

Association between Lactate Dehydrogenase Levels to the Response of Non-Hodgkin Lymphoma in Elderly Patients Who Treated with First-Line Chemotherapy in Sanglah General Hospital

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Abstract

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BACKGROUND: Non-Hodgkin Lymphoma (NHL) is a malignant haematological disease originates in the lymphocytes, caused by an abnormality in lymphocytes development which forms a tumour and may become cancer. Chemotherapy is the main treatment modality for aggressive lymphoma, but only a few patients achieve remission. Several factors such as age, clinical stadium, number of extranodal regions, and Lactate Dehydrogenase (LDH) level played a role in determining response to chemotherapy.

AIM: To measure the association between LDH levels to prognosis of NHL in elderly patients who treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone chemotherapy in Sanglah General Hospital.

METHODS: This study used a retrospective descriptive study on elderly NHL patients in Sanglah General Hospital from January until December 2014. The evaluation was measured using the IPI score to determine the prognosis of patients. Demographic data, the stadium, extranodal region, LDH level, and response to chemotherapy were recorded.

RESULTS: Twenty-five patients were included in the study. The age ranged was between 61-76 years old (Mean $65,68 \pm 4,7$ years; Median 65 years). The number of male patients was 19 (76%). Diffuse Large B-Cell Lymphoma (DLBCL) is the most common histopathological structure observed on the patients (68%). LDH levels were normal in 51.6% of the patients and considered high in the rests (48.4%). Results of the chemotherapy were a good response in 72.2%. Compared to the patients who showed complete response to chemotherapy, patients with no response (partial response and progression) had significantly higher levels of LDH (OR: 13,1; 95%CI: 1,36-126,30; $p = 0,001$).

CONCLUSION: Non-Hodgkin Lymphoma in elderly patients with no response to chemotherapy had significantly higher levels of LDH than patients with complete response.

Introduction

Lactate dehydrogenase (LDH) is a metabolic enzyme widely expressed in different tissues and is detectable in serum, which catalyses the interconversion of pyruvate and lactate during glycolysis and gluconeogenesis [1]. Since a long time, it has been observed that a high level of serum LDH is seen in patients with different malignancies. Increased LDH levels have been reported in solid tumours, leukaemia and diffuse lymphoma, particularly Burkitt's lymphoma, although correlation has been established

with any specific neoplastic disease or with any clinical or histologic parameter. The elevation of LDH in the blood is a relatively nonspecific phenomenon; however, it has been recognized as a tumour marker, as it reflects tumour burden and cellular turnover in several aggressive malignancies, including germ cell tumours [2], sarcomas [3], [4] and non-Hodgkin lymphoma (NHL) [5], [6].

Patients with elevated serum LDH at the time of initial diagnosis have inferior survival outcomes, compared to those with normal LDH levels. Therefore, LDH has been a component of the International Prognostic Index (IPI) [7], a clinical tool for predicting

the prognosis of patients with aggressive NHL. However, the role of serum LDH beyond initial diagnosis, i.e. during active chemotherapy and the post-treatment follow-up period, has not yet been well defined.

In this study, we conducted a retrospective analysis of the prognostic role of serum LDH after the treatment of elderly patients within a homogeneous disease population of NHL, undergoing a standard treatment, three weekly treatments of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) immunochemotherapy.

Material and Methods

Among the patients who fulfilled the inclusion criteria, patients who underwent LDH testing after R-CHOP therapy were selected. The LDH level was tested no more than 5 days after therapy. This study used a retrospective descriptive study on elderly NHL patients in Sanglah General Hospital from January until December 2014. The evaluation was measured using the IPI score to determine the prognosis of patients. Demographic data, histopathology, ECOG performance status, standard IPI, LDH level, and response to chemotherapy were recorded. We used RECIST (Response Evaluation Criteria in Solid Tumours) criteria for response therapy result.

Results

Twenty-five patients were included in the study. The age ranged was between 61-76 years old, with mean $65,68 \pm 4,7$ years and median 65 years. The number of male patients was 19 (76%), and female patients were 6 (24%). A summary of the baseline characteristics of the entire patient population and the groups is shown in Table 1.

Table 1. Patient characteristics

Characteristics	Number of Patients (n = 25)	Percentage
Gender		
Male	19	76%
Female	6	24%
Age, years		
Median (range)	65 (61-76)	
> 65	11	44%
≤ 65	14	56%
LDH		
Normal	13	51,6%
High	12	48,4%
ECOG performance status		
0-1	15	60%
2-4	10	40%
Standard IPI		
Low	10	40%
Low-intermediate	7	28%
High-intermediate	6	24%
High	2	8%
Tumor response		
Complete response	18	72%
Partial response	5	20%
Progression	2	8%

ECOG = Eastern cooperative oncology group.

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common histopathological structure observed on the patients (68%), continued with follicular lymphoma (20%), diffuse mixed small and large cell (8%), and large anaplastic cell (4%) (Figure 1).

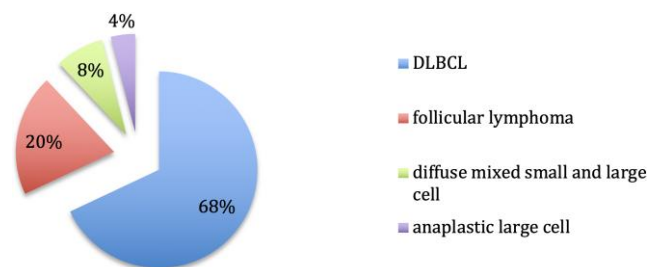


Figure 1: Histopathology of NHL elderly patients

LDH levels were normal in 51.6% of the patients and considered high in the rests (48.4%). Results of the chemotherapy were complete response is 72.2%, a partial response is 20%, and progression tumour is 8%. Because we used a t-test, so patient with partial response and progression tumour, we count in one group to no response therapy (Table 2).

Table 2: Difference of LDH Level between response and no-response patient

Groups	N	LDH (Mean ± SD)	t	t-test	p
No Response		7 781.63 ± 25			
Complete Response	18	444.30 ± 21	7.47		0.001

Compared to the patients who showed good response to chemotherapy, patients with no response had significantly higher levels of LDH (OR: 13,1; 95%CI: 1,36-126,30; p = 0,001) (Table 3).

Table 3: Association between LDH level and therapy response

LDH Level	Therapy Response		Total
	No Response	Complete Response	
High	6 (42.8%)	8 (57.7%)	14 (56%)
Normal	1 (9%)	10 (91%)	11 (44%)
Total	7 (27.8%)	18 (72.2%)	25 (100%)

Discussion

Increased total serum LDH is commonly interpreted as reflecting high tumour burden or tumour aggressiveness. Increased serum LDH has a major prognostic as well as diagnostic significance in a patient with NHL, and total serum LDH is one of the parameters of International Prognostic Index (IPI) used in a patient with NHL [1], [8].

Notably, the prognostic role of serum LDH in oncology has long been recognised. LDH is a key enzyme in the process of energy production in cancer cells; it catalyses the conversion of pyruvate to lactate

in hypoxic conditions [9], [10], [11]. Since its function in anaerobic metabolism, cancer cells grow even after their rapid proliferation that leads to low-oxygen conditions in the tumour microenvironment [12], [13]. Thus, LDH plays an important role in tumour progression and maintenance.

In non-Hodgkin's lymphoma, there has been only a low number of studies on serum LDH as a prognostic factor. Ferraris et al., in a study of 41 patients, reported that an elevated serum LDH was correlated with a shorter survival in all the histological types. In another study, Schneider et al. found that pretreatment serum LDH was the single most important prognostic variable for survival in 30 patients with diffuse HL [14], [15]. We analysed 25 consecutive elderly patients with NHL. After the R-CHOP Chemotherapy, serum LDH was high in 14 patients (%). Compared to the patients who showed a good response to chemotherapy, patients with no response had significantly higher levels of LDH. In our study, patients with increased LDH (more than 250 U/l) experienced a poorer response to therapy.

This study had several limitations. The enrolled patients were restricted to one local hospital, and the sample was relatively small to justify the effect of multiple clinical features on survival. The prognostic value of LDH level should be evaluated in a larger, multicenter setting.

In conclusion, non-Hodgkin Lymphoma (NHL), a cancer of lymphocytes with a preponderance in sixth to the seventh decade of life range, should be paid on the use of additional parameters like LDH levels, estimation of which can be used for prognostic evaluation of patients with NHL. NHL patients with no response to chemotherapy had significantly higher levels of LDH than patients with good response patient.

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