

ORIGINAL ARTICLE

Treatment and prognostic analysis of patients with leptomeningeal metastases from non-small cell lung cancer

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Keywords

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Introduction

Lung cancer is still the most frequently diagnosed cancer, as well as the leading cause of cancer-related death globally.¹ Leptomeningeal metastases (LM) occur in almost 5% of non-small cell lung cancer (NSCLC) patients.² The median survival of patients without treatment is between four to six weeks.³ LM typically presents a devastating complication associated with poor survival and often represents a terminal event.⁴

Abstract

Background: Leptomeningeal metastases (LM) from non-small cell lung cancer (NSCLC) are associated with poor prognosis and optimal treatment for this subgroup of NSCLC patients is controversial. The purpose of this study is to evaluate treatment options and prognostic factors of NSCLC patients with LM.

Methods: We retrospectively analyzed data of 108 patients who had been diagnosed with LM from NSCLC between May 2006 and August 2013.

Results: The median survival time (MST) of the 108 patients was 5.3 months, and the one-year survival rate was 23.7%. Forty-nine patients received whole brain radiotherapy (WBRT) and the MST of patients who received WBRT and those who did not were 6.4 and 4.3 months, respectively. Forty-two patients were treated with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) after being diagnosed with LM. These patients had prolonged survival (11.1 vs. 4.4 months). Patients who received concomitant WBRT and EGFR-TKIs had the longest MST (12.3 months). Eastern Cooperative Oncology Group performance status, whether patients received WBRT, and/or EGFR-TKIs were independent prognostic factors for patients with LM from NSCLC.

Conclusion: WBRT, EGFR-TKIs or combined therapy, could lead to better clinical outcomes for NSCLC patients with LM. EGFR-TKIs plus WBRT has the potential to be the standard strategy for LM in NSCLC patients.

The diagnosis of LM is based on clinical features, the detection of malignant cells in cerebrospinal fluid (CSF), and findings of magnetic resonance imaging (MRI).⁵ Once diagnosed, the prognosis for LM is poor. In clinical work, treatments for LM include systemic chemotherapy (SC), intrathecal chemotherapy (IC), whole brain radiotherapy (WBRT), and epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs). However, because of the lack of evidence from randomized trials, the optimal strategy for LM in NSCLC patients is controversial.

Previous studies have reported that performance status (PS), MRI-proven LM, age, the interval between diagnosis of primary tumor and LM, and EGFR mutation status are important prognostic factors in cancer patients with LM. In this study, we retrospectively analyze the efficacy of different treatments, in an attempt to determine prognostic factors in patients with LM and identify the optimal treatment for this subgroup of NSCLC patients.

Materials and methods

Patients and treatments

Between May 2006 and August 2013, 108 patients who had been diagnosed with LM from NSCLC were considered eligible and enrolled in this cohort. The inclusion criteria were as follows: (i) histology of NSCLC, confirmed by pathological or cytological examination; and (ii) gadolinium enhancement of MRI or the detection of malignant cells in cerebrospinal fluid, or both. Patients with other tumors were excluded. Medical records were reviewed to obtain clinical characteristics, such as age, gender, histological types, performance status according to the Eastern Cooperative Oncology Group (ECOG), and the interval between diagnosis of primary tumor and LM.

The options for treatment were based on patients' age, ECOG PS, and organ function. All treatment modalities including SC, WBRT, EGFR-TKIs, and best supportive care, were evaluated and correlated with patients' treatment outcome and survival time. Subgroup analyses were used to observe differences in prognostic factors and treatment efficacy.

Statistical analyses

Statistical analyses were conducted using SPSS software (version 13.0, SPSS Inc., Chicago, IL, USA). Overall survival (OS) was calculated from the date of diagnosis of LM to the date of death, or the last clinical follow-up. Survival curves were estimated using the Kaplan–Meier curve, and comparison of differences between groups using the log-rank test. Cox proportional hazard models, with confidence intervals (CIs) calculated at a 95% confidence level, were used for multivariate analysis to identify the association between prognostic factors and survival. $P < 0.05$ was considered to indicate statistical significance.

Results

Clinical characteristics

Table 1 summarizes the characteristics of the 108 patients, including 53 men and 55 women. All patients were diagnosed

Table 1 Clinical characteristics of the 108 patients

Characteristics	No. of Patients (%)
Age (years)	
<65	65 (60.2%)
≥65	43 (39.8%)
Gender	
Male	53 (49.1%)
Female	55 (50.9%)
Histology	
Adenocarcinoma	85 (78.7%)
Non adenocarcinoma	23 (21.3%)
ECOG PS	
1–2	87 (80.7%)
3–4	21 (19.3%)
Time between NSCLC and LM	
≤12 months	78 (72.2%)
>12 months	30 (27.8%)

ECOG PS, Eastern Cooperative Oncology Group performance status; LM, leptomeningeal metastases; NSCLC, non-small cell lung cancer.

by pathological or cytological examination and enhanced MRI. Of the 108 patients, nine patients received lumbar puncture and two had malignant cells detected in their cerebrospinal fluid. The median age of the diagnosis of LM was 61 (range: 32–85); 43 patients were aged over 65 years (39.8%). The majority of patients had adenocarcinoma (78.7%), while the remaining patients had adenosquamous carcinoma ($n = 9$), squamous cell carcinoma ($n = 7$), large cell carcinoma ($n = 3$), alveolar cell carcinoma ($n = 1$) and undefined pathological type ($n = 3$). Twenty-one patients (19.3%) had a poor ECOG PS (≥ 3). LM was detected in 44 patients (40.7%) at the initial diagnosis of NSCLC; in 34 patients (31.5%) during the interval between diagnosis of primary tumor and LM, which was less than 12 months; and in the remaining 30 patients (27.8%) after 12 months (Table 1). In addition, the EGFR mutation status was evaluated in 17 patients. Of these 17 cases, 11 patients harbored EGFR mutations: four had exon 19 deletions and seven had a mutation in exon 21.

Clinical treatments

Of the 108 patients, 42 (38.9%) received either Gefitinib ($n = 19$ 250 mg/d) or Erlotinib ($n = 23$ 150 mg/d). A total of 49 (45.4%) patients received WBRT (30Gy/10fx) and 59 (54.6) received SC (27 received a platinum-based double drug regimen and 32 received second/third line chemotherapy regimens). Twelve (11.1%) received best supportive care only. Additional details are shown in Table 2.

Median survival time of leptomeningeal metastases (LM)

The median survival time (MST) of the 108 patients, from the time of first diagnosis of LM, was 5.3 months, and the one-year survival rate was 23.7% (Fig 1).

Table 2 Treatment characteristics

Characteristics	No. of Patients (%)		
	WBRT (n = 49)	SC (n = 59)	EGFR-TKIs (n = 42)
Age (years)			
<65	30	34	26
≥65	19	25	16
Gender			
Male	25	32	17
Female	24	27	25
Histology			
Adenocarcinoma	36	45	36
Non adenocarcinoma	13	14	6
ECOG PS			
1–2	44	59	34
3–4	5	0	8
Time between NSCLC and LM			
≤12 months	39	48	29
>12 months	10	11	13

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitor; LM, leptomeningeal metastases; NSCLC, non-small cell lung cancer; SC, systemic chemotherapy; WBRT, whole brain radiotherapy.

Table 3 summarizes the prognostic factors analyzed by univariate analysis. Gender, age, histology type, ECOG PS, and the time between NSCLC and LM were significant factors. MSTs were 4.7 months for men and 6.4 months for women ($P = 0.532$). MSTs for patients younger than 65 years were 5.7 months and 4.9 months for patients older than 65 years ($P = 0.494$). MSTs for adenocarcinoma patients were 6.3 months and 4.6 months for non-adenocarcinoma patients ($P = 0.879$). MSTs in patients with an ECOG PS of

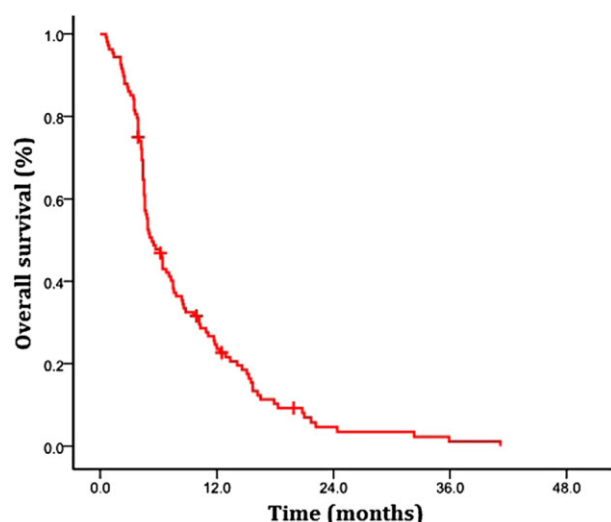


Figure 1 Overall survival for entire cohort. —, overall population (n = 108).

Table 3 Median survival time for LM

Characteristics	Median Survival (months)	P-value
Age (years)		
<65	5.7	0.494
≥65	4.9	
Gender		
Male	4.7	0.532
Female	6.4	
Histology		
Adenocarcinoma	6.3	0.879
Non adenocarcinoma	4.6	
ECOG PS		
1–2	6.8	0.001
3–4	2.8	
Time between NSCLC and LM		
≤12 months	4.9	0.281
>12 months	7.5	

ECOG PS, Eastern Cooperative Oncology Group performance status; LM, leptomeningeal metastases; NSCLC, non-small cell lung cancer.

1–2 were longer compared to patients with an ECOG PS of 3–4 (6.8 vs. 2.8 months, $P < 0.001$). MSTs in patients with an interval between NSCLC and LM >12 months were longer than patients with an interval between NSCLC and LM ≤12 months (7.5 vs. 4.9 months, $P = 0.281$). In conclusion, only ECOG PS had a positive impact on the MST of LM.

Survival time for patients with different treatments

Forty-nine patients received WBRT and the MSTs of patients who had received WBRT and those who did not were 6.4 and 4.3 months, respectively ($P = 0.022$, Fig 2a). There was no significant difference between the MSTs of patients who had received SC and those who did not (4.7 vs. 6.5 months, $P = 0.590$, Fig 2b). Forty-two patients underwent EGFR-TKIs after being diagnosed with LM. These patients had prolonged survival (11.1 vs. 4.4 months, $P < 0.01$, Fig 2c). Furthermore, patients who received concomitant WBRT and EGFR-TKIs had the longest MST among all of the patients (12.3 months). MST was not prolonged in patients treated with EGFR-TKIs combined with SC or with SC and WBRT, compared with those treated by EGFR-TKIs alone (Table 4).

Multivariate analysis of prognostic factors

In multivariate analysis, the Cox regression model was used to evaluate which factors could contribute to patients' prognosis. In this study, we found that ECOG PS, whether patients received WBRT, and whether patients received EGFR-TKIs had a significant effect on patient prognosis, while gender, age, histological type, whether patients' received SC, and the

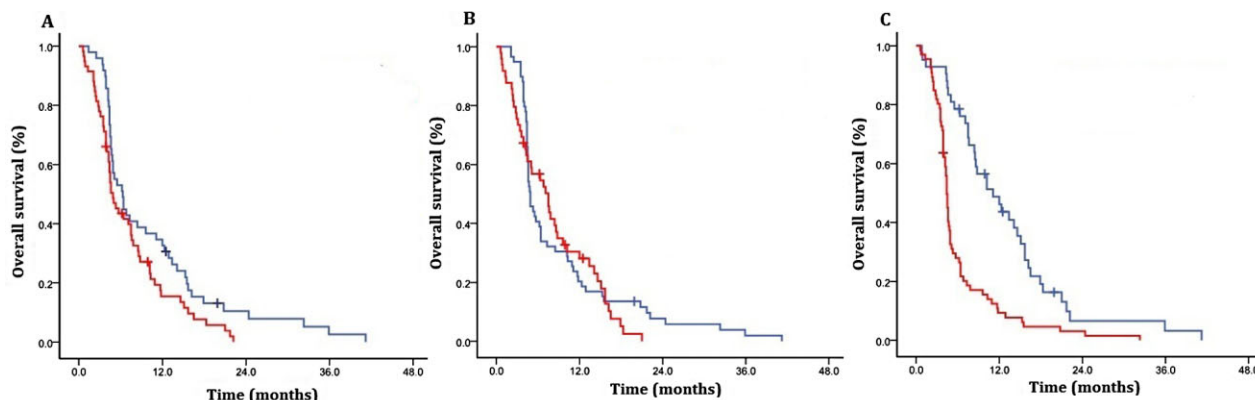


Figure 2 (a) Survival of patients who received whole brain radiotherapy (WBRT) compared with those who did not in entire cohort. (b) Survival of patients who received systemic chemotherapy compared with those who did not. (c) Survival of patients who received epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) compared with those who did not. (a) \square —, WBRT (N = 49); \square —, No WBRT (N = 59) $P = 0.037$; (b) \square —, Chemotherapy (n = 59); \square —, No Chemotherapy (n = 49) $P = 0.59$ (c) \square —, EGFR-TKIs (n = 42); \square —, No EGFR-TKIs (n = 66) $P = 0.001$.

interval between NSCLC and LM had no significant influence on patients’ prognosis. More details are presented in Table 5.

Discussion

LM is a devastating complication of NSCLC, and although treatment methods for LM have improved in the last decades, prognosis is still poor. Even with active treatments, such as SC, IC, and WBRT, the MST of LM is only eight to 16 months.⁶ Few randomized trials have proved the survival benefit of a specific treatment modality, and some results of previous reports are contradictory, thus, optimal treatment modalities for LM patients are still poorly defined.

SC remains the primary treatment for NSCLC patients; however, the efficacy of SC in LM patients is controversial. Park *et al.* analyzed 50 NSCLC patients who were diagnosed with LM and found that the patients who received SC had improved survival compared to those who did not receive SC

(11.5 vs. 2.1 months).⁷ Oechsle *et al.* similarly reported that LM patients who received SC had a longer survival time. They proposed that the significant impact of SC was that it not only treated LM, but also all other extra leptomeningeal tumor lesions.⁸ However, SC is not always the optimum treatment, as demonstrated by another study in LM patients, which suggested that adding SC to IC or radiotherapy would not improve patients’ survival time.⁹ Our data showed that SC was not a significant prognostic factor for LM patients. We attributed the failure of SC to the presence of the blood-brain barrier in the central nervous system, which resulted in limited concentration of chemotherapeutic drugs in cerebrospinal fluid.

WBRT is usually used as the first treatment choice for diffuse-type brain metastases. Reports have demonstrated that NSCLC patients with LM would benefit from WBRT.^{7,10} Nevertheless, WBRT is not always effective. For example, in a retrospective study by Morris *et al.*, there was no significant

Table 4 Survival time for patients with different treatments

Treatment	No. of Patients (%)	Median Survival (months)
WBRT	49 (45.4%)	6.4
SC	59 (54.6%)	4.7
EGFR-TKIs	42 (38.9%)	11.1
WBRT+SC	32 (29.6%)	5.2
WBRT+EGFR-TKIs	19 (17.6%)	12.3
SC+EGFR-TKIs	13 (12.0%)	11.1
WBRT+SC+EGFR-TKIs	9 (8.3%)	11.1
BSC	12 (11.1%)	2.4

BSC, best support care; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; SC, systemic chemotherapy; WBRT, whole brain radiotherapy.

Table 5 Multivariate analysis of prognostic factors

Predictor factor	RR	95% CI of RR	P value
Age	0.986	0.965–1.007	0.188
Gender	1.040	0.683–1.585	0.854
Histology	1.048	0.604–1.818	0.867
ECOG PS	0.210	0.111–0.399	0.000
Time between NSCLC and LM	0.808	0.596–1.097	0.172
WBRT	0.588	0.375–0.920	0.020
SC	0.842	0.574–1.392	0.273
EGFR-TKIs	0.215	0.125–0.371	0.000

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; LM, leptomeningeal metastases; NSCLC, non-small cell lung cancer; RR, relative risk; SC, systemic chemotherapy; WBRT, whole brain radiotherapy.

difference in MST between patients who received WBRT and those who did not.¹¹ In this study, patients who were treated by WBRT had a longer survival. After the failure of WBRT, further analysis determined that EGFR-TKIs were a viable alternative for LM patients.

EGFR-TKIs have been widely used for the treatment of NSCLC patients in clinical work. The clinical benefit of EGFR-TKIs is related to the activation of mutations in exons 19 or 21 of the EGFR gene.^{12,13} Several reports have indicated that EGFR-TKIs are the key factor to improve survival of NSCLC patients with LM. A case report of a 40-year-old NSCLC patient with carcinomatous meningitis showed that his neurological symptoms disappeared within two weeks after gefitinib treatment.¹⁴ A phase II study of 48 patients reported an MST of patients treated with erlotinib of 18.9 months.¹⁵ Katayama *et al.* found that low-dose (150 mg/d) erlotinib had a similar efficacy to high-dose (1250 mg/d) gefitinib for the treatment of NSCLC patients with LM.¹⁶ Masuda *et al.* also proved that erlotinib therapy could improve the clinical symptoms of LM patients with EGFR mutations.¹⁷ In this study, we found that when NSCLC patients with LM were treated with EGFR-TKIs (erlotinib or gefitinib), MST was prolonged up to 11.1 months. In addition, while there were only 11 patients harbouring EGFR mutations, 42 patients received EGFR-TKI treatment, and results indicated that patients without EGFR mutations could benefit from EGFR-TKI treatment.

Recent reports have suggested that EGFR-TKIs plus WBRT therapy may be a more effective treatment for NSCLC patients with LM. A phase II trial of erlotinib plus WBRT therapy in a patient with brain metastases from NSCLC indicated that MST was improved to 11.8 months, and patients with EGFR mutations had a longer MST compared to those with wild-type EGFR.¹⁸ Our data, along with others' evidence, strongly demonstrates that EGFR-TKIs plus WBRT could be considered as the first choice for NSCLC patients with LM. One reason for the greater effectiveness of EGFR-TKIs plus WBRT is that WBRT can injure the blood-brain barrier, thereby increasing the concentration of EGFR-TKIs in cerebrospinal fluid.

Several studies have examined the impact on prognosis of NSCLC patients with LM. Waki *et al.* reported that poor PS and MRI-proven LM were associated with a poor prognosis.¹⁹ Oechsle *et al.* demonstrated that age >50, PS ≤ 70%, an interval between diagnosis of primary tumor and LM ≤ 12 months all presented negative prognostic factors.⁸ LEELLee *et al.* reported that mutant EGFR in NSCLC patients was an independent prognostic factor for a better treatment response.²⁰

Our study analyzed varieties of prognostic factors of NSCLC patients with LM. ECOG PS and whether patients received WBRT and/or EGFR-TKIs were independent prognostic factors for NSCLC patients with LM, while gender, age,

histological type, SC, and the interval between NSCLC and LM had no significant influence on patients' prognosis.

Conclusion

In conclusion, WBRT, EGFR-TKIs, or combined therapy could lead to better clinical outcomes for NSCLC patients with LM. EGFR-TKIs plus WBRT has the potential to become the standard strategy for NSCLC patients with LM.

Disclosure

No authors report any conflict of interest.

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