The utility of lactate dehydrogenase in the follow up of patients with diffuse large B-cell lymphoma

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Background: *Serum lactate dehydrogenase is a non-specific marker for lymphoma whose prognostic significance is well established for both indolent and aggressive lymphomas at the time of diagnosis. The performance characteristics of this enzyme in predicting relapse in patients with diffuse large B-cell lymphoma has not been well studied.*

Methods: *This study compared serum lactate dehydrogenase levels in 27 patients with diffuse large B-cell lymphoma who relapsed after sustaining a complete response versus 87 patients who did not relapse. For relapsed patients, the serum lactate dehydrogenase level at relapse was compared with the level three months before (considered baseline). For non-relapsed patients, the last two levels during follow-up were compared. For statistical analysis the T-test was used to compare differences in mean values between groups. The sensitivity, specificity, positive and negative predictive values for serum lactate dehydrogenase in detecting relapse compared to confirmatory imaging were calculated.*

Results: *At relapse, only 33% patients had increases in serum lactate dehydrogenase above the upper limit of normal. The mean increase was 1.2-fold above the upper limit of normal for relapsed vs. 0.83 for those who did not relapse (p-value = 0.59). The mean increase in serum lactate dehydrogenase, from baseline, was 1.1-fold in non-relapsed vs. 1.3 in relapsed patients (p-value = 0.3). The likelihood ratio of relapse was 4.65 for patients who had 1.5-fold increases in serum lactate dehydrogenase above baseline (p-value = 0.03). The sensitivity, specificity, positive and negative predictive values of 1.5-fold increases for detecting relapse, compared to clinical and imaging findings were 0.18, 0.95, 0.55, and 0.79, respectively.*

Conclusion: *A 1.5-fold increase in serum lactate dehydrogenase, over a period of 3 months, is associated with increased likelihood of relapse from diffuse large B-cell lymphoma.*

Keywords: *Lymphoma, large B-Cell, diffuse; L-Lactate dehydrogenase; Lymphoma, non-Hodgkin; Antineoplastic agents; Follow-up studies*

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the commonest subtype of all non-Hodgkin's lymphoma (NHL) accounting for 31% of all newly diagnosed cases. Although significant advances has been made in the treatment of patients with DLBCL, especially with the introduction of rituximab in the early 1990s, less than half of patients with DLBCL can be cured with upfront chemotherapy alone. It has been proposed that early detection of relapse could improve outcomes after salvage chemotherapy because patients with advanced stage and poor performance status fare poorly[1].

Lactate dehydrogenase (LDH) is a tetrameric enzyme that converts lactate to pyruvate. The prognostic significance of elevated LDH is well established for both indolent and aggressive NHL at the time of diagnosis and is one of the factors listed in the International Prognostic index (IPI)[2]. High LDH activity at the time of lymphoma diagnosis reflects increased tumor bulk and predicts a less favorable prognosis irrespective of the histologic subtype[3]. Total serum LDH activity ≥ 2 the upper limit of normal was also correlated with increased incidence of central nervous system (CNS) involvement[4]. Despite being widely used in practice, the role of LDH in the follow-up of NHL is not well defined. The European Society for Medical Oncology recommends determining LDH levels at 3, 6, 12, and 24 months after attainment of a complete remission[5]. In the US, serial determination of LDH levels with post-treatment surveillance is widely employed also. Despite being widely used in practice, the performance characteristics of LDH, as test for detecting relapse, have not been well defined. This retrospective study aimed to define the accuracy of LDH in predicting relapse in patients with DLBCL.

Methods

The Nebraska Lymphoma Study Group Database (NLSG) was searched to identify patients with DLBCL who were treated with a rituximab-based regimen from 1995 to 2010, who received their entire care at the University of Nebraska Medical Center (UNMC), and had complete clinical follow-up data. Most patients were treated with six cycles of rituximab and

an anthracycline-based regimen; cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was the most commonly used. All patients included in the analysis had a histologic diagnosis of DLBCL centrally confirmed and provided written consent for inclusion in the NLSG database. The study was approved by UNMC institutional review board. The analysis was limited to patients who sustained a complete or a partial response (CR/PR) after upfront immunochemotherapy. All patients were followed every two months for two years after sustaining a CR/PR and then every 3-6 months for the next 3-5 years. An LDH was drawn at each follow up visit. Follow up imaging with computed tomography (CT) or positron emission tomography (PET) was not routinely performed in asymptomatic patients who did not have physical findings suggestive of relapse. An elevation of serum LDH is defined as any value above the upper limit of the normal (ULN). Because of having two different reference ranges for LDH in our laboratory, LDH level is expressed as a ratio to ULN. For the patients who relapsed, after sustaining a CR/PR, we collected the LDH level at the time of relapse and the LDH level three months prior (considered baseline). For patients who never relapsed, we collected the last two LDH levels at follow-up which had to be at least three months apart. The relative increase in LDH was compared to baseline, among the patients who relapsed vs. those who did not. The T-test was used to compare differences in means of LDH values between groups. Patients were grouped into four groups (relapsed/elevated LDH, relapsed/normal LDH, non-relapse/elevated LDH, and non-relapse/normal LDH) and sensitivity, specificity, positive and negative predictive values (PPV, NPV) for LDH in detecting relapse compared to confirmatory imaging were calculated as described previously[6-7]. A two-sided test was used in all calculations. All results were considered statistically significant with an alpha error of 5% (p-value < 0.05). Analyses were performed using SPSS software, version 19 (IBM Corp, Armonk, NY, USA).

Results

We identified 129 patients in the NLSG database who were treated during the study period; 14 patients were excluded from the analysis as their LDH levels were not available. Of the 114 studied patients, 27 relapsed and 87 did not. The median age of patients was 56 years (range: 19-85 years). Most patients had advanced disease at presentation (60% had either stage III or IV disease). The median duration of follow-up was 49 months (range: 2-168 months), the median duration of remission was 47 months (range: 2-164 months) and the median time to relapse was 19 months (range: 4-66 months). The characteristics of studied patients are summarized in Table 1. Only 12 out of 27 relapsed patients (44%) had an increase in LDH at relapse above ULN. The mean increase in LDH at relapse was 1.2-fold above the ULN for relapsed vs. 0.83 for non-relapsed patients (p-value = 0.59). The mean increase in LDH from baseline was 1.3-fold for relapsed vs. 1.1 for non-relapsed patients (p-value = 0.3). The likelihood ratio (LR) of relapse was 4.65 for patients who had 1.5-fold increases in LDH above baseline vs. those who did not (p-value = 0.03). A 1.5-fold increase at relapse was significantly associated with the presence of fever (LR = 5.74; p-value = 0.03) but not with other symptoms including drenching night sweats, anemia, or new/progressive lymphadenopathy. For all elevated LDH levels above the ULN, the sensitivity, specificity, PPV, and NPV of LDH for predicting relapse were 0.44, 0.78, 0.38 and 0.81, respectively (Table 2). For patients who had 1.5-fold increases in LDH above baseline, the sensitivity, specificity, PPV, and NPV of LDH for predicting relapse were 0.18, 0.95, 0.55 and 0.79, respectively (Table 3). Only 44 out of 114 patients (39%) had an international prognostic index of three or higher; 12 relapsed and 32 non-relapsed. These 44 patients were analyzed separately to evaluate the performance characteristics of LDH in detecting relapse in patients with high-risk IPI. For all elevated LDH levels above the ULN, the sensitivity, specificity, PPV, and NPV of LDH for predicting relapse were 0.5, 0.81, 0.5 and 0.81, respectively. For patients who had 1.5-fold increases in LDH above baseline, the sensitivity, specificity, PPV, and NPV of LDH for predicting relapse were 0.27, 0.93, 0.6 and 0.78, respectively.

Table 1 - Patient characteristics

Characteristic	
Age in years, median (range)	56 (19-85)
Male gender - n (%)	56 (49)
Caucasians - n (%)	110 (96)
KPS - median (range)	85 (60-90)
Ann Arbor Stage - n (%)	
Stage I	19 (17)
Stage II	26 (23)
Stage III	16 (14)
Stage IV	53 (46)
Extranodal disease - n (%)	
No	32 (28)
Yes	82 (72)
IPI - median (range)	**2 (0-5)**

KPS: Karnofsky performance status; IPI: International prognostic index

Table 2 - Performance characteristics - serum lactate dehydrogenase (LDH) elevated above upper limit of the normal in detecting relapse

LDH	Relapse	No relapse	Total
Elevated	12	19	31
Normal	15	68	83
Total	27	87	114

Sensitivity = 0.44; Specificity = 0.78; Positive predictive value = 0.38; Negative predictive value = 0.81

Table 3 - Performance characteristics - serum lactate dehydrogenase (LDH) when elevated at least 1.5-fold above baseline in detecting relapse

LDH	Relapse	No relapse	Total
Elevated	5	4	9
Normal	22	83	105
Total	27	87	114

Sensitivity = 0.18; Specificity = 0.95; Positive predictive value = 0.55; Negative predictive value = 0.79

Discussion

Despite being widely used in practice, the role of LDH in the follow-up of NHL is not well defined. Additionally, serum LDH may be spuriously elevated in patients with NHL due to other reasons that are not related to disease activity. In addition to spurious elevations and elevations related to the acquisition of other organ system dysfunctions, LDH elevations were reported secondary to treatment with hematopoietic growth factors and intensive chemotherapy regimens[8-9].

Our findings are, at large, in agreement with other investigators. Weeks et al. followed 215 patients with DLBCL after treatment and reported a sensitivity of elevated LDH of 42% and a specificity of 85%[10]. More recently, El-Sharkawi et al. reported their follow up data on 104 patients with DLBCL who were treated with rituximab-based chemoimmunotherapy[11]. They observed a statistically significant difference in LDH levels at relapse yet they reported a sensitivity, specificity, PPV, and NPV for elevated LDH above ULN of 0.69, 0.39, 0.14 and 0.9, respectively as a predictor of relapse. They, however, used any elevated LDH level as a criterion among all LDH levels drawn at follow up which would explain the discordance between their data and the data of this study. They concluded that elevated LDH above the ULN is not a useful marker in detecting relapse. We agree with this, as modest performance characteristics were observed for elevated LDH above ULN as a marker of relapse. However, this study demonstrated that a 1.5-fold elevation of LDH above baseline was associated with a statistically significant LR of 4.65 of relapse. Such elevation was an uncommon event in our cohort though; only nine out of 114 patients (8%).

Conclusions

A 1.5 fold elevation of LDH above baseline is a specific marker for relapse and observing such an increase would justify further workup to rule out the possibility of relapse. We agree with other investigators that LDH is a non-specific marker and our data do not support the use of LDH for follow up of patients with DLBCL who are in remission given its unsatisfactory PPV and NPV. An elevated LDH level in asymptomatic patients, which is frequently not secondary to relapse, may be associated with increased patient anxiety. A falsely elevated LDH may trigger unnecessary workup that is costly and may be associated with complications including unnecessary radiation exposure from imaging as well as radiocontrast-induced kidney injury.

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