The Correlation between Pretreatment Serum Lactate Dehydrogenase (LDH) Levels and various factors in Advanced Solid Tumor

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Abstract

Objective: This study aimed to examine the relationship between pretreatment serum LDH levels and factors in advanced solid tumor to find out information for clinical use.

Materials and Methods: This is a cross-sectional study. Data of pretreatment LDH levels in 35 patients with advanced solid tumor at Cancer Clinic, Division of Medical oncology, Department of Internal Medicine, Buddhasothorn Hospital, were collected. And each patient was followed up for 6 months.

Results: The results showed that the pretreatment serum LDH levels did not correlate with factors including age, ECOG performance status, body mass index (BMI), tumor burden, site of metastasis, resection of the primary tumor, received systemic treatment, and 6-month mortality. However, High LDH levels were correlated with liver metastasis and being untreated by systemic treatment with statistical significance. (2-tailed significance, $p = 0.001$)

Conclusion: Pretreatment serum LDH levels were not found to correlate with the above mentioned factors; nevertheless, High Pretreatment serum LDH level was found to correlate with liver metastasis and correlate with and being untreated by systemic treatment. Data yet had limitations. However, the benefits of this research can be further studied in the future to find a marker that can help to evaluate and follow-up cancer patients.

Keywords: Lactate Dehydrogenase (LDH), Advanced Solid Tumor, Correlation

Introduction

Some aggressive solid tumors, such as colon cancer and prostate cancer, have a tumor marker that is used to evaluated relapses and to follow up on the treatment. Yet, for many types of solid tumors, there is no specific tumor marker used in the clinic. At present, monitoring of cancer patients mostly still relies on patient history ,physical examination and radiological investigations, such as computed tomography scan (CT scan) or magnetic resonance imaging (MRI) as well as endoscopy and colonoscopy.

Recent evidence suggests that Lactate Dehydrogenase (LDH) is an enzyme found in nearly all living cells used to convert lactate to pyruvic acid in the metabolic partway in glycogen synthesis.[1] LDH is expressed extensively in body tissues. Because it is released during tissue damage, it is a marker of common injuries and disease such as heart failure.[2] Other roles of LDH also include acting as a hypoxic regulator in the alternative metabolism partway in cancer cells.[3] In recent years, several studies have examined the LDH levels in various cancers for clinical benefit.

At present, diagnosis and follow-up on clinical treatment using LDH as tumor marker in lymphoma and acute lymphoblastic leukemia[4], yet uncertain in malignant solid tumor cancers. Although many studies have shown that elevated LDH levels are associated with poorer prognosis[5-9], there are insufficient data available on clinical trials. For example, the study by Andreas Hermes et al.in a single institute using LDH as prognostic factors in small cell lung cancer suggested that LDH levels was

higher than 300 U/L had significantly shorter overall survival.[10]

A retrospective study on using LDH and alkaline phosphatase (ALP) levels as prognostic factor in triple negative breast cancer showed that LDH levels higher than 160.5 U/L with ALP higher than 66.5 U/L were significantly decrease disease-free survival (DFS) and overall survival.[11]

A retrospective study in single institute in Japan used LDH as prognostic factor in EGFR mutation positive non-small cell lung cancer found that patients treated with EGFR TKI, either Gefitinib or Erlotinib, with high plasma LDH (≥ 210 U/L) had significantly shorter overall survival.[12]

A study on predictive marker of LDH levels in pretreatment advanced colorectal cancer with Bevacizumab-based therapy found that in patients with higher LDH levels, there was a better correlation with treatment response, but decreased overall survival.[13]

In addition, from the meta-analysis study of Jiao Zhang et al., data analyzed from a total of 68 eligible studies that included 31,857 patients on the use of LDH in pretreatment were used in prognosis in solid tumor patients showed that elevated LDH levels were significantly associated with poorer overall survival.[14]

In previously data on serum LDH in solid tumors are still diverse in each cancer group and the cut-off point of serum LDH still varies. Therefore, using serum LDH in clinical decisions still requires further studies.

Therefore, the purpose of this study is to study the correlation between pretreatment serum LDH level in advanced solid tumor and various factors, including tumor burden, site of metastasis, resection of the primary tumor, received systemic treatment, and 6-month mortality, and to utilize such data in clinical practice, such as follow-up and surveillance of the patients with advanced cancers.

Materials and methods

This is a cross-sectional study. Patients' information collected were pretreatment serum LDH, number of metastatic site, site of metastasis, resection of the primary tumor, received systemic treatment, 6-month mortality, age, ECOG performance status and BMI. The correlation between pretreatment serum LDH and various factors were analyzed.

Population

Patients with advanced solid tumor at Cancer Clinic, Division of Medical Oncology, Department of Internal Medicine, Buddhasothorn Hospital, from January 1,2017 to April 30,2017, and each patient was followed up for 6 months after participating the study.

Inclusion criteria

Patients with advanced solid tumor aged 18 years and older and never been treated for advanced cancer.

Exclusion criteria

Patients who lost to follow-up before 6 months after participating the program.

Statistical analysis

To study the relationship between pretreatment serum LDH and various factors by correlation analysis.

Results

Firstly, there were 40 patients with advanced solid tumor in this study, but 5 patients were excluded because 4 patients were loss 6-month follow up and the other one later found to be non-metastatic cancer. Therefore, there were 35 patients participated in the study with the following data -- average age 61.97 years, average body mass index 20.41 kg/m2, serum pretreatment LDH in range of 209 - 882 U/L (normal range 240 - 480 U/L), average serum LDH 399.4 U/L, standard deviation 142.096, and the background information as shown in Table 1.

Background information of patients N= 35	number	percent (%)
ECOG performance status		
0	0	0
1	30	85.71
2	4	11.43
3	1	2.86
4	0	0
Primary tumor		
NSCLC	12	34.29
Breast	10	28.57
Colon	2	5.71
Rectum	1	2.86
Stomach	2	5.71
Hepatocellular carcinoma	2	5.71
Pancreas	1	2.86
Head and Neck	2	5.71
Thymic carcinoma	1	2.86
Soft tissue sarcoma	1	2.86
Cancer of unknown primary	1	2.86
Resection of the primary tumor		
resectable primary tumor	13	37.14
unresectable primary tumor	22	62.86
number of metastatic site (tumor burden)		
0	0	0
1	8	22.86
2	12	34.29
3	10	28.57
4	4	11.43
5	1	2.86
site of metastasis		
Lung	21	60
Liver	11	31.43
Pleura	10	28.57
Lymph node (LN)	20	57.14
Bone	13	37.14
Brain	3	8.57
Peritoneum	1	2.86
Skin	1	2.86
Ovary	2	5.71
Pretreatment serum LDH level		
Normal level	27	77.14
High LDH level	8	22.86

Table 1 : Clinical characteristics of 35 patients with advanced solid tumor

After following up each patient for 6 months, 33 patients (94.29%) received systemic treatment, 2 patients (5.71%) not received systemic treatment, they were found that 13 patients (37.14%) died and 22 patients (62.86%) stayed alive at the sixth month.

All data were analyzed to determine the relationship between pretreatment serum LDH and various factors using correlation analysis. The results indicated that LDH did not correlate with all factors including age, ECOG performance status, BMI, tumor burden, site of metastasis, resection of the primary tumor, received systemic treatment, and 6-month mortality as shown in Table 2.

		age	BMI	ECOG	Tumor burden	Resectable tumor	Site of metastasis										
							Lung	Liver	Pleura	LN	Bone	Brain	Peritoneum	Skin	Ovary	Treat	Dead
LDH	Pearson Correlation	0.116	-0.025	0.203	0.267	0.100	0.124	0.113	0.135	0.155	0.179	0.144	0.068	-0.029	-0.291	-0.332	0.168
	Sig. (2 tailed)	0.116	-0.025	0.203	0.267	0.100	0.124	0.113	0.135	0.155	0.179	0.144	0.068	-0.029	-0.291	-0.332	0.168
	N	0.116	-0.025	0.203	0.267	0.100	0.124	0.113	0.135	0.155	0.179	0.144	0.068	-0.029	-0.291	-0.332	0.168

Table 2 : Correlation analysis between pretreatment serum LDH and various factors

However, when analyzing data of 8 patients with higher LDH level (normal LDH level 240-480 U/L), it was found that 6 patients in this group had non-small cell lung cancer (75%), one had breast cancer and the other one had thymic carcinoma.

The analysis results of the relationship between higher LDH and various factors also showed that high LDH correlated with liver metastasis with Pearson Correlation 0.922, p sig. (2 tails) = 0.001, and contrarily correlated with received systemic treatment of the patient with Pearson Correlation -0.922, p sig. (2 tails) = 0.001 with statistical significance as shown in Table 3.

		Liver metastasis	Received systemic treatment
High LDH	Pearson Correlation	0.922**	-0.922**
	Sig. (2-tailed)	0.001	0.001
	N	8	8

**. Correlation is significant at the 0.01 level (2-tailed)

Table 3 : Correlation analysis between high serum pretreatment LDH and liver metastasis and Received systemic treatment

Discussion

The results of the study indicated that the pretreatment serum LDH levels in advanced solid tumors did not correlate with factors including age, ECOG performance status, body mass index (BMI), tumor burden, site of metastasis, resection of the primary tumor, received systemic treatment, and 6-month mortality. Reviewing previous literatures, there were no studies of the overall relationship between pretreatment LDH and various factors. There were only studies of the relationship between high LDH or high pretreatment LDH and prognostic factors or predictive markers in different types of solid tumor. Some studies even have not clearly separated investigation in the early stage or advance stage of cancer. Moreover, the cut-off point of high LDH in each study for clinical use also varied.

Therefore, this study merely provided overall preliminary information on applying pretreatment LDH for clinical use, yet there were no such factors related to LDH. However, when analyzing the relationship between higher LDH and various factors, it significantly correlated with the liver metastasis and non-systemic treatment. It also found that most patients with high LDH in this study (75%) usually had non-small cell lung cancer.

This was consistent with Lee DS et al.[15] who studied non-small cell lung cancer and found that pretreatment LDH did not correlated with age, gender, histology, tumor differentiate, and smoking history; but high LDH correlated with metastasis progression. In addition, there was information that non-small cell lung cancer with high LDH mostly contained LDH2.[16]

Nevertheless, there was limited information about LDH and liver metastasis in non-small cell lung cancer. The study of Wu XZ et al.(17) found that, in colorectal cancer, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), LDH, and carcinoembryonic antigen (CEA) usually were higher in patients with liver metastasis than patients without liver metastasis. LDH of more than 180 U/L can be used for screening liver metastasis, with a sensitivity of 64.3% and a specificity 64%.

A study on breast cancer also reported that alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and carbohydrate antigen 153 (CA153) were significantly higher in breast cancer patients with liver metastasis than patients without liver metastasis by using LDH higher than 174 U/L.[18]

In this study, there was a limitation as the study result showing that high LDH correlated with non-systemic treatment, the population in high LDH group had a high dispersion. This is to say there was 1 patient with highest LDH (LDH 882 U/L) did not consent to systemic treatment, while 7 patients with high LDH received systemic treatment. Thus the data obtained was still limited.

Although this study found that high pretreatment serum LDH correlated with liver metastasis factor, which was a new interesting knowledge for follow-up and monitoring for metastasis in advanced solid tumor, the data was still limited due to the small population.

Conclusion

The analysis results of this study on the relationship between high pretreatment serum LDH and liver metastasis may be useful but still has limitation as described. Therefore, to apply the information for clinical use required a further study with a larger population. The further study should study specific factors and interested cancer groups and find the optimal cut off of LDH based on the knowledge provided in this study to determine the relationship between high pretreatment serum LDH in patients with non-small cell lung cancer and liver metastasis for further clinical benefits.

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