Clin Oncol Cancer Res (2010) 7: 44-47
DOI 10.1007/s11805-010-0044-8

Analysis of Prognostic Factors in 108 Patients with Non-Hodgkin's Lymphoma

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OBJECTIVE To analyze the prognostic factors in patients with non-Hodgkin's lymphoma (NHL) and to investigate the prognostic value of the absolute lymphocyte count (ALC) in peripheral blood in NHL patients at admission.

METHODS The clinical features and follow-up data from 108 NHL patients whose diagnosis was confirmed through pathologic examination during a period from January 2000 to January 2008 were reviewed. SPSS 14.0 package was used for statistical analysis, and the Kaplan-Meier curve method for assessment of survival probability. Furthermore, the Cox regression model was utilized for multivariate analysis for all parameters which were statistically significant and confirmed by univariate analysis.

RESULTS In the 108 NHL patients, the male-female ratio was approximately 1.5 : 1 and the median age was 48 years. Before treatment, 61.1% of the patients had stage I and II disease, based on the Ann Arbor Clinical Classification. The ECOG performance status (PS) score reached a range from 0 to 1 in about 93% of total patients, and an elevated serum lactate dehydrogenase (LDH) was seen in 19.2%. Based on the international prognostic index (IPI) score, 80.6% of patients were in the low risk group. On admission, 35.2% of patients had an ALC $\leq 1 \times 10^9$/L. Anemia, i.e. hemoglobin (Hb) ≤ 110 g/L was seen in 29.6% and B-symptoms in 26.9% of patients. The mean value of Hb was 129.2 ± 17.5 g/L in patients with ALC $> 1 \times 10^9$/L (n = 70) and 98.1 ± 20.6 g/L in those with ALC $\leq 1 \times 10^9$/L (n = 38), and the difference between the 2 groups was statistically significant ($P < 0.05$). With a median follow-up period of 2 years, the median survival time was 2.3 years among all patients. The 2-year and 5-year overall survival (OS) rates were 73.2% and 39.6%, respectively. It was shown by univariate analysis that ALC $\leq 1 \times 10^9$/L, Hb ≤ 110 g/L, B-symptoms, and the IPI ≥ 2 were statistically significant unfavorable prognostic factors in NHL patients. Multivariate analysis revealed that ALC $\leq 1 \times 10^9$/L, B-symptoms, and the IPI ≥ 2 were independent unfavorable prognostic factors in NHL patients.

CONCLUSION The numerical value of ALC and the presence of B-symptoms are prognostic factors independent of IPI in NHL patients. Clinically, determining prognosis based on the IPI combined with simple clinical parameters, such as the numerical value of ALC and B-symptom status, might be of more practical value in determining individualized treatment regimens for NHL patients.

KEY WORDS: lymphocyte count, non-Hodgkin's lymphoma, prognosis.

Introduction

Non-Hodgkin's lymphoma (NHL) is a group of immune system malignant tumors with significant differences in prognosis among patients with the disease. A precise prediction on of prognosis would serve as a valuable clinical guide when devising individual treatment strategies, so as to improve treatment outcome and reduce treatment-related side effects. The international prognostic index (IPI) is a criterion for predicting the prognosis of patients with NHL, and it has been widely used on a clinical basis. Nevertheless, different prognoses may be made in NHL cases with the same IPI value. It has been reported recently that there is a close relationship between the absolute lymphocyte count (ALC) in peripheral blood and the prognosis of diffuse large B-cell and follicular lymphomas[1,2]. The data from 108 NHL cases were reviewed in our study in order to further investigate the relationship between ALC and the prognosis of NHL patients.

Patients and Methods

Patients

The data from 108 NHL patients with relatively complete clinical and prognostic information during a period from January 2000 to January 2008 were collected. The diagnoses of all patients were confirmed through pathologic examination. The clinical staging was based on the Ann Arbor Clinical Classification. The grouping was made based on B-symptoms (fever, emaciation, night sweats), i.e., group A was designated as patients without B-symptoms, and group B as patients with B-symptoms.

Treatment methods

Owing to the various phases of the disease, the treatment modalities used in the 108 patients were not the same. Among the 108 cases, simple surgery was performed in 6 patients with early extra-nodular lymphoma, and chemotherapy was the main treatment for the other 102 patients. One of the 102 patients received re-transfusion of autologous hemopoietic stem cells after complete remission following combined chemotherapy. The combination chemotherapy COP was most frequently used in cases with indolent lymphoma, and a regimen with adriamycin or pirarubicin as a major component, such as CHOP or CTOP etc., was usually employed in the invasive lymphoma cases.

Follow-up

The deadline of the follow-up period was May 29, 2009. The overall survival (OS) time was measured from the time of final diagnosis to death or the last follow-up visit. Collection of pertinent clinical data from patients via telephone was most frequently used during follow-up.

Statistical analysis

The Chi-test was used for the inter-group numeration data, and the *t*-test for the measurement of data. The survival probability was evaluated using the Kaplan-Meier curve, and the significance test on the results was conducted using the log-rank test. The Cox regression model was used for multivariate analysis, and ENTER was used for analysis of the variances. The value of $P < 0.05$ was considered statistically significant. The SPSS14.0 software package was also utilized.

Results

Clinical features

The male-female ratio of the 108 patients was approximately 1.5: 1, and the age of the patients ranged from 17 to 82 years, with a median age of 48. Before treatment, patients with a score of 0-1, evaluated using Eastern Cooperative Oncology Group (ECOG) Performance Status Scales, accounted for about 93% of the total. In the 108 patients, 61.1% were at Ann Arbor stage I-II. An increased lactate dehydrogenase level was found in 19.2% of patients. Based on the IPI, 80.6% of patients were classified into the low risk group. When admitted, 26.9% of patients were accompanied by B-symptoms, while anemia was found in 29.6%, and thrombocytopenia was found in 28.3%. A decreased ALC ($\leq 1 \times 10^9$/L) was seen in 35.2% of patients. The 108 patients were divided into 2 groups based on the ALC level at admission. The comparison of the basic characteristics between cases in the 2 groups is shown in Table 1.

Overall survival rate

By the end of the follow-up period, 62 of the 108 patients had died, and the remaining 46 survived or were lost to follow-up. Within the groups, the median follow-up period was 2 years and the median survival time was 2.3 years. The 2 and 5-year OS rates were 73.2% and 39.6%, respectively among patients.

Univariate analysis of survival

The effect of ALC and Hb levels, platelet count (PLT) at admission, and the presence or absence of B-symptoms on the prognosis of NHL patients was respectively analyzed. The analytic results showed that the ALC, Hb, and B-symptoms correlated with the prognosis of NHL patients, while the PLT count did not. The median survival time of the patients in the group with ALC $\leq 1 \times 10^9$/L and in the group with ALC $> 1 \times 10^9$/L was 1.8 years and 4.8 years, respectively ($P < 0.05$). The median survival time in the group with Hb ≤ 110 g/L and in the gorup with Hb > 110 g/L was 2.6 years and 4.2 years, respectively ($P < 0.05$), and that in group A and group B was 4.2 years and 2.5 years, respectively ($P < 0.05$). For the effect of various factors on the survival rates, see Figs.1-3.

Table 1. Comparison of basic characteristics of 108 patients with NHL.

Characteristics	Lymphocyte		*P*
	≤ 1 × 10^9/L *n* = 38 (%)	> 1 × 10^9/L *n* = 70 (%)	
Sex			> 0.05
Male	21 (55.3)	44 (62.9)	
Female	17 (44.7)	26 (37.1)	
Mean age (years)	55.6 ± 12.2	51.8 ± 10.1	> 0.05
Stage			> 0.05
I-II	21 (55.3)	45 (64.3)	
III-IV	17 (44.7)	25 (35.7)	
General symptoms			> 0.05
A	27 (71.1)	53 (75.7)	
B	11 (28.9)	17 (24.3)	
Mean corpuscular hemoglobin (g/L)	98.1 ± 20.6	129.2 ± 17.5	< 0.05
Platelet count (× 10^9/L)	104 ± 38.6	111.1 ± 32.5	> 0.05

Table 2. Effect of various factors of Cox regression analysis on overall survival rate of HNL patients.

Factors	HR (95% CI)	*P*
IPI	2.159 (1.604, 2.906)	0.000
0-1		
≥ 2		
ALC	0.141 (0.076, 0.260)	0.000
> 1 × 10^9/L		
≤ 1 × 10^9/L		
B-symptoms	1.827 (1.095, 3.048)	0.021
Negative		
Positive		
Hb	0.673 (0.401, 1.130)	0.134
> 110 g/L		
≤ 110 g/L		

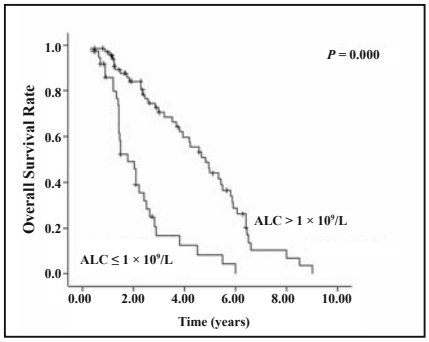

Fig.1. Overall survival curves of NHL patients with ALC ≤ 1 × 10^9/L or > 1 × 10^9/L.

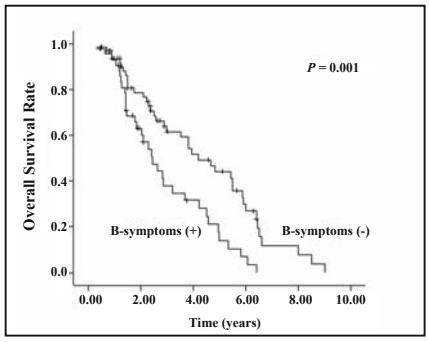

Fig.2. Overall survival curves of NHL patients with or without B-symptoms.

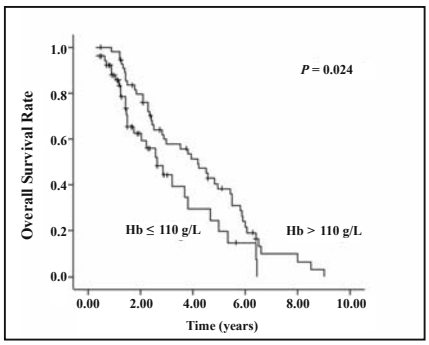

Fig.3. Overall survival curves of NHL patients with Hb ≤ 110 g/L or > 110 g/L.

Multivariate analysis

The ALC and Hb levels, B-symptom status, and IPI were included in the multivariate analysis, and the ENTER method was used for analysis of the variances. The analytic results indicated that, exclusive of Hb, the other 3 parameters were independent prognostic factors of NHL patients. For details of the results, see Table 2.

Discussion

NHL has shown its significant heterogeneity through the cellular origins of the disease, through gene expression, genetic features, immunophenotype, clinical characteristics, and therapeutic reactions among other ways. So far, it has been found that a variety of factors correlate with the prognosis of NHL patients. With continued developments in molecular biology, quite a few biological markers of NHL have been found to be closely related with the prognosis of the disease. For example, utilization of the gene expression spectrum may identify the origin of the malignant cells and help predict the prognosis of NHL patients. However, owing to limitations in technology as well as technical conditions, it is difficult clinically to utilize molecular biological markers of NHL for the prediction of prognosis in individual cases. A simple and feasible prognostic indicator could be more practical for clinical use. In the clinical setting, the international prognostic

index (IPI) is usually used to evaluate the prognosis of NHL patients. IPI is a relatively simple and practical parameter, which includes 5 factors, i.e. age over 60 years, stage-III or IV, at least 1 extra-nodular lesion, whether ambulatory or bound to bed or level of care of daily life needed, and rise in serum LDH. The grouping is made based on the IPI of cases, i.e. the low risk (0-1), moderately low risk (2), moderately high risk (3) and high risk (4-5) groups. Our study showed that the IPI was a readily available independent prognostic indicator of NHL, which was similar to the results from most of the previous studies. It was also shown in our study that besides the simple and practical IPI, ALC and B-symptom status at admission were also independent prognostic indicators of NHL patients, and that these parameters can be easily carried out in clinic.

In our study, it was found that cases with a decreased ALC at admission accounted for 35.2% of the total. Anemia and thrombocytopenia were found in 29.6% and 28.3% of the cases, respectively. NHL accompanied with B-symptoms accounted for 26.9%. It was reported by Talaulikar et al.[3] that a decreased ALC occurred in 35.8% of the 165 patients with diffuse large B-cell lymphoma 1 month before the final diagnosis. Recently, Ray-Coquard[4] also reported that there was a decrease in ALC in 27% of diffuse large B-cell NHL patients before treatment. Hou et al.[5] analyzed the hemograms of 203 NHL patients at admission, and the results from his study revealed that pancytopenia was found in 34.1% of patients, anemia in 55.7%, leukocytopenia in 37.4%, thrombocytopenia in 35.0%, leukocytosis in 8.4%, and thrombocytosis in 6.4%. Duan et al.[6] reported that B-symptoms presented in 39.1% of NHL patients. These results demonstrate that anemia, decreased ALC and B-symptoms are commonly seen in NHL cases. Our univariate analysis indicated that anemia was an unfavorable prognostic factor in NHL patients, which was in accord with the outcome of previous reports[5]. However, it was shown in multivariate analysis that anemia was not an independent prognostic parameter of NHL. Decreased ALC and complicated B-symptoms were unfavorable prognostic indicators of NHL patients that are independent of IPI, and this was similar to the results from previous reports[1-4,6]. Since there was an apparent heterogeneity among NHL cases with the same IPI value, fundamental clinical parameters should also be considered when considering prognosis, and these might be of a greater practical value in the implementation of individualized treatment regimens.

It was reported[1-4,7-11] that ALC could predict not only the prognosis of NHL patients, but also the prognosis of patients with one of the following: Hodgkin's lymphoma, multiple myeloma, acute leukemia, ovarian cancer, metastatic breast cancer, and progressive soft tissue sarcoma. The reason for a poor prognosis in patients with decreased ALC remains uncertain. It may be that a decreased ALC induces an immunological hypofunctioning, which may be unfavorable to the organism in the clearance of tumor cells remained after treatment, and, as a result, relapse and progression of the disease may easily develop.

It was suggested in our study that the ALC in peripheral blood at admission and the presence or absence of B-symptoms are prognostic indicators of NHL patients independent of IPI. Further investigation is needed to confirm the results from our research, since the number of the cases is relatively small and the treatment regimens are not the same for all patients in our study.

Conflict of interest statement

No potential conflicts of interest were disclosed.

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