Original Article

The Prognostic Role of Tumor Marker CA-125 in B-Cell non-Hodgkin's Lymphoma

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Abstract

Background: B-cell non-Hodgkin's lymphoma (NHL) is a common malignancy of lymphoid tissues. Different types of NHL show various behaviors, prognoses, and responses to treatment. Evaluation of disease activity in NHL can be helpful in managing and even increasing the patient's survey.

Methods and Results: In total, 121 patients (76 males and 45 females), and their age range were 18-53 years, were evaluated in this study. The mean level of serum carbohydrate antigen 125 (CA-125) was 89.3±18.5 u/ml, ranging from 27 to 135 u/ml. There were significant differences in International Prognostic Index (IPI) score (p=0.002), stage of the disease (p=0.006), mortality rate (p=0.02), and relapse rate (p=0.04) between patients with serum CA-125 level <35 u/ml and patients with CA-125 level >35 u/ml.

Conclusion: CA-125 seems to be a useful and reliable tumor marker for monitoring a patient with NHL. It might be the time to consider CA-125 in staging, prognostic scoring, or decision making about NHL treatment.

Keywords: B cell non-Hodgkin's lymphoma (NHL); tumor marker; CA-125; mortality rate

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Introduction

Non-Hodgkin's lymphomas (NHLs) are a group of lymphoproliferative malignancies with different behaviors and prognoses [1]. Different types of NHL vary in severity, from indolent to aggressive lymphomas [1]. Longer survival is expected in less aggressive NHLs, while aggressive NHLs can be rapidly fatal, if not treated properly [2].

NHLs can be also histologically classified as B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, hairy cell leukemia, plasma cell myeloma/plasmacytoma, extranodal marginal zone B-cell lymphoma (MALT type), mantle cell lymphoma, follicular lymphoma, nodal marginal zone B-cell lymphoma, diffuse large B-cell lymphoma, and Burkitt's lymphoma [2].

Prognosis of NHLs depends on the histological type, stage (or extent of spread) of the disease, and treatment [1-3]. However, laboratory findings and biomarkers have not played a significant role in the prediction of NHL outcomes. Therefore, measuring a biomarker as an indicator of disease activity can be very helpful in evaluating treatment efficacy.

Recently, significant attention has been paid to carbohydrate antigen 125 (CA-125), which is a biomarker for ovarian cancer follow-up [1]. It seems that lymphoma cells induce CA-125 production on mesothelial cells by releasing cytokines [4]. CA-125 has been suggested to be used as a prognostic indicator for NHLs. However, neither a cut-off point nor the survival rate has been determined for CA-125 in NHLs.

The aim of this study was to evaluate the serum CA-125 level in a large series of NHL patients and also to investigate its role in mortality prediction of patients suffering from NHLs.

Materials and Methods

This cross-sectional, descriptive study was conducted over a period of four years (from July 2005 to August 2009) on 121 patients referring to Omid hospital, Therapeutic and Educational Center of Cancer in Mashhad, with the diagnosis of B-cell NHL. Patients who had received treatment prior to the study or were not new cases of NHLs were excluded from the study. Also, patients with incomplete clinical and pathological characteristics of NHLs were excluded.

A database of demographic information (including age, gender, and race), clinical signs and symptoms, histology and stage of the disease, and laboratory data was created by collecting patient information.

Symptoms at the onset of disease including B symptoms (fever, sweating, and weigh loss) and site of lymphadenopathy were recorded for each patient. Laboratory data included complete blood count (CBC) and levels of urea, creatinine, calcium, total bilirubin, lactate dehydrogenase (LDH), aspartate transaminase (AST), and alanine transaminase (ALT) were collected and recorded in patients file. Since viral infections have been previously reported in NHL patients [5], possible infections with hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and human T-cell lymphoma virus (HTLV-I) were also evaluated for some of the patients.

According to imaging, pathology, and immunohistology results of lymph node biopsy and bone marrow aspiration, the type and stage of NHL were determined, based on World Health Organization (WHO) criteria [6]. The International Prognostic Index (IPI), in accordance with age, stage of the disease, number of extranodal sites, performance status, and LDH level [2], was calculated for each patient. Serum CA-125 level was also measured, using ELISA (CanAg-Swedwn) test. Participants in this study were followed-up at given intervals and were divided into four groups (good, fair, ill, dead) during the last check-up. According to the assumed normal range of CA-125, which is up to 35 u/ml, patients were divided into two groups with CA-125 level lower and higher than 35 u/ml (group 1 and 2), respectively.

The patients were informed about the main objectives of the study and they filled out a consent form before participating in the study. The study was approved by the ethics committee of Mashhad University of Medical Sciences.

SPSS version 16 was used for statistical analysis. Descriptive data were presented as mean ± standard deviation (mean±SD). Kolmogorov-Smirnov test indicated the normal distribution of the data. Hence, statistical procedures were performed, using independent sample t-test for two groups of patients with CA-125 level higher and lower than 35 u/ml, respectively.

Survival analysis using log-rank test was performed for evaluating the serum level of CA-125 and NHL outcomes. The significance of survival difference was also examined. Pearson's correlation test was performed for evaluating the strength of association between CA-125 and the recorded data. The significance level was considered less than 0.05, with a confidence interval of 95%.

Results

In total, 121 patients (76 males and 45 females, 18-53 years old) with B-cell NHLs were evaluated in this study. The mean serum CA-125 level was 89.3±18.5 u/ml (ranging from 27 to 1356 u/ml).

According to the suggested cut-off point of 35u/ml for CA-125, serum CA-125 levels of 69 (57%) and 52 (43%) of the patients were lower and higher than the determined point, respectively. The

Table 1. It shows frequency, gender, B symptoms, relapse rate, and mortality rate in NHL patients with serum CA-125 level <35 u/ml and patients with CA-125 level >35 u/ml.

	CA-125<35u/ml	**CA-125>35u/ml**
Frequency	57%	43%
Gender	46.2% male, 53.8% female	53.8% male, 46.2% female
B symptoms	46.4%	79.6%
Relapse Rate	14.9%	32.6%
Mortality rate during four years	21.5%	41.3%

Table 2. It shows the IPI score of patients with serum CA-125 level < 35 u/ml and patients with CA-125 level > 35 u/ml.

	Low	Low intermediate	High intermediate	High
CA-125 <35u/ml	57.8%	28.1%	7.8%	6.2%
CA-125>35u/ml	23.9%	41.3%	26.1%	8.7%

Table 3. It shows NHL staging in patients with serum CA-125 level < 35 u/ml and patients with CA-125 level > 35 u/ml.

	Stage I	Stage II	Stage III	Stage IV
CA-125 <35u/ml	49.3%	34.3%	11.9%	4.5%
CA-125>35u/ml	22.4%	36.7%	22.4%	18.4%

serum CA-125 level in 40 (53.8%) of male patients was higher than 35 u/ml, whereas 21 (46.2%) of female patients had a serum level higher than 35 u/ml; no significant difference was observed between the two genders (p>0.05) (Table 1).

Out of 69 patients with serum CA-125 level lower than 35 u/ml, 32 patients (46.4%) had B symptoms (fever, sweating, and weigh loss), whereas 40 patients (76.9%), out of 52 cases with serum level higher than 35 u/ml, had B symptoms. A significant association was observed between the high level of CA-125 and B symptoms (p=0.001). In addition, the IPI score was significantly different in two groups of patients with normal and high levels of CA-125 (p=0.002) (Table 2).

In total, 10 (14.9%) and 17 (32.6%) of the patients with CA-125 lower and higher than 35 u/ml experienced relapses, respectively. A significant difference was found between the groups in terms of relapse rate (p=0.042).

In a total of 67 patients with serum level of CA-125 lower than 35u/ml, 33 patients (49.3%) were in stage I, 23 (34.3%) were in stage II, 8 (11.9%) were in stage III, and 3 (4.5%) were in stage IV. However, out of 46 patients with CA-125 higher than 35 u/ml, 11 patients (22.4%) were in stage I, 18 (36.7%) were in stage II, 11 (22.4%) were in stage III, and 9 (18.4%) were in stage IV. There was a significant association between high level of CA-125 and the stage of the disease (p=0.006) (Table 3).

The CA-125 serum level was compared between the two groups of patients with or without B symptoms and a significant difference was observed (p=0.026).

Nineteen (41.3%) out of 46 patients with CA-125 higher than 35 u/ml were died during the study. However, the mortality rate of patients with CA-125 lower than 35 u/ml was 21.5% (14 out of 65 patients). A significant difference was observed between the mortality rate of these two groups (p=0.025). According to the odds ratio (OR), the risk of mortality increased by about two times in patients with serum CA-125 level higher than 35 u/ml (OR=2.56).

The log-rank test during the 20-month follow-up after disease diagnosis showed that patients with serum CA-125 level lower than 35 u/ml had better outcomes. However, after 35 months of follow-up, the difference in the mortality rate decreased.

Discussion

CA-125 is a glycoprotein with a molecular weight of about 200 Kilo Dalton (KD) [7]. CA-125 is presented on the cell surface of mesothelial cells, gastric mucosa, colon, female urogenital tract, and ovarian germinal epithelium [2]. This protein has been used as a tumor marker, particularly for the follow-up of ovarian cancer. However, elevation in serum CA-125 level has been reported in other malignancies including gynecological adenocarcinomas, lymphomas, malignant mesotheliomas, immature teratomas, and carcinomas of pancreas, colon, breast, and lung [2, 4].

In the current study, significant differences in IPI score, stage of the disease, mortality rate, and relapse rate were observed between patients with serum CA-125 level < 35 u/ml and patients with CA-125 level > 35 u/ml. Similarly, in 1998,

Lazzarino et al. indicated that high CA-125 level in 157 NHL patients was associated with advanced stage of disease, aggressive histology, mediastinal and abdominal involvement, and extranodal extension [8].

In the current study, we observed a significant correlation between CA-125 level and stage and prognosis of NHLs. In 2005, Dileki et al. also showed that CA-125 can be used as a predictive prognostic marker in advanced NHLs [9]. They suggested that serum CA-125 level could be a reliable biological marker for the staging and re-staging of patients with NHLs and even monitoring the patient's response to treatment [9].

In 2005, Batlle and colleagues evaluated CA-125 as a marker for assessing the patient's response to treatment in subjects with NHLs; they suggested the use of CA-125 in monitoring patients with NHL [10]. Birgen et al. also showed that high CA-125 level would return to the normal range four weeks after chemotherapy in patients with complete remission [11]. Moreover, Zacharos et al. demonstrated that high CA-125 level was correlated with treatment failure and relapse [12]. In another study, CA-125 was suggested as a reliable marker for staging, assessing tumor activity, and survey in patients with NHLs [13]. Bonet et al. showed that CA-125 level had a significant correlation with some features of more aggressive diseases; however, it was not considered a standard prognostic marker in the management of patients with NHL [14].

Russo et al. also showed that complete remission reduced in patients with high CA-125 level. According to a long-term follow-up, they indicated that the survival rate of patients with CA-125 level lower than 35 u/ml at diagnosis would be 92% [15].

Conclusion

Serum CA-125 is a non-invasive and cost-effective biomarker, which can be considered for evaluating NHL prognosis and even evaluating the patient's response to treatment. Measurement of CA-125 level, as a simple and reliable biomarker, can help improve the screening and follow-up of patients with NHLs. However, this biomarker has not been included in the staging and prognostic scoring of NHL. It seems that it is time for CA-125 to be included in NHL staging for better decision-making about the treatment.

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Conflict of Interest

The authors declare no conflicts of interest in the present study.

Authors' Contribution

Mitra Ahadi, Mehdi Farzadnia, and Hamid Reza Raziee analyzed the data. Naser Tayebi Meybodi, Sakineh Amouian, and Bahram Memar interpreted the results. Amir Aledavood and Sedighe Noori revised the manuscript, and Soodabeh Shahid Sales and Samira Mohtashami translated the manuscript.

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