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Serum Lactate Dehydrogenase (LDH) as a Prognostic Index for Non-Hodgkin's Lymphoma*

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Abstract—*According to pretreatment values of serum lactate dehydrogenase (LDH), 113 consecutive patients with non-Hodgkin's lymphoma were divided into three levels: level 1 (within normal range) with LDH less than 250 U/l; level 2 (moderately increased) with LDH between 250 and 500 U/l; level 3 (highly increased) with LDH more than 500 U/l. LDH was elevated in 46 of 113 patients (41%). Normal values of LDH were associated with a better response to therapy and a longer survival, independent of histological type and clinical stage, with one exception; in stage IV patients conclusions could not be drawn concerning the response to therapy (complete remission occurred only in 8 of 44). Even though level 2 patients behaved slightly better than level 3 patients, no statistical difference has been observed between the two levels. Accordingly, serum LDH can be considered a useful predictor of response to therapy and of survival in non-Hodgkin's lymphoma.*

INTRODUCTION

AN INCREASED level of serum lactate dehydrogenase (LDH) represents a common finding in many diseases (hemolytic anemias, active hepatitis, myocardial infarction ...) [1]. It has also been suggested as an indicator of active disease in several different tumors [2]. Brereton *et al.* [3] and Glaubiger *et al.* [4] described LDH as a prognostic index in patients with Ewing's sarcoma; Boyle and Samuels [5], Wampler and Hazra [6] and Lippert and Javadpour [7] underlined its value in the follow-up of patients with testicular cancer; Anderson *et al.* [8] and Arsenau *et al.* [9] noticed that serum LDH is proportional to tumor bulk and can predict prognosis both in African and in 'non-epidemic' Burkitt's lymphoma. More recently, Ferraris *et al.* [10] and Schneider *et al.* [11] studied serum LDH level as a predictive index of survival in patients with non-Hodgkin's lymphoma (NHL). This study was undertaken to clarify whether the pretreatment LDH level may be a prognostic index of therapeutic response and survival in NHL.

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MATERIALS AND METHODS

One hundred and thirteen consecutive previously untreated patients with proved histological diagnosis of NHL, referred to the Medical Oncology Department of the Padua General Hospital from January 1973 to June 1980, were included in this analysis. According to the Rappaport classification [12], the patients were subdivided as follows: 43 had well-differentiated lymphocytic lymphoma (WDLL), 48 poorly differentiated lymphocytic lymphoma (PDLL) and 22 histiocytic lymphoma (HL). There were 53 males and 60 females, aged 15–78 yr (mean, 47.5).

All patients were evaluated by physical examination, complete blood counts, chest X-ray, lymphangiography, bone marrow biopsy and aspiration, and in most cases also by laparoscopy with liver biopsy. Stage was defined by the Ann Arbor classification [13]: 27 patients were stage II, 42 stage III and 44 stage IV.

Patients with clinical signs of hemolysis, active hepatitis, recent myocardial infarction were excluded. Forty-one patients admitted before January 1976 were treated with 6 courses of MOPP [14] followed by 6 courses of ABVD [15]; after which, according to a new protocol, 72 further patients were treated with 6–8 courses of CHOP [16] followed by radiotherapy on 'bulky tumor' ('iceberg' irradiation).

The LDH assay was performed employing the Technicon SMAC (normal values, 98–230 U/l). The values used in this analysis were those obtained just prior to therapy.

The patients were divided into three levels, based on pretreatment LDH values: level 1 (within normal range) with LDH less than 250 U/l; level 2 (moderately increased) with LDH between 250 and 500 U/l; level 3 (highly increased) with LDH more than 500 U/l (Table 1).

Response to therapy

Complete remission (CR) was defined as total disappearance of every symptom, sign and/or measurable lesion for at least 2 months. The work-up for assessing CR was done very carefully, including a second bone marrow biopsy and a second laparoscopy with biopsy for patients shown to have bone marrow involvement or liver deposits.

Statistical methodology

Contigency tables were analysed using the chi-square statistic. Fisher's exact test [17] was applied to the results of the 2 × 2 table. Survival curves were calculated by the Kaplan–Meier product limit method [18] with survival time measured in months from entry into the study; for comparison of curves the log-rank test [19] was applied. All reported *P*-values refer to the two-sided tests.

RESULTS

At diagnosis LDH values were elevated in 41% (46/113) of the patients. In our series, even though level 2 patients (LDH between 250 and 500 U/l) behaved slightly better than level 3 patients (LDH more than 500 U/l), no statistically significant difference was observed either in overall response to therapy ($P = 0.210$) or survival ($P < 0.1$) between the two higher levels, and therefore they will be considered together.

As shown in Table 2, the percentage of patients with increased LDH correlates with extent of disease (increasing from stage II to stage IV, $P < 0.005$), but not with histological forms (P = NS), although the percentage of patients with increased LDH is greater within histiocytic type.

Table 1. LDH values at presentation

	No. of patients	(%)
Normal range		
Level 1 (LDH < 250 U/l)	67	(59)
Increased values		
Level 2 (250 < *P* < 500 U/l)	27	
Level 3 (LDH > 500 U/l)	19	46 (41)

Table 2. Dependence of the LDH increase on the clinical stage and on the histological form

	Clinical stages			
	II	*III*	*IV*	Total
Normal LDH	23	25	19	67
Increased LDH	4	17	25	46
$P < 0.005$	27	42	44	113
	Histological forms			
	WDLL	PDLL	HL	Total
Normal LDH	29	29	9	67
Increased LDH	14	19	13	46
P = NS	43	48	22	113

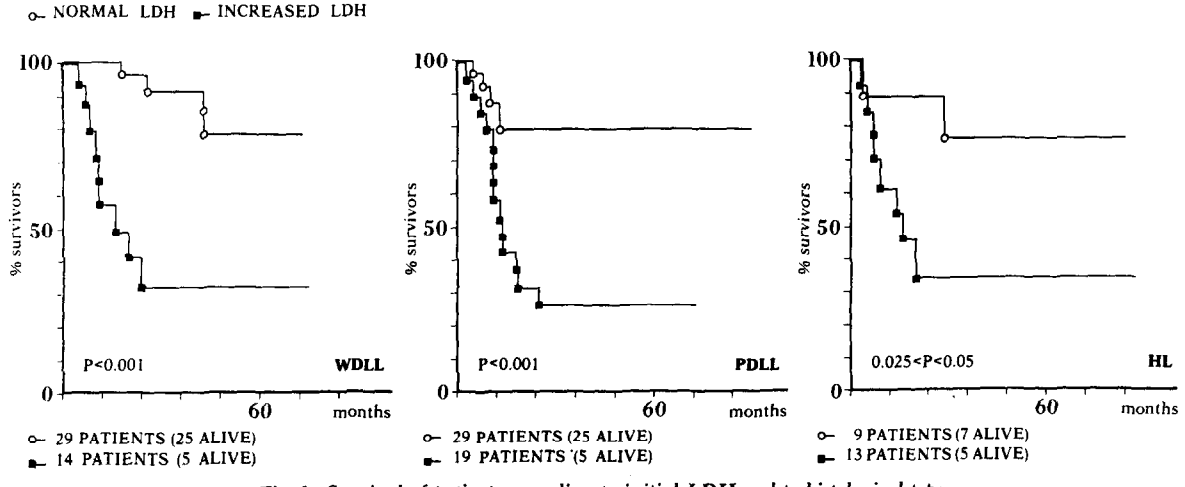

Fig. 1. Survival of patients according to initial LDH and to histological type.

Table 3. Relationships between LDH at diagnosis and probability of obtaining complete remission (within histological types)

	Complete remissions (%)		
	Normal LDH	Increased LDH	(*P*)
WDLL	13/29(44.8)	2/14(14.3)	(0.003)
PDLL	16/29(55.2)	3/19(15.8)	(0.010)
HL	5/9(55.5)	2/13(15.4)	(0.027)
Total	34/67(50.7)	7/46(15.2)	(0.001)

Table 4. Relationships between LDH at diagnosis and probability of obtaining complete remission (within clinical stages)

	Complete remissions (%)		
	Normal LDH	Increased LDH	(*P*)
Stage II	15/23(65.2)	0/4 (—)	(0.028)
Stage III	15/25(60.0)	3/17(17.6%)	(0.047)
Stage IV	4/19(21.0)	4/25(16.0%)	(0.518)
Total	34/67(50.7)	7/46(15.2%)	(0.001)

We examined our patients according to their histological classification and observed a statistically significant correlation between normal LDH values at diagnosis and: (a) a better response to therapy: in WDLL, 44.8% of patients with normal LDH attained CR versus 14.3% of patients with increased LDH ($P = 0.003$); in PDLL, 55.2 versus 15.8% ($P = 0.01$); in HL, 55.5 versus 15.4% ($P = 0.027$) (Table 3); (b) a longer survival: in WDLL 78.5% of patients with normal LDH survived 5 years versus 32.6% of patients with increased LDH ($P < 0.001$); in PDLL, 78.9 versus 26.3% ($P < 0.001$); in HL, 76.2 versus 34.6% ($P < 0.05$) (Fig. 1).

Survival and response to treatment also showed a correlation with clinical stages; the analysis was repeated within clinical stages and we observed the following relationships: (a) regarding response to treatment: stage II patients did not respond to treatment significantly better than stage III patients ($P = 0.531$), while the latter had a CR rate significantly higher than stage IV patients ($P = 0.025$). LDH maintained its prognostic value within stage II ($P = 0.028$) and stage III ($P = 0.047$ but not in stage IV, whose CR were 4/19 with normal LDH versus 4/25 with increased LDH (P = NS) (Table 4); (b) regarding survival: stage II patients lived longer than stage III ($P < 0.05$) and the latter experienced a better survival than stage IV patients, even if the difference is not statistically significant ($P < 0.1$). LDH maintained its prognostic value also in stages II ($P < 0.01$), III ($P < 0.005$) and IV ($P < 0.001$) (Fig. 2).

In our series, 50 patients (44%) who showed initial extranodal (EN) disease experienced a shorter survival: only 48% had a 5-yr survival in contrast to 76% of patients with only nodal disease ($P < 0.01$). However, also among EN patients LDH levels proved to be a significant prognostic indicator of survival ($P < 0.01$).

No statistically significant difference emerged regarding the two cited modalities of treatment when separate analyses for response to therapy ($P = 0.356$) and survival ($P < 0.5$) were performed.

DISCUSSION

The importance of serum LDH as a direct indicator of tumor burden has already been pointed out in other clinical studies [3–9]. Indeed, mechanisms for energy production involved in cell duplication require a high LDH cell content and renewal of NAD resynthesis, in

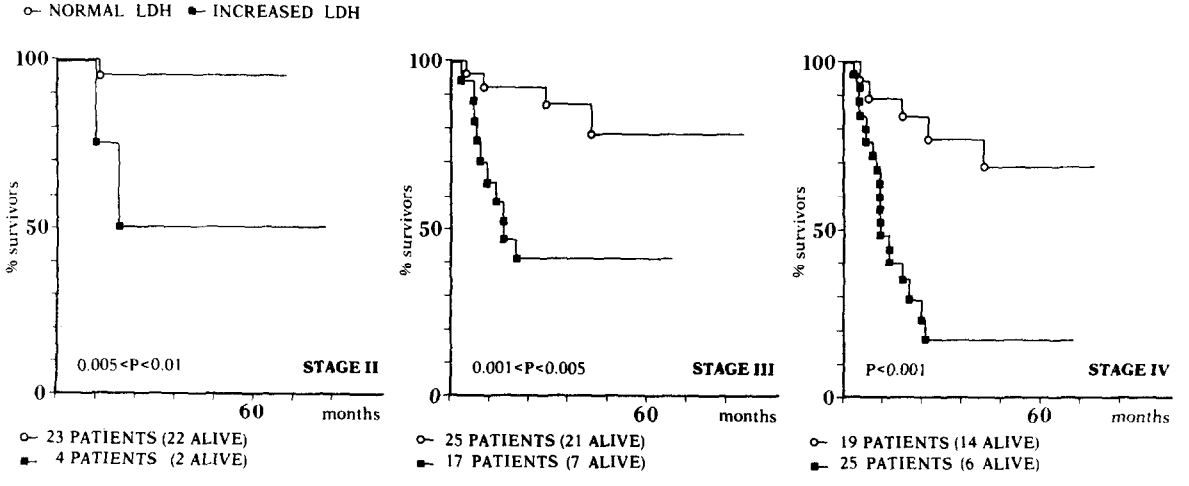

Fig. 2. Survival of patients according to initial LDH and to clinical stage.

support of a continuing glycolysis. For a given tumor bulk LDH production is conceived as being proportional to its metabolic and proliferative activity. Accordingly, high LDH production suggests either a large tumor bulk or a fast proliferation in a smaller tumor, and this could explain an aggressive course and a poorer response to therapy.

In non-Hodgkin's lymphoma there has been only a low number of studies on serum LDH as a prognostic factor. Ferraris *et al.* [10], 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.* [11] found that pretreatment serum LDH was the single most important prognostic variable for survival in 30 patients with diffuse HL.

We analysed 113 consecutive patients with NHL. At diagnosis serum LDH was elevated in 46 of 113 patients (41%). In our series, patients with increased LDH (more than 250 U/l) experienced a poorer response to therapy and a shorter survival in all the histological types and in stages II and III. No patient was in stage I. In stage IV patients conclusions could not have been drawn concerning the response to therapy as CR occurred only in 8 out of 44, while survival was correlated with LDH level also in this stage.

The present study indicates that pretreatment LDH is a useful predictor of response to therapy and survival in patients with NHL and can be used, along with other prognostic factors, to identify 'poor risk' patients in need of different therapeutic approaches.

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