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Incidence and risk factors of central nervous system recurrence in aggressive lymphoma—a survey of 1693 patients treated in protocols of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL)

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Background: Central nervous system (CNS) relapse is a devastating and usually fatal complication of aggressive lymphoma. The extent of the disease, the proliferation rate and the sites of extranodal involvement have been discussed as risk factors. We analyzed the patients treated on protocols of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) between 1990 and 2000, evaluated the rate and prognostic factors for CNS recurrence and developed a risk model trying to identify subsets of patients suitable for future prophylactic strategies.
Patients and methods: From 1993 to 2000, 1399 patients [≤60 years with normal lactate dehydrogenase (LDH) and >60 years irrespective of LDH] were randomized to receive six cycles of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-21, CHOP-14 or six cycles of CHOP + etoposide (CHOEP)-21, CHOEP-14 in a 2×2 factorial study design in the NHL-B1/B2 studies. From 1990 to 1997, 312 patients ≤60 years with an elevated LDH were randomized to five cycles CHOEP + involved field (IF) radiotherapy or three cycles CHOEP followed by high-dose BCNU, etoposide, cytarabine and melphalan (BEAM) and autologous stem-cell transplantation (NHL-A study).
Results: A total number of 1711 patients were initially eligible for this study, of whom 18 patients had to be excluded due to primary CNS involvement. In the remaining 1693 assessable patients, 37 cases of relapse or progression to the CNS (2.2%) were observed. The protocol asked for an intrathecal (i.th.) prophylaxis in patients with lymphoblastic lymphoma only ($n = 17$), but overall 71 patients (71 of 1693 = 4.2%) received prophylaxis by decision of the treating physicians. Multivariate Cox regression analysis identified increased LDH ($P < 0.001$) and involvement of more than one extranodal site ($P = 0.002$) as independent predictors of CNS recurrence in the NHL-B1/B2 study population. Treatment with etoposide also evolved as a prognostic factor because the risk of CNS failure was significantly reduced after CHOEP ($P = 0.017$). Elderly patients presenting with both an elevated LDH and lymphoma involvement in liver, bladder or adrenals had an up to 15-fold risk of spread of the disease to the CNS.
Conclusion: The incidence of CNS relapse in 1693 patients treated for aggressive lymphomas on DSHNHL protocols from 1990 to 2000 was low (2.2%), although CNS prophylaxis was administered to <5% of patients. Thus, a general prophylaxis for all patients is not warranted, the less so since the effectiveness of i.th. prophylaxis itself is judged controversially. Increased LDH and involvement of more than one extranodal site were confirmed as independent risk factors. A cumulative 20% incidence of CNS disease in certain prognostic subgroups of elderly patients may render these candidates for i.th. prophylaxis; however, this approach would imply a potential overtreatment of ~80% of these patients deemed at high risk.
Key words: aggressive lymphoma, CNS recurrence, prognostic factors, prophylaxis

introduction

Central nervous system (CNS) relapse is a serious and usually fatal complication of aggressive lymphoma [1–3]. It is widely accepted that due to the low probability of CNS relapse prophylaxis for all patients cannot be recommended. Instead, the identification of patient subgroups at increased risk has been reported and various risk factors for CNS recurrence have been described [4, 5]. However, up to date there is no general agreement either on risk groups or on the optimal prophylaxis. The majority of the studies indicate that CNS relapse is related to parameters reflecting the extent and proliferation of the disease and also is associated with specific

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sites such as bone marrow, testicles or paranasal sinus [4, 6, 7]. In order to identify risk factors for patients with aggressive lymphoma, we analyzed 1693 patients treated on protocols of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) from 1990 until 2000. The main objective was to determine risk models which might be used to establish guidelines for future prophylactic strategies.

patients and methods

patients

Between 1990 and 2000, adult patients (aged ≥18 years) with newly diagnosed aggressive lymphoma according to the Revised European-American Lymphoma Classification [8] (translated into the World Health Organization classification [9]) were enrolled in the NHL-A or NHL-B1/B2 studies of DSHNHL [10–12].

For the NHL-A protocol, patients aged 18–60 years, with stage II–IV disease according to the Ann Arbor classification of malignant lymphomas and serum lactate dehydrogenase (LDH) levels above the normal value were eligible [10]. The NHL-B1 study enrolled young patients (aged ≤60 years) with a normal LDH. Elderly patients >60 years with aggressive lymphoma (any LDH) were recruited into the NHL-B2 protocol. For all patients, initial staging work-up included clinical examination, laboratory tests, chest radiograph, abdominal sonography, computed tomography of thorax and abdomen and a bone marrow biopsy [11, 12]. Histologic diagnosis of aggressive lymphoma had to be confirmed by an expert panel of hematopathologists.

treatment protocols

In the NHL-A protocol, patients were randomized to receive either five cycles of CHOEP (arm A) or three cycles of CHOEP followed by high-dose therapy (HDT) BEAM and autologous stem-cell transplantation (arm B). The CHOEP protocol consisted of cyclophosphamide (750 mg/m^2 on day 1), doxorubicin (50 mg/m^2 on day 1), vincristine (2 mg on day 1), etoposide (100 mg/m^2 on days 1–3) and prednisone (100 mg orally on days 1–5). Treatment was repeated on day 22. In arm B, treatment was intensified with HDT comprising carmustine (300 mg/m^2 on day −5), etoposide (100 mg/m^2 on days −5 to −2 bd), cytarabine (200 mg/m^2 on days −5 to −2 bd) and melphalan (140 mg/m^2 on day −5) (BEAM protocol) followed by transplantation of hematopoietic stem cells. Patients were restaged after completion of chemotherapy. In both treatment arms, in case of at least partial remission, patients were to receive involved-field radiotherapy.

The NHL-B1 and -B2 studies investigated whether the reduction of treatment intervals from 3 to 2 weeks [combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-14], the addition of etoposide to CHOP (CHOEP-21 [13]) or a combination of both (CHOEP-14) improved outcome after chemotherapy [11, 12]. The CHOP regimen [14, 15] consisted of cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2) and vincristine (2 mg) i.v. (all on day 1) and prednisone (100 mg orally) days 1–5. CHOEP was identical to CHOP with etoposide (100 mg/m^2 i.v.) added on days 1–3. Treatment was repeated for a total of six cycles every 3 weeks (CHO(E)P-21) or every 2 weeks (CHO(E)P-14). Granulocyte colony-stimulating factor (filgrastim) was given from day 4 to 13 to accelerate hematopoietic recovery in the two-weekly schedule.

According to the protocol, consolidating radiotherapy on initial bulky disease was obligatory and also recommended for extranodal disease localizations.

In both the NHL-A and -B1/B2 trials, CNS prophylaxis was recommended only for patients with lymphoblastic lymphoma and consisted of 15 mg methotrexate given intrathecally on days 1 and 5 of the first two chemotherapy cycles. In addition, prophylactic radiation of the CNS with 25.2 Gy was recommended for these patients after completion of the systemic chemotherapy.

diagnosis of CNS relapse/progression

For this analysis, both patients with CNS recurrence after having achieved systemic CR/CRu and patients with spread of disease to the CNS during primary therapy were included.

A lumbar puncture and cerebral imaging were carried out whenever CNS involvement was clinically suspected. The diagnosis was on the basis of the detection of lymphoma cells in the spinal fluid or on the combination of typical symptoms and radiologic findings and in a few cases on additional brain biopsies.

statistical analysis

The primary end point was time to CNS recurrence and was defined as time from the beginning of therapy to disease progression with CNS involvement, treatment failure with CNS involvement at the end of therapy or CNS relapse after complete remission (CR)/complete remission with uncertainty due to residual mass (CRu).

The secondary end point was survival after CNS recurrence and was defined as time from the CNS recurrence until death from any cause.

The time to CNS recurrence and survival after CNS recurrence were estimated according to Kaplan and Meier [16]. The estimators at 3 and 6 years are given with 95% confidence intervals (CIs).

To identify prognostic factors for CNS recurrence, we used the proportional hazard model. Separate models were formulated for the following three groups: NHL-A, NHL-B1/B2 and NHL-B2 population. We did not use automatic selection procedures but proceeded in a stepwise approach for including single factors as suggested by Collet [17]. We constructed one multivariate model for each population following standard procedures of variable selection. The following clinically relevant predictors were examined: Eastern Cooperative Oncology Group (ECOG) performance status (PS), increased LDH, more than one extranodal site, stage, age, sex, bone marrow involvement, pathology and B symptoms. We arrived at a model with LDH and more than one extranodal involvement being significant. To select the extranodal sites, we adjusted the P values from univariate analysis according to the method of Bonferroni ($P < 0.002$).

To investigate which localizations contributed mostly to an increased risk in elderly patients, we replaced the variable of 'more than any extranodal involvement' by the variable 'liver or bladder or adrenal' involvement jointly as these three were significant in univariate Bonferroni-adjusted tests.

The strength of the prognostic factors was estimated by calculating relative risks (RRs) and the corresponding 95% CIs. All P values <0.05 were considered to be significant.

The patient characteristics were compared by chi-square tests and, if required, by Fisher's exact tests. All calculations were made in SPSS/PC+ V 10.0.

results

patient characteristics and incidence of CNS recurrence

A total number of 1711 patients (NHL-A $n = 312$; NHL-B1/B2 $n = 1399$) were eligible for the study protocols. Of these, 18 patients (NHL-A $n = 5$; NHL-B1/B2 $n = 13$) had primary CNS involvement at diagnosis and were excluded from this analysis. Patient- and disease-related characteristics of the 1693 assessable patients are listed in Table 1. More than half of the patients were men and 40% of all patients were older than 60 years. Most of the lymphomas were of B-cell origin (∼90%) with about two-thirds being classified as diffuse

Table 1. Clinical characteristics in 1693 patients with aggressive lymphoma

Characteristics	Patients with CNS relapse	Patients without CNS relapse	Total	*P* value
Age (years)				
>60	19 (51%)	662 (40%)	681 (40%)	0.163
Sex				
Male	22 (59%)	933 (56%)	955 (56%)	0.705
Female	15 (41%)	723 (44%)	738 (44%)	
Histology[a]				
B cell	33 (97%)	1212 (90%)	1245 (90%)	0.245
T cell	1 (3%)	136 (10%)	137 (10%)	
Histology[a]				
DLCL	19 (58%)	886 (73%)	905 (73%)	0.048
Other B cell	14 (42%)	326 (27%)	340 (27%)	
Histology[a]				
DLCL	19 (90%)	886 (97%)	905 (96%)	0.174
Burkitt	2 (10%)	32 (3%)	34 (4%)	
B symptoms[b]				
Yes	14 (38%)	549 (33%)	563 (33%)	0.566
LDH				
Elevated	19 (51%)	598 (36%)	617 (36%)	0.057
ECOG[b]				
>1	9 (24%)	249 (15%)	258 (15%)	0.123
Stage				
III/IV	20 (54%)	737 (45%)	757 (45%)	0.248
Extranodal[c]				
>1 site	15 (44%)	253 (19%)	268 (19%)	<0.001
Bone marrow involved[c]				
Yes	3 (9%)	113 (8%)	116 (8%)	0.759
IPI[c]				
0, 1	12 (35%)	825 (61%)	837 (60%)	0.010
2	8 (24%)	239 (18%)	247 (18%)	
3	5 (15%)	161 (12%)	166 (12%)	
4, 5	9 (26%)	127 (9%)	136 (10%)	
IPI >60 years[d]				
0, 1	1 (5%)	200 (30%)	201 (30%)	0.011
2	5 (26%)	181 (27%)	186 (27%)	
3	4 (21%)	154 (23%)	158 (23%)	
4, 5	9 (47%)	127 (19%)	136 (20%)	
Age-adjusted IPI ≤60[e] (LDH, ECOG and stage)				
0	9 (50%)	464 (47%)	473 (47%)	0.523
1	6 (33%)	287 (29%)	293 (29%)	
2	1 (6%)	167 (17%)	168 (17%)	
3	2 (11%)	69 (7%)	71 (7%)	

[a]1382 NHL-B1/B2 patients.
[b]Nine, respectively, seven patients in NHL-A without data on B symptoms, respectively, ECOG status.
[c]1386 NHL-B1/B2 patients.
[d]681 NHL-B2 patients.
[e]1005 NHL-A and -B1 patients; no complete International Prognostic Index (IPI) in seven patients in NHL-A.
CNS, central nervous system; DLCL, diffuse large cell lymphoma; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

large cell lymphomas (DLCLs). A complete overview of the histologic subtypes being enrolled into the protocols is given in Table 2.

In the NHL-B1/B2 study, failure to the CNS occurred in 34 of 1386 patients (2.5%) and in NHL-A in three of 307 eligible patients (1.0%). Thus, the overall incidence of CNS failure was 2.2% (37 of 1693 patients).

In 22 of these 37 patients, relapse to the CNS occurred after a complete remission (CR/CRu) had been achieved, the other 15 patients developed progression to the CNS during primary chemotherapy. The risk factors of the International Prognostic Index (IPI) were balanced between the two groups except for more advanced diseases in the 15 patients with primary progression to the CNS (73% stage III/IV versus 41% in 22 patients with CNS relapses; $P = 0.052$). In 11 of the 22 patients relapsing after initial CR/CRu the CNS was the only site of relapse. Of the 15 progressive patients, only four had exclusive CNS involvement, whereas in the remaining 11 patients CNS failure was part of systemic progression. A univariate analysis in all patients with CNS involvement showed that 'CNS relapse

Table 2. Diagnosis of patients after histopathologic review

	%
NHL-B1/B2	
B cell	89.8
Diffuse large	65.2
Centroblastic	49.0
Immunoblastic	8.2
Anaplastic	2.0
T-cell rich	1.7
Not otherwise specified (NOS)	4.3
Mediastinal B cell	1.8
Follicular grade 3b	7.6
Burkitt lymphoma	2.5
Lymphoblastic	0.1
Not otherwise specified	7.3
Unspecified for technical reasons[a]	5.3
T cell	9.6
Anaplastic large cell	6.6
Lymphoblastic	0.2
Peripheral T, unspecified	2.1
Angioimmunoblastic	0.2
Extranodal NK/T, nasal type	0.4
Unspecified for technical reasons[a]	0.1
Lymphoblastic, NOS	0.6
NHL-A	
Diffuse large cell	59.5
Centroblastic	50.5
Immunoblastic	9.0
Mediastinal B cell	12.5
Lymphoblastic	4.0
Anaplastic large cell	9.5
Burkitt	4.0
T cell	3.5
Other	7.0

[a]Diagnosis of aggressive B-cell lymphoma was confirmed on pathology review; however, due to quality or quantity of the biopsy material, a further subclassification was not possible.

alone' versus 'CNS as part of systemic relapse' had no significant influence on the time to CNS recurrence.

The median time between initial diagnosis and CNS progression was 4.7 months (range: 1.3–12.6); it was 17.8 months for those patients relapsing after CR/CRu (range: 6.9–85.2). Symptoms leading to the diagnosis of CNS recurrence were predominantly neurologic deficits (paresthesia, pareses, ataxia) or changes in mental status (i.e. confusion, lethargy) and in fewer cases headaches and visual impairment. Radiologic imaging showed parenchymal CNS involvement in 21 cases; a positive lumbar puncture indicating meningeosis was found in eight cases. Four patients had both leptomeningeal and brain involvement. In the remaining four patients, this diagnostic information was not available. About 80% of the relapsed patients received intrathecal (i.th.) and radiation therapy either alone or in combination. Systemic treatment with chemotherapeutic agents crossing the blood-brain barrier was done in 10 patients.

Age, gender, histology (B- versus T-cell phenotype), the presence of B symptoms, the PS and the stage of the disease were balanced between patients with and without CNS relapse. In contrast, an elevated LDH was detected in only 36% of all patients, but in 51% of the patients with CNS relapse and involvement of more than one extranodal site was observed in 19% of all, but in 44% of the patients with a subsequent CNS involvement (Table 1). Moreover, there was a slightly higher proportion of 'other B-cell lymphoma' versus DLCL in patients with CNS relapse when compared with all other patients ($P = 0.048$); however, this difference was not observed in a separate evaluation of DLCL versus 'Burkitt-lymphoma' (Table 1).

Of the patients, 41% with CNS failure had three to five risk factors of the IPI (intermediate-high/high-risk group), whereas in patients without CNS involvement the corresponding risk group comprised 21% of all patients ($P = 0.010$, Table 1). In elderly patients (>60 years), 47% of the patients with CNS involvement initially belonged to the high-risk group, whereas in the group of patients without later CNS affection only 19% scored high risk ($P = 0.011$). In contrast, the risk groups according to the age-adjusted IPI for the younger patients (≤60 years) showed a similar partition for patients with and without CNS recurrence.

Three of the 17 patients with lymphoblastic lymphoma received i.th. chemoprophylaxis with methotrexate at least during one cycle of the initial chemotherapy. Further 68 patients were given i.th. prophylaxis by decision of the responsible physician. These patients (total 71 of 1693 = 4.2%) had a more advanced disease (57.7% stage III/IV in the prophylaxis group versus 43.8% stage III/IV in those patients without prophylaxis, $P = 0.021$) and a trend to frequent involvement of more than one extranodal site (in NHL-B 30% versus 18.9%, $P = 0.051$). The only extranodal site which was more frequently involved by lymphoma in the prophylaxis patients than in patients without prophylaxis in NHL-B was the nasal cavity (6% versus 1.2%, $P = 0.029$), whereas involvement of bone marrow, orbita, sinuses or the testes was not seen more often in these patients. Of the 71 patients receiving CNS prophylaxis, three developed CNS involvement in the course of their disease (3 of 71 = 4.2%). In the majority of 1622 patients without CNS prophylaxis, 34 relapses to the CNS were observed (34 of 1622 = 2.1%). This unexpected trend toward a higher incidence of CNS failures in patients with prophylaxis did not prove to be significant ($P = 0.2$). To analyze the effect of 'prophylaxis' on the time to CNS failure, a univariate (Kaplan–Meier) and a multivariate (Cox) model for prophylaxis adjusted for 'elevated LDH' and 'extranodal disease >1' in the NHL-B1/B2 population and for 'elevated LDH' in the entire study cohort was constructed, showing that prophylaxis had no significant influence on the time to CNS failure.

The median survival after diagnosis of CNS recurrence was 4.4 months. The particularly poor prognosis of patients with CNS failure was confirmed by univariate analysis of NHL-B1/B2 data showing a 3-year survival rate of 11% for patients with CNS involvement compared with 27% for those patients with primary lymphoma progression or subsequent relapse without CNS affection ($P = 0.004$). Adjusted for the risk factors of the IPI in a multivariate Cox model, CNS involvement, when compared with other sites of relapse or primary progressive disease without CNS localizations, evolved as an independent risk factor for survival (RR = 2.0; $P = 0.001$). Further adjustment looking at relapses versus primary treatment failure, which predicts for poor prognosis, showed that CNS affection remained a strong risk factor (RR = 2.1; $P < 0.001$).

risk factor analysis

By univariate analysis (Table 3), an increased risk for CNS relapse was associated with elevated LDH ($P = 0.003$), impaired ECOG PS at diagnosis ($P = 0.023$) and initial involvement of more than one extranodal site ($P < 0.001$). Furthermore, a high/high-intermediate IPI score for all patients in the B1/B2 protocol ($P < 0.001$) as well as for the elderly patients only ($P = 0.003$) was significantly associated with an increased risk of CNS recurrence in poor-prognosis versus good-prognosis patients. Age *per se*, sex, histology, presence of B symptoms, stage of the disease and the age-adjusted IPI for patients ≤60 years ($P = 0.827$) did not influence the rate of CNS relapses. Notably, a trend toward more frequent CNS recurrences was observed in the elderly patients, but this did not reach statistical significance ($P = 0.06$).

The role of specific extranodal sites involved at presentation as risk factors for CNS relapse was studied in 1386 patients of the NHL-B trials only, because the necessary information was not completely available for the participants of the NHL-A protocol. In a multivariate Cox regression analysis, elevated LDH and involvement of more than one extranodal site were identified as independent prognostic factors for CNS recurrence (LDH: $P < 0.001$; extranodal >1: $P = 0.002$; Table 4). Notably, treatment with etoposide also evolved as an independent prognostic factor because the risk of CNS recurrence was significantly reduced after CHOEP (RR = 0.4; $P = 0.017$), whereas the treatment interval between chemotherapies (3 versus 2 weeks) did not influence the relapse rate ($P = 0.903$). As the population of 1386 NHL-B patients included the younger patients with normal LDH (NHL-B1), the group of the elderly patients (NHL-B2, any LDH) was also evaluated separately. In this cohort, an elevated LDH ($P = 0.002$) and involvement of more than one extranodal site

Table 3. Risk factors and probability of central nervous system (CNS) recurrence at 3 years in 1693 patients with aggressive lymphoma

Risk factor	CNS relapse/ all patients (n = 37 of 1693)	3-year rate	95% confidence interval	P value
Age (years)				
≤60	18 of 1012	1.4	0.6, 2.1	0.060
>60	19 of 681	3.2	1.7, 4.7	
Sex				
Male	22 of 955	2.3	1.3, 3.3	0.667
Female	15 of 738	1.7	0.7, 2.8	
Histology[a]				
B cell	33 of 1245	2.3	1.4, 3.2	0.195
T cell	1 of 137	0.9	0.0, 2.6	
DLCL[a]	19 of 905	2.0	1.0, 3.0	0.068
Other B cell	14 of 340	3.2	1.2, 5.2	
DLCL[a]	19 of 905	2.0	1.0, 3.0	0.123
Burkitt	2 of 34	3.9	0.0, 11.2	
B symptoms[b]				0.273
No	14 of 563	1.8	1.0, 2.7	
Yes	23 of 1121	2.6	1.1, 3.9	
LDH				
Normal	18 of 1076	1.3	0.6, 2.0	0.003
Elevated	19 of 617	3.7	1.9, 5.5	
ECOG[b]				
0, 1	28 of 1428	1.7	1.0, 2.5	0.023
>1	9 of 258	4.3	1.3, 7.3	
Stage				
I/II	17 of 936	1.5	0.6, 2.3	0.101
III/IV	20 of 757	2.8	1.4, 4.0	
Extranodal >1[c]				
0, 1	19 of 1118	1.4	0.7, 2.1	<0.001
>1	15 of 268	5.8	2.7, 9.0	
Bone marrow[c]				
No	31 of 1270	2.1	1.3, 3.0	0.728
Yes	3 of 116	3.0	0.0, 6.4	
IPI[c]				
0–2	20 of 1084	1.5	0.8, 2.3	<0.001
3–5	14 of 302	5.0	2.2, 7.8	
IPI (patients >60)[d]				
1–2	6 of 387	1.8	0.2, 3.3	0.003
3–5	13 of 294	5.2	2.3, 8.1	
Age-adjusted IPI (patients ≤60)[e]				
0, 1	15 of 766	1.5	0.6, 2.4	0.827
2, 3	3 of 239	1.2	0, 2.8	

[a]1382 NHL-B1/B2 patients.
[b]Nine, respectively, seven patients in NHL-A without data on B symptoms, respectively, ECOG status.
[c]1386 NHL-B1/B2 patients.
[d]681 NHL-B2 patients.
[e]1005 NHL-A and -B1 patients; no complete International Prognostic Index (IPI) in seven patients in NHL-A.
DLCL, diffuse large cell lymphoma; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

(P = 0.055) again represented the most relevant risk factors for CNS recurrence, confirming the results of the entire B1/B2 population (data not shown).

Table 4. Covariates associated with central nervous system recurrence in final multivariate logistic regression analysis (NHL-B1/B2; n = 1386)

Factor	Relative risk	95% confidence interval		P value
		Lower value	Upper value	
LDH >upper normal value	3.7	1.8	7.5	<0.001
Extranodal sites >1	2.9	1.5	5.9	0.002
Etoposide given	0.4	0.2	0.9	0.017

LDH, lactate dehydrogenase.

Figure 1 indicates the RR of CNS relapse according to initial extranodal disease localizations showing that specific sites such as liver, sinuses and adrenals were associated with a distinctly increased risk for CNS disease; other localizations such as orbita, ascites, bladder and kidney showed a moderately increased risk in univariate analysis. Notably, patients with bone marrow involvement did not have an elevated risk for CNS spread in the course of their disease. Further to the localizations listed in Figure 1, patients with gastrointestinal, pulmonary, pericardial, mouth, tongue, salivary glands, breast, thyroid, peritoneal, ovary, skin, bone or soft tissue involvement did not show an increased risk for CNS relapse.

An age-related analysis of testicular, orbita and sinus involvement showed that an association of these sites with later CNS disease was observed predominantly in the younger patients of the B1 protocol (≤60 years). Patients with testicular involvement had a 6-year probability of CNS relapse of 22.1% versus 2.1% in patients without testicular involvement ($P < 0.001$). The respective probability of CNS failure at 6 years for patients with or without orbita and sinus involvement was 33.3% (versus 2.0%; $P = 0.021$) and 25.9% (versus 1.8%; $P < 0.001$). Two of 11 patients with testicular involvement, one of seven patients presenting with orbita and four of 18 with sinus involvement relapsed to the CNS. No significant correlation of these extranodal lesions to the risk of CNS disease was seen in the elderly patients.

The risk factor analysis was used to develop prognostic models for CNS recurrence. In the group of the elderly patients, 96 patients had both an elevated LDH and involvement of more than one extranodal site. These patients had a cumulative risk of CNS recurrence of 7.9% at 1 year after diagnosis compared with 1.2% for the remaining 585 patients without these risk factors (Figure 2).

Replacing the variable ''more than any extranodal involvement'' by the variable ''liver or bladder or adrenal'' involvement, which had been significant in univariate Bonferroni-adjusted tests, described a group of elderly patients with further increased risk. Consequently, the probability of CNS relapse was found at 17.5% 1 year after diagnosis for 33 patients with an elevated LDH and involvement of the liver, bladder or the adrenals (Figure 3).

discussion

The problem of CNS recurrence in patients with aggressive lymphoma is well recognized; the identification of risk factors

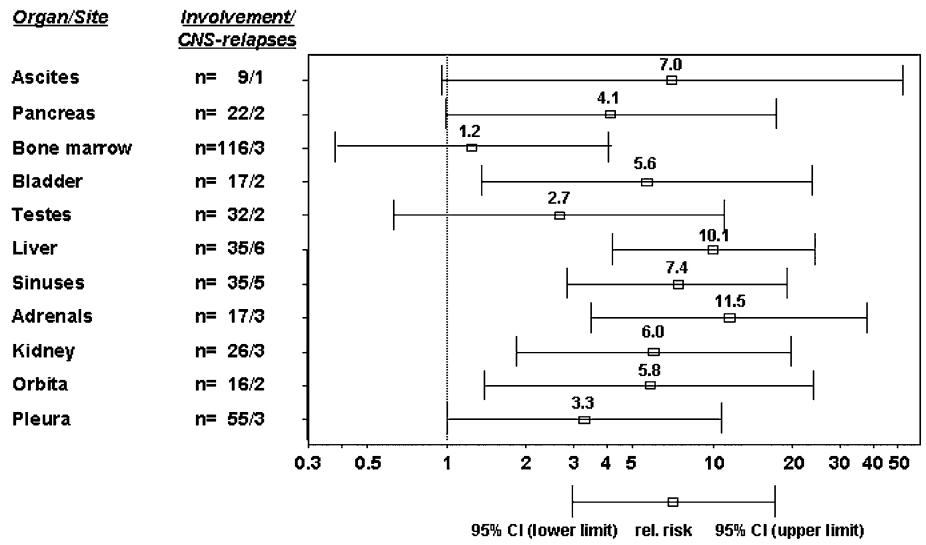

Figure 1. Central nervous system relapse according to main initial extranodal involvement in 1386 patients (NHL-B1/B2).

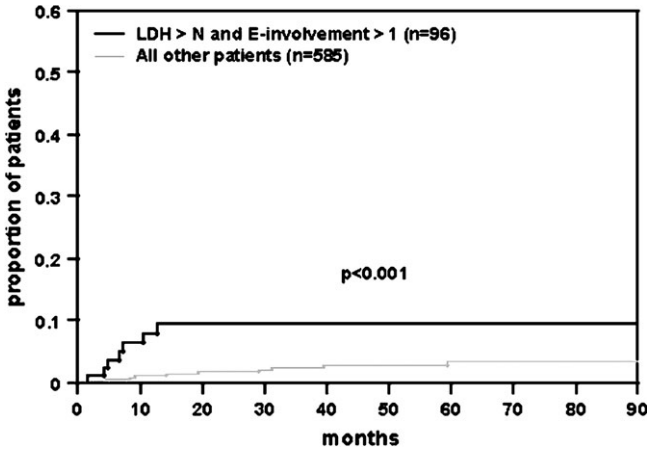

Figure 2. Cumulative risk of central nervous system recurrence in patients with elevated lactate dehydrogenase and involvement of more than one extranodal site versus all other patients (Kaplan–Meier estimate, n = 681 NHL-B2 patients).

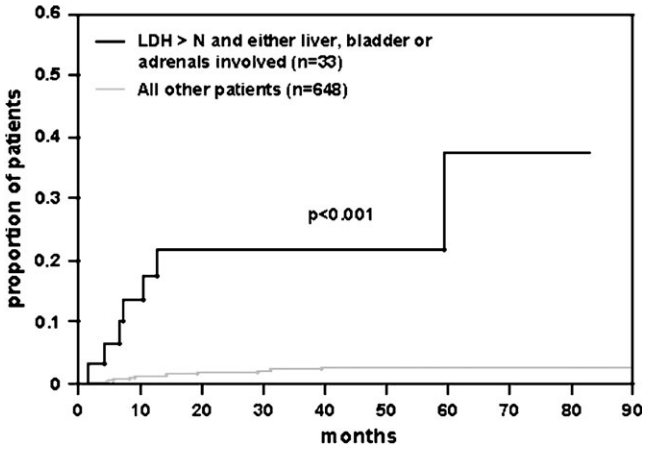

Figure 3. Cumulative risk of central nervous system recurrence in patients with elevated lactate dehydrogenase and involvement of liver, bladder or adrenals versus all other patients (Kaplan–Meier estimate, n = 681 NHL-B2 patients).

for CNS disease, however, has generated different, partly controversial results.

The incidence of CNS recurrence has been reported to be ~5% in recent series of patients who did not receive i.th. prophylaxis as part of their initial treatment [4, 6, 18], but was found at 2.2% in 974 patients treated on various Groupe d'Etudes des Lymphomes de l'Adulte (GELA) studies. These patients had received CNS prophylaxis consisting of repeated i.th. injections and two courses of high-dose methotrexate in the consolidation phase [5]. In this series of 1693 patients, we observed an identical overall incidence of CNS relapse of 2.2% although only 71 patients (4.2% of all patients) had received i.th. prophylaxis with methotrexate. This finding indicates that other factors than i.th. prophylaxis (i.e. treatment schedules, chemotherapeutic agents) influenced the relapse rate in our patient population. Yet, the shortening of the time intervals from 3 to 2 weeks between cycles showed no impact on the CNS recurrence rate. In 103 NHL-A patients (6.1% of all patients), HDT was part of the initial treatment strategy and might have contributed to the low overall incidence of CNS events. However, two of the three CNS relapses in this cohort were observed in patients who had received HDT. Thus, a meaningful conclusion concerning the impact of HDT in the prevention of CNS disease is not possible. Treatment with etoposide, a substance crossing the blood-brain barrier, was associated with a lower risk of CNS relapse (RR = 0.4; P = 0.017). The application of etoposide to half of the NHL-B1/B2 patients as well as to all NHL-A patients may therefore have contributed to the comparatively low rate of CNS recurrences in our study population, although no vigorous CNS prophylaxis was administered.

Various risk factors for CNS recurrence have previously been described. Advanced stage [19, 20], an increased LDH and presence of more than one extranodal site [4, 5, 7] as well as higher IPI scores [5] were reported as independent prognostic

factors. Our data confirm an elevated LDH and involvement of more than one extranodal site at initial presentation as independent predictors for CNS relapse in aggressive lymphoma.

Consequently, the IPI for patients >60 years including LDH and extranodal involvement was associated with an increased risk of CNS relapse ($P = 0.003$), whereas the age-adjusted IPI for patients ≤60 years (LDH, stage and ECOG) did not show such a correlation ($P = 0.827$, Table 3). Apparently, an elevated LDH alone is not strongly predictive, but in combination with widespread extranodal disease reflects an increased risk profile. Applying these two factors to our study population, >60 years allows to identify a subgroup, for whom the risk of CNS recurrence is 7.9% at 1 year representing a seven-fold increase over the remaining patients without these prognostic factors. Selection of these patients would mean that 14% of all patients were to receive prophylactic therapy. On the other hand, only seven of the 19 patients (37%) with CNS relapse would have been identified at the time of diagnosis using this algorithm.

A comparable risk model was applied by van Besien et al. [4] reporting on 605 newly diagnosed adult patients with intermediate-grade or immunoblastic lymphoma. Increased serum LDH and multiple extranodal sites emerged as the only significant features in multivariate analysis and selected a patient subgroup at increased risk of CNS relapse comprising 15% of all patients. In their population, 11 of the 24 patients with later CNS disease would have been identified with this model, resulting in a slightly better but still not satisfactory sensitivity of <50%. An alternative model with five variables having shown independent impact on CNS failure was applied retrospectively in 1220 patients with high-grade lymphomas by a Norwegian institution [7]. Besides LDH and the number of extranodal sites, low albumin, retroperitoneal involvement and age <60 years had been identified as risk factors. Patients having four or five risk factors represented 12% of all patients with a risk of CNS recurrence ≥25% within 5 years and comprised 54% of those with a subsequent CNS relapse. Thus, the sensitivity in predicting CNS failure seemed somewhat higher compared with van Besien's and our data. However, Hollender's report is, to our knowledge, the only one out of seven larger studies over the last decade (including the present data), where age <60 years, low albumin and involvement of retroperitoneal lymph nodes emerged as independent risk factors. In contrast, we observed higher rates of CNS involvement in the elderly patients (>60 years) and were unable to confirm the other prognostic factors. Whether the role of age is a consequence of different patient characteristics in the Norwegian and the German study is unknown. It may be, however, that the different histologic classification systems contributed to the observed differences.

Whether involvement of specific extranodal sites is associated with an increased risk of CNS failure is still controversial. Localizations reported to be associated with CNS disease included bone marrow [6, 18, 19], testicles [21, 22], paranasal sinuses [3, 22] and retroperitoneal lymph nodes [23]. In more recent studies with large numbers of patients, however, these findings were not confirmed. Haioun et al. [5] reporting on 1371 patients pointed out, that only one of 11 patients presenting with testicular involvement and none of 75 patients presenting with sinus or orbita involvement relapsed in the CNS. In the same study and other recent data including our own report, the formerly presumed association of bone marrow involvement and CNS failure was not confirmed [4, 5]. Other series reported that the numbers of patients presenting with lymphoma at distinct localizations were too small in order to test for an association with CNS disease [6]. The evaluation of involvement of orbita, sinus and testes in our dataset was inconclusive; to some extent again due to fairly small numbers even in a large study population and secondly because these relations could not be assessed for the entire cohort. Excluding the young high-risk patients of the NHL-A study, a significant correlation was seen for orbital and paranasal sinuses, but not for testicular involvement. However, an age-related analysis revealed that the relevant CNS relapses mostly occurred in the patient group ≤60 years and for these patients an association was also seen with testicular involvement. Yet, the limited numbers of patients with involvement of these particular sites allow no definite conclusions.

Those extranodal localizations remaining significant in multivariate analyses were incorporated into different risk models for the elderly patients. A subgroup of 21 patients presenting with both an elevated LDH and involvement of the liver was identified with a risk of CNS relapse of 10.9% at 1 year and 33 patients with increased LDH and involvement of liver, bladder or the adrenals had a probability of CNS recurrence of 17.5%. Using the latter score, seven of the 19 relapsed patients of the entire group would have been identified and eventually been treated with the aim of preventing a CNS failure. On the other hand, 26 of the 33 patients with the respective characteristics would have been treated with i.th. prophylaxis, although CNS disease did not occur.

For the combinations of 'liver or bladder' or 'liver or adrenals' involvement, respectively, a similar risk was found. In any of these subgroups, the cumulative incidence of CNS disease amounted to ∼20%. A prophylactic strategy for this small portion of the entire cohort (<5%) would potentially save every fifth of these individuals from developing progression to the CNS.

The effectiveness of i.th. chemoprophylaxis itself is also uncertain. Tomita et al. [24] retrospectively analyzed the therapeutic outcome in patients with aggressive NHL with or without CNS prophylaxis. Initially, all 68 adults had been treated uniformly with systemic chemotherapy and had attained complete remission. The decision to use CNS prophylactic chemotherapy (29 patients) or no prophylaxis (39 patients) was made by the attending physician. The groups were balanced for clinical variables except for female gender and bulky disease which were overrepresented in the prophylaxis group. All six CNS relapses occurred in patients without prophylaxis representing a significant difference. The authors concluded, that prophylactic i.th. therapy reduces the incidence of CNS recurrence following CR [24]. This report focused on patients in complete remission where i.th. prophylaxis was on the basis of individual decisions rather than designated criteria. Therefore, the results are of limited help in defining patients for whom a prophylaxis might be useful. Controversially, the CNS recurrence rate in 26 patients of the Peter MacCallum Cancer Institute all receiving prophylactic i.th. chemotherapy was still

26% at 3 years [25]. Although the authors could not exclude that the prophylaxis did actually reduce the incidence of CNS recurrence, they concluded that i.th. prophylaxis alone was inadequate. Their recommendation for high-risk patients included systemic methotrexate therapy in addition to i.th. prophylaxis. Both retrospective analyses have the problem of relatively small cohorts of patients, rendering the interpretation of such apparently contrary results even more difficult.

In conclusion, the risk of CNS recurrence seen in a large group of 1693 patients with aggressive lymphomas treated with modern regimens was low. An overall incidence of only 2.2% does not warrant the use of a general prophylaxis for all patients, yet the poor prognosis of CNS involvement, which we confirmed in multivariate analysis, emphasizes the need to search for strategies minimizing this fatal event.

Some previously identified risk factors including the predictive value of increased LDH and involvement of multiple extranodal sites could be confirmed. Yet the sensitivity of such an approach, rendering ~15% of all patients candidates for i.th. prophylaxis, is suboptimal. Far less patients would be candidates for CNS prophylaxis using risk models combining increased LDH and specific extranodal sites such as liver, adrenals and the bladder, as shown in the elderly patients; however, this approach would still imply a potential overtreatment. Due to data on the risk of CNS disease after testicular, orbita and paranasal sinus involvement in our analysis and in the literature, these patients should be considered for prophylaxis as well [26].

Any clinical feature presently used to identify patients at high risk for CNS disease must be considered as surrogate parameter for a biologically defined subtype of lymphoma, which needs further characterization. For example, expression of cell adhesion receptors or the lack of specific adhesion molecules has been associated with lymphoma dissemination and malignant behavior [27, 28]. Especially, the CD44 family with its capability to enhance lymphoma dissemination and contribution to lymphoma aggressiveness has recently been discussed [28]. Further investigation and understanding of the underlying pathophysiology may help to more precisely identify those patients whose lymphomas are destined to disseminate to distinct clinical sites such as the CNS. Moreover, more sensitive detection methods for occult leptomeningeal disease by flow cytometry might assist in the identification of patients at risk for CNS relapse [29].

Finally, it has to be pointed out, that we and others analyzed data of patients not treated with rituximab. This antibody improved response and survival of patients with aggressive lymphoma and might as well contribute to reduced incidences or different patterns of CNS recurrences. Data on CNS disease for patients treated in more recent DSHNHL studies which combined chemotherapy with rituximab are currently being analyzed.

references

1. Levitt LJ, Dawson DM, Rosenthal DS, Moloney WC. CNS involvement in the non-Hodgkin's lymphomas. Cancer 1980; 45: 545–552.
2. Recht L, Straus DJ, Cirrincione C et al. Central nervous system metastases from non-Hodgkin's lymphoma: treatment and prophylaxis. Am J Med 1988; 84: 425–435.
3. MacKintosh FR, Colby TV, Podolsky WJ et al. Central nervous system involvement in non-Hodgkin's lymphoma: an analysis of 105 cases. Cancer 1982; 49: 586–595.
4. van Besien K, Ha CS, Murphy S et al. Risk factors, treatment, and outcome of central nervous system recurrence in adults with intermediate-grade and immunoblastic lymphoma. Blood 1998; 91: 1178–1184.
5. Haioun C, Besson C, Lepage E et al. Incidence and risk factors of central nervous system relapse in histologically aggressive non-Hodgkin's lymphoma uniformly treated and receiving intrathecal central nervous system prophylaxis: a GELA study on 974 patients. Ann Oncol 2000; 11: 685–690.
6. Bos GM, van Putten WLJ, van der Holt B et al. For which patients with aggressive non-Hodgkin's lymphoma is prophylaxis for central nervous system disease mandatory? Ann Oncol 1998; 9: 191–194.
7. Hollender A, Kvaloy S, Nome O et al. Central nervous system involvement following diagnosis of non-Hodgkin's lymphoma: a risk model. Ann Oncol 2002; 13: 1099–1107.
8. Harris NL, Jaffe ES, Stein H et al. A revised European–American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84: 1361–1392.
9. Harris NL, Jaffe ES, Diebold J et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting—Airlie House, Virginia, November 1997. J Clin Oncol 1999; 17: 3835–3849.
10. Kaiser U, Uebelacker I, Abel U et al. Randomized study to evaluate the use of high-dose therapy as part of primary treatment for 'aggressive' lymphoma. J Clin Oncol 2002; 20: 4413–4419.
11. Pfreundschuh M, Trümper L, Kloess M et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 2004; 104: 626–633.
12. Pfreundschuh M, Trümper L, Kloess M et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 2004; 104: 634–641.
13. Koppler H, Pflüger KH, Eschenbach I et al. Randomised comparison of CHOEP versus alternating hCHOP/IVEP for high-grade non-Hodgkin's lymphomas: treatment results and prognostic factor analysis in a multi-centre trial. Ann Oncol 1994; 5: 49–55.
14. McKelvey EM, Gottlieb JA, Wilson HE et al. Hydroxyldaunomycin (adriamycin) combination chemotherapy in malignant lymphoma. Cancer 1976; 38: 1484–1493.
15. Fisher RI, Gaynor ER, Dahlberg S et al. Comparison of a standard regimen (CHOP) with tree intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993; 328: 1002–1006.
16. Kaplan EI, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 55: 457.
17. Collet D. Modelling Survival Data in Medical Research, Boca Raton, FL: Chapman & Hall/CRC 1999; 80–81.
18. Zinzani PL, Magagnoli M, Frezza G et al. Isolated central nervous system relapse in aggressive non-Hodgkin's lymphoma: the Bologna experience. Leuk Lymphoma 1999; 32: 571–576.
19. Keldsen N, Michalski W, Bentzen SM et al. Risk factors for central nervous system involvement in non-Hodgkin's lymphoma—a multivariate analysis. Acta Oncol 1996; 35: 703–708.
20. Bollen EL, Brouwer RE, Hamers S et al. Central nervous system relapse in non-Hodgkin lymphoma. A single-center study of 532 patients. Arch Neurol 1997; 54: 854–859.
21. Fonseca R, Habermann TM, Colgan JP et al. Testicular lymphoma is associated with a high incidence of extranodal recurrence. Cancer 2000; 88: 154–161.
22. Liang R, Chiu E, Loke SL. Secondary central nervous system involvement by non-Hodgkin's lymphoma: the risk factors. Hematol Oncol 1990; 8: 141–145.
23. Litam JP, Cabanillas F, Smith TL et al. Central nervous system relapse in malignant lymphomas: risk factors and implications for prophylaxis. Blood 1979; 54: 1249–1257.

24. Tomita N, Kodama F, Kanamori H et al. Prophylactic intrathecal methotrexate and hydrocortisone reduces central nervous system recurrence and improves survival in aggressive non-Hodgkin lymphoma. Cancer 2002; 95: 576–580.
25. Chua SL, Seymour JF, Streater J et al. Intrathecal chemotherapy alone is inadequate central nervous system prophylaxis in patients with intermediate-grade non-Hodgkin's lymphoma. Leuk Lymphoma 2002; 43: 1783–1788.
26. Zucca E, Conconi A, Mughal TI et al. Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. J Clin Oncol 2003; 21: 20–27.
27. Horstmann WG, Timens W. Lack of adhesion molecules in testicular diffuse centroblastic and immunoblastic B cell lymphomas as a contributory factor in malignant behaviour. Virchows Arch 1996; 429: 83–90.
28. Drillenburg P, Pals ST. Cell adhesion receptors in lymphoma dissemination. Blood 2000; 95: 1900–1910.
29. Hegde U, Filie A, Little RF et al. High incidence of occult leptomeningeal disease detected by flow cytometry in newly diagnosed aggressive B-cell lymphomas at risk for central nervous system involvement: the role of flow cytometry versus cytology. Blood 2005; 105: 496–502.