospital as early as in the mid 1980s, and it has later been included in the International Index (24).

Finally, clinical materials with a low grade of selection are the optimal basis for evaluating treatment outcome and the value of pretreatment prognostic factors in high-grade NHL. Our remission and survival rates are maintained at a high level when compared with other clinical materials, unbiased with regard to major prognostic factors as, for example, age. To individualize anticancer therapy according to aggressiveness and risk of relapse of the lymphoma, evaluation of pretreatment prognostic factors could be of great value. In our group of HG-NHL patients, age, performance status, haemoglobin levels, and LDH levels were found to have independent prognostic value.

ACKNOWLEDGEMENTS

The assistance by our data manager Ann G. Dahl at the Clinical Research Office is greatly appreciated. Furthermore, we thank the Norwegian Cancer Society for the financial support.

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