Original Article

Central Nervous System Involvement of Non-Hodgkin's Lymphomas

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Abstract: *To determine the incidence and risk factors of central nervous system (CNS) involvement in adult patients with non-Hodgkin's lymphomas (NHL), three hundred and thirty three patients with biopsy-proven NHL treated at Ramathibodi hospital between January 1997 to June 2002 were reviewed. The incidence rate of CNS involvement in NHL was 5 /100 patients/year. The probability of CNS involvement at 1 and 3 years after diagnosis of NHL were 7.24% (95% Confidential Interval (CI): 4.52, 11.49) and 13.62% (95% CI: 8.88, 20.60), respectively. Cox regression analysis showed that elevated serum LDH levels (Hazard ratio (HR) 17.61, 95% CI: 3.23, 95.96), lymphomatous involvements of the bone marrow (HR 4.95, 95% CI: 1.91, 12.78), sinonasal area (HR 5.98, 95% CI: 1.86, 19.20), orbit (HR 23.38, 95% CI: 5.24, 104.32), and reproductive organs (HR 36.93, 95% CI: 8.87, 153.81) were significantly associated with CNS involvement in NHL.*

Key Words : ● *Central nervous system* ● *Non-Hodgkin's lymphomas*

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Central nervous system (CNS) involvement by systemic non-Hodgkin's lymphoma (NHL) is a devastating complication with a median survival of 1-18 months.[1] Features of high risk for CNS involvement in NHL include high grade lymphoma of Burkitt's and lymphoblastic types,[2] multiple extranodal sites,[3] elevated serum LDH levels,[3,4] and lymphomatous involvements of the bone marrow,[5] testis,[6] breast[7] orbit[8] and sinonasal area.[8,18] CNS prophylaxis is now usu-

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ally part of the treatment for Burkitt's and lymphoblastic lymphomas[2] but it is less clear for other subtypes which constitute most of the NHL cases. Therefore, it is important to identify "patients at risk" for whom CNS prophylaxis may be required, especially when histopathology of NHL in Thailand is more aggressive than those reported from Western countries[9]. We undertook this study to find the incidence and risk factors of CNS involvement in Thai patients with NHL.

Patients and Methods

A historical cohort study of the patients with biopsy-proven NHL, newly diagnosed at Ramathibodi hospital between January 1997 and June 2002 was performed. Patients with primary CNS lymphoma, CNS involvement from the outset and HIV infection were excluded. Study entry and exit were date of NHL diagnosis and date of CNS involvement, respectively. Diagnosis of "definite CNS involvement" was established if spinal fluid cytology, biopsy or autopsy of CNS tissue showed malignant lymphoma; and of "probable CNS involvement" if all of the following criteria were met[6], i.e. known extracranial NHL, otherwise unexplained CNS signs and symptoms, "suspicious" spinal fluid cytology, structural abnormality of the CNS documented by radiological study except epidural localization and spinal cord compression, and resolution or improvement of symptoms associated with cranial irradiation and/or intrathecal chemotherapy. Both definite and probable CNS involvement were combined in analysis. Patients were censored on the date of death without CNS involvement, loss to follow up, and if they did not have CNS involvement at the end of study (30 June 2002).

Features evaluated were age, sex, histopathologic subtype and malignancy grade according to the Working Formulation (WF) classification, immunophenotype (CD3 and/or CD45 RO reactivity for T cell, CD20 and/or CD79a reactivity for B cell, and null cell if both T and B cell markers were negative), extent of disease, maximum size of tumor (bulky if >10 cm), Ann Arbor stage, serum LDH level, performance status (ECOG), International Prognostic Index[10] (IPI), initial chemotherapeutic regimen, patients' response to treatment and CNS prophylaxis (according to the attending physicians' decision).

Statistical analysis

The probability of CNS involvement was estimated by Kaplan-Meier's method. In univariate analysis, log-rank test was used to compare the probability of CNS involvement between groups of each risk factor. Multivariate analysis was performed using Cox regression model and factors examined were those with p values less than 0.1 from univariate analysis. Likelihood ratio test was used to select parsimonious model to explain the CNS involvement. Hazard ratio (HR) and its 95% confidence interval (CI) were estimated and presented. All analyses were performed using STATA version 7.0.[11] P value less than 0.05 indicates statistically significant difference.

Results

Patient characteristics

Four-hundred and seven patients with biopsy-proven NHL, newly diagnosed at Ramathibodi hospital were registered during the study period. Of these, 370 records were available. Thirty seven patients were excluded: 7, 10, 8 and 12 patients because of HIV infection, CNS involvement from the outset, primary CNS lymphoma, and prior treatment at other hospitals, respectively.

Table 1 shows the initial clinical features of 333 NHL patients. The mean age (± SD) was 53.2±16.97 years. Two thirds had intermediate and high grade lymphomas according to the WF classification, and more than half had stage III-IV diseases and B symptoms. Approximately two thirds had elevated serum LDH levels (>upper normal limit), and one third had diseases at more than one extranodal sites. The IPI could be calculated in 248 patients and more than half had high intermediate or high scores indicating poor risk cases. Thirty-nine patients were "not classified in the WF" i.e. mantle cell lymphoma (9 patients), anaplastic large cell lymphoma (13 patients), T/NK nasal lymphoma (6 patients), angioimmunoblastic T cell lymphoma (6 patients), follicular lymphoma (2 patients), posttransplant lymphoproliferative disorders (2 patients) and marginal zone lymphoma (one patient).

CNS involvement

Twenty-four patients developed CNS involvement, 8 (33.33 %) and 16 (66.67%) with definite and probable CNS involvement, respectively. Their clinical features are detailed in Table 2. The CNS involvement rate was 5 /100 patients/ year. The probability of CNS involvement at 1, 3 and 5 years after diagnosis of NHL was 7.24% (95% CI: 4.52, 11.49), 13.62% (95% CI, 8.88, 20.60) and 13.62% (95% CI, 8.88, 20.60), respectively (Fig.1).

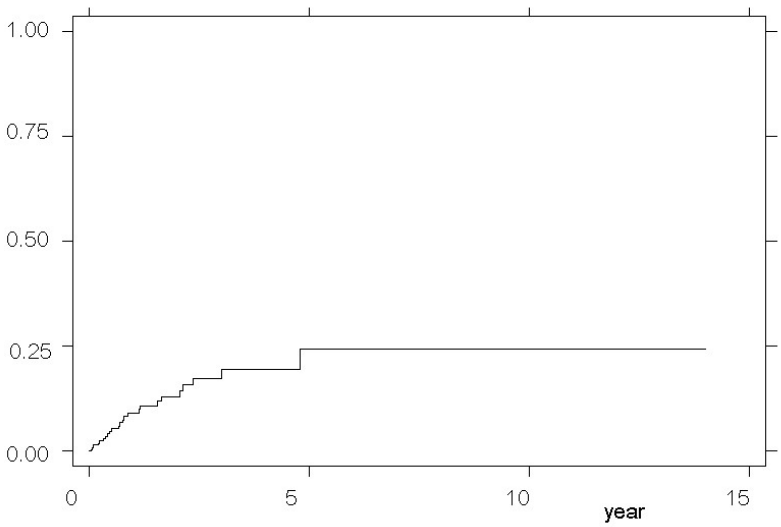

Fig. 1 Probability of CNS involvement after NHL diagnosis

Table 1 Patient characteristics and CNS involvement rate according to the potential risk factors

Factors	No. of Patients (%)	No. of CNS Involvement	CNS Involvement Rate (/100patients/year)	p
Total patients	333	24	4.82	
Age	333			0.610
≤ 60	202 (60.6)	15	4.44	
> 60	131 (39.4)	9	5.64	
Sex	333			0.700
Male	171 (51.4)	11	4.40	
Female	162 (48.6)	13	5.26	
Performance status	294			0.301
ECOG 0-1	169 (57.5)	12	4.09	
≥2	125 (48.6)	9	6.97	
WF Grading	333			0.600
Low	34 (10.2)	0	0	
Intermediate	185 (55.5)	18	6.74	
High	46 (13.8)	2	2.60	
Not classified in the WF*	39 (11.8)	2	5.11	
Unclassifiable	29 (8.7)	2	5.06	
Immunophenotype	180			0.612
T	37 (20.6)	4	12.34	
B	124 (68.9)	10	5.61	
Null cell	19 (10.5)	2	6.45	
Serum LDH level	281			0.020
Elevated	209 (74.4)	19	7.43	
Normal	72 (25.6)	2	1.30	
Bulky (>10 cm)	309			0.025
Yes	87 (28.2)	11	9.14	
No	222 (71.8)	12	3.60	
Ann Arbor stage	322			0.004
I-II	127 (39.4)	4	1.72	
III-IV	195 (60.6)	20	7.80	
IPI	248			0.002
Low/Low Intermediate	120 (48.4)	4	1.76	
High/High Intermediate	128 (51.6)	13	10.23	
Extranodal site(s)	333			0.001
0	64 (19.2)	2	1.86	
1	162 (48.7)	7	2.80	
≥ 2	107 (32.1)	15	11.48	
Chemotherapy	333			0.218
CHOP/COP	266 (79.9)	18	4.02	
None	40 (12.0)	2	11.00	
Mega III/ALL protocol	17 (5.1)	2	11.83	
Others	10 (3.0)	2	13.08	
CNS Prophylaxis	333			0.191
Yes (high risk cases)	13 (3.9)	1	3.67	
No	320 (96.1)	23	4.89	

**For detail, see text.*

Table 2 Findings of patients with CNS involvement

	No. of patients
Total	24
Definite CNS involvement	8
Probable CNS involvement	16
CNS prophylaxis	10
Neurologic symptoms/signs	22
Mental status change	11
Seizure	4
Headache	5
Cranial nerve(s) palsy	13
Sensory/Motor symptoms	14
Lumbar puncture	
Positive lymphoma cells	10
Negative	6
Not done	8
Radiologic study	
Leptomeningeal enhancement	8
Brain parenchymal lesions	8
Negative study	2
Not done	6
Status of systemic lymphomas at the time of CNS involvement	
Refractory/Progressive diseases	17
Systemic relapse with CNS relapse	4
Isolated CNS relapse	2
Unknown	1
Treatment of CNS involement	
Cranial radiation	10
Intrathecal methotrexate	11
Intrathecal cytarabine	2
None	9

Risk factors

Univariate analysis

As shown in Tables 1, 3 and 4, there were statistically significant association between CNS involvement and advanced diseases (Ann Arbor stages III or IV, p = 0.004), elevated serum LDH levels (p = 0.020), bulky diseases (p = 0.025), high intermediate/ high IPI scores (p = 0.002), multiple extranodal sites (p = 0.001), and lymphomatous involvements of the bone marrow (p = 0.007), reproductive organs (p = 0.001) and orbit (p = 0.029).

Multivariate analysis

Cox regression identified the independent predictors of CNS involvement in NHL as elevated serum LDH levels (p = 0.001), and lymphomatous involvements of the bone marrow (p = 0.001), sinonasal area (p = 0.03), orbit (p < 0.001) and reproductive organs (p < 0.001) (Table 5). The sites of reproductive organs were testes (n = 5), vagina (n = 1) and uterus (n = 1).

Survival after CNS involvement

Of the 24 patients, 15 (62.5%) had refractory/progressive diseases at the time of CNS involvement. Survival probability was estimated, and median survival after diagnosis of CNS involvement was 8.8 months (range 0.1 to 39.24 months) (Fig.2).

Discussion

The incidence of CNS involvement of NHL in our study was 5 /100 patients /year. Elevated serum LDH levels, lymphomatous involvement of the bone marrow, sinonasal area, orbit, and reproductive organs were the significant risk factors for CNS involvement.

Our findings were similar to the previous studies,[18] which showed the incidence ranging from 5-10%. Prevalence of neurological complications of NHL including intracranial mass,

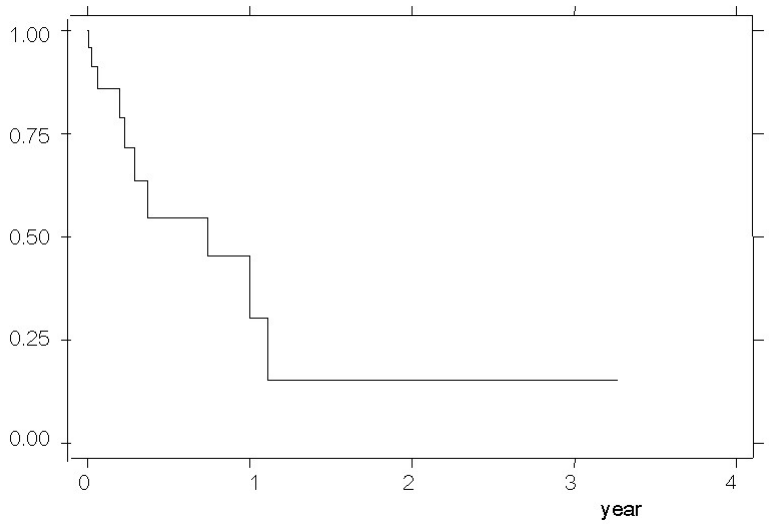

Fig. 2 Probability of survival after CNS involvement

Table 3 CNS involvement according to extranodal site of involvement

Site	No.of Patients (%)	No. of CNS Involvement	CNS Involvement Rate (/100patients/year)	p
Marrow				
Yes	118 (64.6)	14	8.87	0.007
No	215 (35.4)	10	2.94	
GI tract				
Yes	57 (17.1)	4	4.48	0.946
No	276 (82.9)	20	4.90	
Waldeyer's ring				
Yes	45 (13.5)	3	5.17	0.950
No	288 (86.5)	21	4.79	
Skin/soft tissue				
Yes	18 (5.4)	3	15.98	0.053
No	315 (94.6)	21	4.39	
Sinonasal				
Yes	25 (7.5)	4	11.64	0.064
No	308 (92.5)	20	4.32	
Bone				
Yes	12 (3.6)	1	4.14	0.910
No	321 (96.4)	23	4.86	
Orbit				
Yes	14 (4.2)	3	18.98	0.028
No	319 (95.8)	21	4.36	
Breast				
Yes	6 (1.8)	0	0	0.498
No	327 (98.2)	24	4.96	
Reproductive organs*				
Yes	7 (2.1)	3	23.33	0.001
No	326 (97.9)	21	4.33	

**male = testis; female = uterus, vagina*

Table 4 CNS involvement according to histopathologic subtype (Working Formulation classification)

Histopathology	No. of Patients	No of. CNS Involvement	CNS Involvement Rate (/100patients/year)	p
Small lymphocytic	15	0	0	0.556
Follicular, small cleaved	9	0	0	
Follicular, mixed small & large	10	0	0	
Follicular, predominantly large	3	0	0	
Diffuse small cleaved	26	2	6.11	
Diffuse mixed small and large	77	9	8.27	
Diffuse large cell	79	7	5.26	
Large cell immunoblastic	14	0	0	
Lymphoblastic	14	2	14.56	
Small non-cleaved	18	0	0	

Table 5 Risk factors for CNS involvement (Cox regression analysis)

Factors	Hazard ratio (95% CI)	Standard error	p
Elevated serum LDH levels	17.61 (3.23-95.96)	15.23	0.001
Lymphomatous involvements of			
Bone marrow	4.95 (1.91-12.78)	2.40	0.001
Sinonasal area	5.98 (1.86-19.20)	3.56	0.030
Orbit	23.38 (5.24-104.32)	17.84	< 0.001
Reproductive organs	36.93 (8.87-153.81)	26.88	< 0.001

leptomeningeal lesions, spinal cord compression, and peripheral nerve compression were 9.7% in another study from Thailand.[12] Our analysis was confined to the CNS proper only. Epidural lesions and spinal cord compression were excluded in view of the different prognosis.[19] Majority of our patients had intermediate grade histology with advanced Ann Arbor stages. Only 10% had low grade histology. The findings were similar to a previous large study of NHL in Thailand.[9]

Diagnosis of CNS involvement in our study was mainly "probable." Although lumbar punctures were performed in 66.67% of the patients, the negative tests were not repeated. There are still no conclusive data on the numbers of lumbar punctures required to rule in or rule out leptomeningeal involvement. With more than one CSF examinations, the positive yield rose to 93%[1]. Improved CSF analytical technique may also increase the yield.[14]

We did not use the IPI scores in the multivariate analysis because they could be calculated in only 248 patients. Alternatively, we used their components, i.e. age, Ann Arbor stages, serum LDH levels, number of extranodal sites and performance status to get a larger number of patients. We identified elevated serum LDH levels, stages III or IV diseases, and involvements of the bone marrow, orbit, sinonasal area and reproductive organs as the independent risk factors of CNS involvement. Of these, elevated serum LDH levels, advanced Ann Arbor stages and bone marrow involvement reflect the extent of disease and their proliferative activities, and were also shown to be associated with CNS involvement.[3,4,8] Testicular lymphoma is well known for its association with CNS disease[2,6]. However, little is known about the lymphomas of female genital tract. Vaginal and uterine lymphomas are relatively more heterogeneous, and have unpredictable prognosis.[15,16] A retrospective analysis from Hong Kong did not demonstrate an increased risk of CNS involvement in female genital tract lymphomas.[8] However, the present study lumped together the reproductive organ lymphomas of both genders in order to give each an equal chance for analysis, and found an increased risk of CNS involvement in both uni- and multivariate analyses.

The sinonasal lymphomas are not that rare in Thailand[9] and the Orient,[17] and high incidence of CNS involvement have been reported.[8,18,20] Although the incidence was lower, our findings were similar. Orbit was also the risk site in our series in agreement with a previous study.[8] However, one third of our patients with lymphoma involving the orbit were in advanced stages. For lymphoma of the ocular adnexa (conjunctiva, orbit, and lacrimal gland), the extent of disease is the strong predictor for persistent disease and lymphoma related death.[21]

CNS prophylaxis was performed in a small number and selected patients (13 of 333 patients). Half of these had lymphoblastic lymphoma (data not shown). Although we did not find a reduced risk of CNS involvement either in the group with CNS prophylaxis (Table 1) or the lymphoblastic lymphoma group (Table 4), the effect of CNS prophylaxis was rather difficult to conclude in this study because of lack of control group.

Conclusion

Incidence of CNS involvement in NHL in our studies was 5/100 patients/year. Features associated with high risk of CNS involvement were elevated serum LDH levels, lymphomatous involvements of the bone marrow, sinonasal area, orbit, and reproductive organs.

Acknowledgement

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การกระจายของมะเร็งต่อมน้ำเหลือง non-Hodgkin's มาที่ระบบประสาทส่วนกลาง

ฐิรภัทร จิตต์โสภักตร์, วิชัย อติชาตการ, แสงสุรีย์ จูฑา, สุภร จันท์จารุณี, อาทิตย์ อังกานนท์, พันธุ์เทพ อังชัยสุขศิริ, สุรพล วรพงศ์ไพบูลย์*, สยมพร ศิรินาวิน, ศศิวิมล รัตนสิริ** และ อัมรินทร์ ทักขิญเสถียร****

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บทคัดย่อ : *การศึกษานี้มีวัตถุประสงค์เพื่อประมาณอุบัติการณ์และศึกษาปัจจัยเสี่ยงของการกระจายของโรคมะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin's มาที่ระบบประสาทส่วนกลาง โดยรูปแบบการศึกษาเป็น historical cohort ซึ่งมีการเก็บข้อมูลทั้งแบบย้อนหลัง และได้ติดตามผู้ป่วยไปข้างหน้าบางส่วน ระหว่างเดือนมกราคม 2540 ถึงเดือนมิถุนายน 2545 ที่โรงพยาบาลรามาธิบดี มีผู้ป่วยโรคมะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin's อายุ15 ปีขึ้นไป ที่ได้รับการวินิจฉัยจากตรวจทางพยาธิวิทยาจำนวน 333 คน อุบัติการณ์ของการกระจายของโรคมะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin's มาที่ระบบประสาทส่วนกลางคิดเป็น 5 คนต่อผู้ป่วย 100 คนต่อปี โดยโอกาสของการกระจายของโรคมะเร็งมาที่ระบบประสาทส่วนกลางที่ 1 และ 3 ปี คิดเป็น 7.24% (95% confidential interval (CI) : 4.52, 11.49) และ 13.62% (95% CI: 8.88, 20.60) ตามลำดับ การศึกษาปัจจัยที่มีความสัมพันธ์กับการกระจายของโรคโดยใช้ Cox regression analysis พบว่า ระดับของ LDH ในเลือดที่สูงกว่าปกติ (Hazard Ratio (HR) 17.61, 95% CI: 3.23, 95.96) โรคมะเร็งต่อมน้ำเหลืองที่ไขกระดูก (HR 4.95, 95% CI:1.91, 12.78) โรคมะเร็งต่อมน้ำเหลืองที่เบ้าตา (HR 23.38, 95% CI: 5.24, 104.32) โรคมะเร็งต่อมน้ำเหลืองที่โพรงจมูกหรือไซนัส (HR 5.98, 95% CI: 1.86, 19.20) และโรคมะเร็งต่อมน้ำเหลืองที่ระบบสืบพันธุ์ (HR 36.93, 95%: 8.87, 153.81) เป็นปัจจัยที่มีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติกับการกระจายของโรคมะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin's มาที่ระบบประสาทส่วนกลาง*

Key Words : ● *Central nervous system* ● *Non-Hodgkin's lymphomas*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2547;14:251-61.

คติธรรมนำกำยัดจุดย่อน

รักมีให้ค้า รักหน้าให้คิด

พระครูปริยัติปัญญาวุธ
วัดโคกงาม อ.ด่านซ้าย จ.เลย