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Pleural LDH as a prognostic marker in adenocarcinoma lung with malignant pleural effusion

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Abstract

To study the performance of serum and pleural lactate dehydrogenase (LDH) level in predicting survival in patients with adenocarcinoma lung presenting with malignant pleural effusions (MPE) at initial diagnosis.

Retrospective cohort study of the patient hospitalized for adenocarcinoma lung with MPE in year 2012.

Univariate analyses showed lower pleural fluid LDH 667 (313–967) versus 971 (214–3800), $P = 0.04$, female gender 9 (100%) versus 27 (41.5%), $P = 0.009$, never smoking status 9 (100%) versus 36 (55.3%), $P = 0.009$, and epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy 8 (89%) versus 26 (40%), $P = 0.009$ to correlate with survival of more than 1.7 year versus less than 1.7 year. In multivariate analysis, low pleural fluid LDH and female gender maintained significance. The pleural LDH level of ≤ 1500 and >1500 U/L discriminated significantly ($P = 0.009$) between survival.

High pleural LDH (>1500 IU/L) predicts shorter survival (less than a year) in patients with adenocarcinoma lung presenting with MPE at the time of initial diagnosis. This marker may be clinically applied for selecting therapeutic modality directed at prevention of reaccumulation of MPE. Patients with low pleural LDH may be considered suitable for measures that provide more sustained effect on prevention of reaccumulation such as chemical pleurodesis or tunneled pleural catheter.

Abbreviations: ECOG = eastern cooperative oncology group, EGFR = epidermal growth factor receptor, LDH = lactate dehydrogenase, MPE = malignant pleural effusion, TKI = tyrosine kinase inhibitor.

Keywords: adenocarcinoma, Asian, cancer (lung), pleura, pleurodesis, tunneled pleural catheter

1. Introduction

Up to 50% of patients with various metastatic malignancies develop para-malignant or malignant pleural effusion (MPE). MPE tend to recur rapidly after an initial thoracentesis in most patients.[1,2] Reported median survival in patients with MPE from various malignancies ranges from 4 to 7 months.[3–5] The management of these patients is 2-fold, one targeted at the cancer itself such as chemotherapy, radiotherapy, or tyrosine kinase inhibitor (TKI), and the other targeted at the drainage and prevention of reaccumulation of pleural effusion with tunneled

pleural catheter, chemical pleurodesis, pleurectomy, or pleuro-peritoneal shunt.[6–10] Among approaches for the prevention of reaccumulation of pleural effusion after initial thoracentesis, rate of reaccumulation of the pleural effusion, patient's prognosis, expandability of the lung, and patient preference are the main determinant factors for the choice of therapy.

Repeat therapeutic thoracentesis is recommended for patients with an expected survival of <1–3 months and in whom effusion reaccumulates slowly.[11] Tunneled pleural catheter is recommended for patients with trapped (unexpandable) lung and with an expected survival of <6 months.[11] Talc slurry instilled via small bore chest tube is recommended for patients with an expected survival of more than 6 months, and thoracoscopic talc insufflation is recommended for those with longer survival and when lysis of adhesions is needed.[11] However, difficulty in identifying a particular patient's survival accurately puts a limit on this method of management. Furthermore, improving survival trends for example in patients with adenocarcinoma lung treated with epidermal growth factor receptor (EGFR)-TKI necessitates greater adoption of methods that allow sustained effect on prevention of reaccumulation.

Where literature on predictors of survival in patients with MPE from mixed cancer group is available, such information in newly diagnosed lung cancer patients presenting with MPE is sparse. Most studies examining the prognostic factors affecting survival in patients with MPE have been done on mixed cancer groups. These studies have identified high pleural fluid lactate dehydrogenase (LDH) (>1500 IU/L),[12] high eastern cooperative

oncology group (ECOG) score (3–4),[12–14] high neutrophil: lymphocyte ratio (>9),[12] cancer type (lung),[12] low pleural fluid pH (<7.28),[15] and high sVEGFR-1[16] pleural fluid level as the factors predicting poor survival. In studies assessing prognostic factors affecting survival specifically in lung cancer patients presenting with MPE, high ECOG score has been described to predict poor survival, and EGFR mutation and EGFR-TKI therapy to predict longer survival.[17,18]

LDH level has been shown to be raised in cancer and predict survival.[19–23] However, their role in adenocarcinoma lung, the most common histological subtype of lung cancer, has not been studied. We studied the performance of serum and pleural fluid LDH in predicting survival in patients with adenocarcinoma lung presenting with MPE at initial diagnosis.

2. Methods

The current study was conducted on the patients hospitalized for the management of MPE as the first manifestation of the adenocarcinoma lung in year 2012. We retrospectively collected data on biomarkers such as serum LDH, and the pleural fluid analysis results, done within 24 hours of admission of these patients. Additionally, we collected data on smoking status, performance status, epidermal growth factor mutation result, type of therapy, and survival on these patients. EGFR status was established by isolating DNA from the prepared sections of the formalin fixed, paraffin-embedded tissue with the DNeasy Blood & Tissue Kit (Qiagen GmbH, Germany), according to the manufacturer's protocol. Serum and pleural fluid LDH levels were measured using the enzymatic rate method described as P to L (pyruvate to lactate) with NADH/NAD+ monitoring method. Approval from institutional review board (DSRB) was obtained.

2.1. Data analysis

We used software (SPSS, version 17; SPSS, Chicago, IL) for all statistical analyses. The results were compared using a Wilcoxon 2-sample test or Fisher exact test. P values were 2 sided and considered indicative of a significant difference if less than 0.05. Various clinical variables such as gender, smoking status, ECOG status, therapy received, biochemical variables such as serum LDH, serum C-reactive protein, and pleural fluid variables such as pleural LDH, and pleural adenosine deaminase were analyzed using the Univariate analysis and multivariate analysis.

3. Results

One hundred patients with MPE were screened. Out of these, 74 patients had MPE from adenocarcinoma lung. Clinical characteristics are presented in Table 1.

Univariate analyses showed lower pleural fluid LDH 667 (313–967) versus 971 (214–3800), $P = 0.04$, female gender 9 (100%) versus 27 (41.5%), $P = 0.009$, never smoking status 9 (100%) versus 36 (55.3%), $P = 0.009$, and EGFR-TKI therapy 8 (89%) versus 26 (40%), $P = 0.009$ to correlate with survival of more than 1.7 year versus less than 1.7 year (Table 2).

In multivariate analysis, low pleural fluid LDH maintained significance. The pleural LDH of ≤1500 and >1500 U/L showed significant discrimination ($P = 0.009$) between survival (Table 3). Based on the results of multivariate analysis and previously published evidence of association of pleural LDH of >1500 U/L with the poor survival,[12] 1500 U/L was identified as the cut-off for survival difference.

Adenocarcinoma lung with malignant pleural effusion	N = 74
Age	71 (38–92)
Females	36 (49)
Males	38 (51)
Ever smokers	35 (47.2)
Never smokers	29 (39)
ECOG status	
0–2	68 (91.8)
3–4	6 (8.1)
EGFR mutation positive (exon 19 or 21)	38 (51)
Administration of TKI as first line therapy	34 (46)
Number of deaths	49 (66)
Serum LDH level	634 (324–1868)
Pleural LDH level	930 (214–3800)
Pleural ADA level	10 (4–28)
Serum CRP level	37 (1.2–194)
Pleural LDH:S LDH level	1.5 (0.3–5.6)
Median survival (days)	238 (3–1195)
Survival > 1 year	24 (32)
Survival > 2 years	6 (8)
Survival > 3 years	3 (4)

Data presented in number (%) or median (range). ADA = adenosine deaminase, CRP = C-reactive protein, ECOG = Eastern Cooperative Oncology Group, EGFR = epidermal growth factor receptor, LDH = lactate dehydrogenase, TKI = tyrosine kinase inhibitor.

4. Discussion

Our findings show that high pleural LDH (>1500 IU/L) predicts shorter survival (less than a year) in patients with adenocarcinoma lung presenting with MPE at the time of initial diagnosis. This marker may be clinically applied for selecting therapeutic modality directed at prevention of reaccumulation of pleural effusion. Patients with low pleural LDH may be considered suitable for measures that provide more sustained effect on prevention of reaccumulation such as chemical pleurodesis or tunneled pleural catheter. Repeated therapeutic thoracentesis or best supportive care (BSC) may be reserved for those with high pleural LDH.

4.1. Survival

Median survival was 238 days (7.9 months) in our cohort with 1 year survival of 32%. The survival was higher (13.3 months) in those receiving EGFR-TKIs. This is in contrast to studies published prior to advent of TKIs. Median survival in patients with MPE from nonsmall cell lung cancer has been 6.5 to 8 months prior to the advent of EGFR-TKIs.[24] In the studies comparing survival in MPE from various cancer types, the lung cancer has been associated with poorest survival. Pilling et al[4] reported median survival of 138 days in the lung cancer patients versus 258 and 297 days in breast and malignant mesothelioma, respectively. Clive et al[12] reported median survival of 74 days in the lung cancer versus 192 and 339 days in breast and mesothelioma, respectively. The better survival in our cohort is attributable to high prevalence (51%) of EGFR mutation in adenocarcinoma and high proportion of such patients (46%) receiving EGFR-TKI therapy. Nonsmokers and females treated with EGFR-TKI had a better survival in our cohort due to greater prevalence of EGFR mutation in this subgroup consistent with previous reports describing high prevalence of EGFR mutation in

Table 2

Univariate analyses of survival.

Adenocarcinoma lung with malignant pleural effusion	Survival ≤ 1.7 years N = 65	Survival > 1.7 years N = 9	P value
Age	72 (38–92)	67 (48–78)	0.21
Females	27 (41.5)	9 (100)	0.0009
Males	38 (66)	0	–
Never smokers	36 (55.3)	9 (100)	0.009
Ever smokers	29 (45)	0	–
ECOG status			
0–2	60	8	0.55
3–4	5	1	0.55
EGFR mutation positive (exon 19 or 21)	32 (49)	6 (67)	0.42
Administration of TKI as first line therapy	26 (40)	8 (89)	0.009
Number of deaths	43 (66.1)	6 (67)	1.0
Serum LDH level	641 (324–1868)	560 (378–998)	0.30
Pleural LDH level	971 (214–3800)	667 (313–967)	0.04
Pleural ADA level	9.9 (4–28)	10.2 (5.9–17.4)	0.48
Serum CRP level	34.5 (1.2–194.1)	47.2 (1.5–126)	0.81
Pleural LDH: serum LDH level	1.5 (0.28–5.6)	1.2 (0.5–2.21)	0.32
Survival (days)	207 (3–630)	826 (718–1195)	0.0001

Data presented in number (%) or median (range). ADA = adenosine deaminase, CRP = C-reactive protein, ECOG = Eastern Cooperative Oncology Group, EGFR = epidermal growth factor receptor, LDH = lactate dehydrogenase, TKI = tyrosine kinase inhibitor.

females and never smokers in Asian population.[18,25–27] Multivariate analysis however limited the better survival to low pleural fluid LDH and female gender.

These findings are clinically relevant in the context of strategies for the prevention of reaccumulation of MPE. They highlight the need for offering methods that provide long-lasting effect on prevention of reaccumulation of MPE such as chemical pleurodesis or tunneled pleural catheter as indicated, in contrast to methods that provide only episodic or one time relief such as thoracentesis and chest drain, and do not obviate the need for seeking medical aid repeatedly for reaccumulation.

4.2. Serum and pleural fluid LDH

LDH is an omnipresent cellular enzyme, the level of that rises as a result of tissue injury in a nonspecific manner.[28,43] Hence, it is elevated in several clinical conditions.[28,43] However, a disproportionately high and isolated serum LDH is specific to certain diagnostic groups such as sepsis and cancer patients. It is a marker of poor prognosis in these conditions.[19,20,29–37,43]

High level of pleural LDH in pleural space and its relationship with poor survival has been described in mixed cancer groups although underlying mechanism is not completely understood.

Table 3

Survival difference between various levels of serum lactate dehydrogenase (LDH) and pleural LDH.

LDH level	Median survival (days)	P value
Serum LDH ≤ 800	275 (3–1195)	Ref
Serum LDH > 800	105 (19–826)	0.09
Serum LDH ≤ 900	267 (3–1195)	Ref
Serum LDH > 900	93.5 (19–826)	0.09
Serum LDH ≤ 1000	275 (3–1195)	Ref
Serum LDH > 1000	47 (19–413)	0.01
Pleural LDH ≤ 1000	321 (3–1195)	Ref
Pleural LDH > 1000	189 (23–859)	0.04
Pleural LDH ≤ 1500	306.5 (3–1195)	Ref
Pleural LDH > 1500	102.5 (3–630)	0.009

Data presented in median (range).

Upregulation of the LDH enzyme to allow preferential use of glycolysis over oxidative phosphorylation for energy by tumor cells has been described. High rate of glycolysis is advantageous to growing cells because it is capable of producing adenosine triphosphate (ATP) considerably faster than oxidative phosphorylation.[23,43] The mechanism of poor survival is the association of high LDH level with high degree of necrosis in pleural cavity. Our findings confirm the relationship between pleural LDH and prognosis in the Asian population affected by adenocarcinoma lung with MPE and indicate validity of pleural LDH as a predictor of survival in this population.[38,41]

4.3. ECOG PS versus pleural LDH

ECOG status did not show any relationship with the short or long survival in our cohort. Performance status has been used for predicting life expectancy. However, it can be affected by age of onset of cancer (e.g., younger patient may be fitter than elderly with same stage) and cancer type (e.g., lung cancer being more debilitating than breast cancer). In addition, the ECOG performance status varies with management and hence may not be suitable for predicting prognosis.[12] Two large randomized controlled trials (RCTs) evaluating treatment strategies in MPE have indicated inaccuracy of clinicians' ability in predicting survival in MPE. In the TIME2 trial, despite excluding patients with predicted survival of <3 months, 34% died within 3 months of trial entry. In another study, 17% of patients died within 30 days of trial entry who were predicted to survive >2 months.[39,40] This highlights that clinical judgement on which ECOG scale is based, alone is imprecise at estimating patient survival. Pleural LDH is more objective in that sense and may be more precise in identifying patients with poor survival.

Our study has following limitations. First, it is a retrospective single center study. Second, along with the low pleural LDH, we also found association of longer survival with EGFR-TKI therapy. Although in multivariate analysis, only low pleural LDH maintained significance, it is arguable that EGFR-TKI therapy would have contributed to longer survival. In the context of our study, this suggests that patients on TKI therapy should also be offered methods that carry the potential to have

long-lasting effect on reaccumulation of MPE such as chemical pleurodesis. However, this is debatable. Investigators from Taiwan have reported significantly better pleural effusion recurrence-free survival in an EGFR positive group treated with TKIs versus EGFR negative group regardless of pleurodesis (7.1 vs 1.1 months), and concluded that pleurodesis can be withheld in nonsmall cell lung cancer patients taking TKIs because TKIs alone can control effusion and prevent it from reaccumulating.[42]

The strengths of our study are that it addresses the specific population of MPE, that is, adenocarcinoma lung which is the most prevalent histological subtype of lung cancer, and in which the profile of survival is changing. Application of our results to this group of patients may lead to more robust outcomes.

In conclusion, pleural LDH level in patients with adenocarcinoma lung presenting with MPE at the time of diagnosis may be used to select the therapeutic modality directed at prevention of reaccumulation. This parameter in patients with rapid reaccumulation rate of pleura effusion may be used to offer methods providing sustained effect on the prevention of reaccumulation of pleural effusion such as chemical pleurodesis or intrapleural catheter as indicated, whereas chest drain alone, repeated thoracentesis, or best supportive care may be considered more suitable alternative for patients with pleural LDH >1500 IU, and slow reaccumulation rate. As survival is improving in lung cancer, future studies should seek to identify methods, or pleural sclerosing agents that can offer prolonged effect on prevention of reaccumulation.

Acknowledgements

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