Journal of Clinical Neuroscience xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical commentary

Lactate dehydrogenase as a prognostic marker in neoplastic meningitis

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ARTICLE INFO

Article history:
Received 19 October 2017
Accepted 4 February 2018
Available online xxxx

Keywords:
Neoplastic meningitis
Meningeal carcinomatosis
Lactate dehydrogenase
Prognosis
Survival

ABSTRACT

This study aimed to establish the prognostic utility of lactate dehydrogenase (LDH) levels in the cerebrospinal fluid (CSF) of patients with neoplastic meningitis (NM). Patients with a confirmed diagnosis of NM at a cancer referral center were included. Data on demographic and oncological background, clinical symptoms, diagnostic tests, treatment, and survival were analyzed. In total, 119 patients were included, 74% of whom were females. The mean age was 44.2 years at the time of cancer diagnosis and 46.6 years at the time between NM diagnosis. Primary cancers were mostly breast cancer, lung cancer, or hematologic malignancies. The mean Karnofsky performance score (KPS) was 65. Frequent clinical symptoms were visual complaints, headache, cranial neuropathy, focal weakness, and decreased awareness. Diagnosis was made based on clinical symptoms, cytological CSF analysis results, and/or magnetic resonance imaging findings. The median overall survival (OS) was 4 months (95% CI 2.48–5.52). Prognostic variables associated with a better OS were hematopoietic malignancies, KPS $\geq$ 70, absence of meningeal signs, receiving any form of treatment, normal CSF glucose levels, and normal CSF LDH levels. After bivariate analysis, high LDH in the CSF remained statistically significant as a poor prognostic indicator.

The LDH level is a useful parameter to assess the prognosis of patients with NM. Other factors associated with the prognosis of these patients were tumor type, CSF glucose levels, performance status, and receiving any form of treatment.

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1. Introduction

Neoplastic meningitis (NM) refers to the involvement of the meninges or cerebrospinal fluid (CSF) in metastases of any origin, either solid (meningeal carcinomatosis or carcinomatous meningitis) or hematopoietic (lymphomatous or leukemic meningitis) [1]. In solid tumors, the most common causes of NM are breast cancer, lung cancer, and melanoma [2–4]. Previous studies have attempted to find prognostic indicators [2], but few such indicators have been identified. Lactate dehydrogenase (LDH) is a tetrameric enzyme that increases the rate of inter-conversion of pyruvate to lactate and nicotinamide adenine dinucleotide (NAD)H to NAD^+ and has been identified as a prognostic marker and a potential therapeutic target for many tumors, including primary brain tumors [5,6]. The present study aimed to determine the prognostic utility of lactate dehydrogenase (LDH) levels in the CSF of patients with NM.

2. Material and methods

A prospectively acquired database was generated for patients who visited the neuro-oncology unit at a cancer referral center (National Institute of Cancer, Mexico) from May 2011 to November 2016. Our local scientific and ethical investigation committees (IRB) approved all interventions. Data on demographic and oncological background, functional capacity, clinical symptoms, diagnostic tests that led to the diagnosis of NM, treatment, and overall median survival (OMS) were analyzed.

2.1. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 21 software. Descriptive statistics (mean, frequency, range, and percentage) were used to describe socio-demographic variables. Kaplan–Meier curves with log-rank analysis were used to describe OMS; OMS was defined as the time between NM diagnosis and death. For comparison between groups, the chi-square test or Student's *t*-test were used according to variable type. Bivariate and

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https://doi.org/10.1016/j.jocn.2018.02.014
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Please cite this article in press as: Cacho-Díaz B et al. Lactate dehydrogenase as a prognostic marker in neoplastic meningitis. J Clin Neurosci (2018), https://doi.org/10.1016/j.jocn.2018.02.014

multivariate logistic regression analyses were also performed, and confidence intervals (CIs) were defined at the 95% confidence level. Two-tailed statistical significance was defined as p value of < 0.05.

3. Results

In total, 119 patients with NM were included, 73% of whom were females ($n = 78$). Primary cancers were most commonly breast cancer (44%), followed by hematologic malignancies (34%) and lung cancer (8%), as presented in Table 1. The mean Karnofsky performance score (KPS) at the time between NM diagnosis was 60 ± 20. Frequent clinical symptoms were visual complaints including diplopia, headache, decreased awareness/altered metal status, cranial neuropathy, and focal weakness.

To confirm NM diagnosis, magnetic resonance imaging (MRI) was performed in 97% patients and cytological CSF analysis in 93% patients (Table 2). MRI results indicated NM in 93% patients, and the mean number of lumbar punctures required to confirm the diagnosis was 2.86. Cytological CSF analysis revealed low glucose levels (<60 mg/dL) in 67% patients, very low glucose levels (<40 mg/dL) in 32%, high protein levels in 65%, positive cytology in 66%, and high CSF LDH (>40 UI/L) levels in 51%.

The studied variables that were associated with prognostic significance, including KPS (≥70 vs. < 70), solid vs. hematopoietic tumor, CSF glucose levels (<40 vs. ≥ 40 mg/dL), treatment modality, and LDH levels in CSF (<40 vs ≥ 40 IU/L), are presented in Table 3. Of the 119 patients with NM, LDH in CSF was measured in 107 (90%), and high levels were found in 55 (51%); thus 107 patients who had LDH registered were included in the MOS analyses. After bivariate analysis, high CSF LDH levels remained a significant marker of MOS, as shown in Table 4 (online). Fig. 1 shows the Kaplan–Meier curve for patients with high vs. normal LDH levels in their CSF. Multivariate Cox regression analysis showed only prognostic significance in the group that received specific NM treatment (Table 3). Hazard ratio for 2-year mortality in patients with normal vs. elevated CSF LDH was 0.158 (95% CI, 0.033–0.763) p 0.011. Factors not associated with MOS were: age, gender, clinical symptoms, line of cancer treatment, CSF glucose level, and CSF protein level (Table 5, online).

The median overall survival (MOS) was 4 months (95% CI, 2.48–5.52 months); it was 7 (95% CI, 0–15.4 months) for hematologic malignancies, 2 (95% CI, 0.24–3.76 months) for solid primary tumors; 1 (95% CI, 0–2.12 months) for lung cancer patients, and 4 (95% CI, 2.45–5.56 months) for breast cancer patients. Among breast cancer patients, luminal B type had the worst MOS 2 (95% CI, 0–9.2 months).

Table 1
General characteristics of 119 patients with neoplastic meningitis.

Median age at the time of cancer diagnosis (Years + SD)	44.2 ± 12
Age in years at the time of neoplastic meningitis (Median + SD)	46.6 ± 12
Gender	n (%)
Female	88 (74)
Male	31 (26)
<60 years	100 (84)
≥60 years	19 (16)
Primary site of cancer	
Breast	52 (44)
Hematologic	38 (32)
Lung	12 (10)
Gastrointestinal	4 (3)
Cervix uteri	4 (3)
Urologic	3 (3)
Melanoma	2 (2)
Ovarian	2 (2)
Head and neck	1 (1)
Endometrium	1 (1)
Clinical symptoms	
Visual complaint/diplopia	71 (60)
Headache	63 (53)
Decreased awareness	40 (34)
Cranial neuropathy	39 (33)
Focal weakness	34 (29)
Meningeal signs	31 (26)
Sensitive complaint	24 (20)
Ataxia	18 (15)
Seizures	14 (12)
Speech disorder	12 (10)
Vertigo	9 (8)
Abnormal movements	2 (2)

Table 2
Diagnostic tests that led to the diagnosis of neoplastic meningitis.

MRI, n (%)	**115 (97)**
Positive n (%)	106/115 (93)
CSF, n (%)	**111 (93)**
Positive cytology, n (%)	72/109 (66)
Median protein level (mg/dL)	157
High protein level (>45 mg/dL) n (%)	69/107 (65)
Median glucose level (mg/dL)	53
Low glucose level (≤60 mg/dL), n (%)	72/107 (67)
Very low glucose level (≤40 mg/dL,) n (%)	34/107 (32)
Median LDH level (IU/L)	84
High LDH level (>40 IU/L), n (%)	55/107 (51)
Mean cell count	91
≥5 cells/mm^3, n (%)	45/107 (42)
≥100 cells/mm^3, n (%)	14/107 (13)
Flow cytometry	2/111 (2)

4. Discussion

We evaluated a large series of patients with NM and found that patients with high LDH levels in CSF had poor prognosis. The primary cancer sites identified in this study were similar to that reported in previous studies [2–4,7,8]; clinical symptoms and confirmatory diagnostic tests described in our study were also similar to those previously described [8–11]. All included patients were diagnosed based on clinical symptoms, neurological examination, MRI, and/or cytological CSF analysis.

Negative prognostic factors in NM found in the present study were solid tumors, poor performance (KPS < 70), presence of meningeal signs, low glucose levels (<40 mg/dL) in CSF, no specific NM treatment, and high LDH levels in CSF. Other studies have also demonstrated that a poor performance status [12–14], low glucose levels in CSF [14], elevated lactate and albumin levels in CSF [15], no systemic therapy [7], and no intrathecal chemotherapy [13,14] are markers of poor prognosis. The National Comprehensive Cancer Network guidelines (Version 1.2017 – August 18, 2017) consider patients with NM at a low risk if their KPS is > 60, with no major neurological deficits, minimal systemic disease, and reasonable systemic treatment options. The MOS for patients with breast cancer according to their subtype was similar to previous reports [16]; the triple negative subtype carried the worst prognosis.

LDH level in CSF increases after cerebral infarction, polyneuropathies, and head injury [17]. These levels are uniformly elevated in malignant primary and metastatic tumors and have been suggested to be useful in the early diagnosis of NM [18] and CNS involvement in hematopoietic tumors [19,20]. In the present study, 51% of patients with NM had high LDH levels in CSF. Elevated CSF LDH levels remained persistently significant as a negative prognostic marker after bi-variate, but not multivariate analysis.

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