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Prolonged Survival of Non-Small Cell Lung Cancer Patients With Leptomeningeal Carcinomatosis in the Modern Treatment Era

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Abstract

Introduction: Leptomeningeal carcinomatosis (LM) is a severe complication of NSCLC historically associated with poor prognosis. New chemotherapeutic and targeted treatments could potentially impact the natural history of LM.

Methods: Patients with a pathologic diagnosis of NSCLC with LM treated at Stanford between 2003 and 2011 were identified via institutional databases and medical records. LM was defined by positive CSF for malignant cells or LM enhancement by MRI with gadolinium contrast. Retrospective, landmark analyses were performed to estimate survival. Statistical analyses performed using SAS Enterprise Guide v4.3.

Results: LM was identified in 30 patients. All cases were adenocarcinoma, 60% of patients had a known or suspected driver mutations, mean age was 58, 67% were women, 70% were non-smokers, 27% initially presented with LM, 84% received systemic treatment at or after development of LM and 53% of these patients received modern systemic therapy for their LM defined as a regimen containing pemetrexed, bevacizumab or a tyrosine kinase inhibitor.

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Conflict of Interest Statement:

None of the authors have any conflicts of interest related to the content of this manuscript.

Mean OS after LM diagnosis was 6 months (95% CI 3–12 months). Patients who received modern systemic treatment for LM had decreased hazard of death (HR 0.24, $p=0.007$).

Conclusion: In this retrospective, single institution analysis median survival with LM was higher compared with historical experience. Patients who received modern systemic treatment for their LM had particularly good outcomes. Our data provides evidence for improving survival outcomes in the modern treatment era for this difficult to treat complication.

MicroAbstract

LM is a severe complication of NSCLC historically associated with poor prognosis. New chemotherapeutic agents and targeted treatments could potentially impact the natural history of LM. Our data in 30 NSCLC patients with LM provides evidence for improving survival outcomes in the modern treatment era for this difficult to treat complication.

Keywords

Leptomeningeal Carcinomatosis; Chemotherapy; Non-Small Cell Lung Cancer

Introduction:

Of the over 220,000 cases of new lung cancer diagnosed in the United States annually, over 85% of cases are non-small cell lung cancer (NSCLC), and 30–40% of those patients will develop central nervous system (CNS) metastases¹. Parenchymal brain metastases represent the vast majority of CNS disease in NSCLC: only about 510% of these patients will develop leptomeningeal carcinomatosis (LM)^{2,3}.

LM is a devastating complication of non-small cell lung cancer historically associated with poor prognosis. A recent retrospective analysis of LM outcomes in NSCLC indicated a poor median survival for patients with LM of only 3 months and no difference in survival in patients who received whole brain radiotherapy. There was, however, a survival benefit in the small number of patients who received intrathecal chemotherapy, but this may be due to selection bias⁴. A Korean retrospective analysis showed a longer median survival for NSCLC patients with LM of 4.3 months and an overall survival benefit in patients with a good performance status who received intrathecal chemotherapy, epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) therapy or systemic chemotherapy with modern treatment⁵.

Recently approved chemotherapeutics and targeted agents have improved survival and clinical outcomes in patients with NSCLC. Newly FDA approved agents over the past decade include: the EGFR-inhibitors erlotinib and afatinib, pemetrexed and bevacizumab for non-squamous NSCLC, nab-paclitaxel and the ALK targeted agent crizotinib for patients with ALK-rearranged NSCLC. Pemetrexed improves survival in non-squamous NSCLC patients both in the frontline and relapsed/refractory setting and has activity in patients with CNS metastases^{6–9}. EGFR-TKIs substantially improve progression free survival in patients whose tumors harbor EGFR-activating mutations^{10,11}. Erlotinib, in particular, has demonstrated CSF penetration and CNS activity; pulsatile dosing schemes have been utilized to treat CNS disease with some effect^{12,13}. Bevacizumab improves survival in

patients with metastatic non-squamous NSCLC when given in combination with first-line carboplatin and paclitaxel¹⁴. Though bevacizumab is contraindicated in untreated parenchymal brain metastases, it is safe in treated stable brain metastases¹⁵. Bevacizumab also demonstrated activity in CNS choroidal metastases and is used to treat radiation necrosis of the brain and glioblastoma multiforme^{16–18}. Recent data also support the safety of this agent, and even efficacy, in patients with untreated asymptomatic brain metastases¹⁹.

These targeted agents and chemotherapeutics may alter the natural history of LM in NSCLC. We undertook this retrospective analysis to explore how adoption of these new therapies potentially improve outcomes of NSCLC patients with LM in a US population.

Methods:

Patients with a pathologic diagnosis of NSCLC with LM who were treated at Stanford University Medical Center and Clinics between 2003 and 2012 were identified via institutional databases and medical records under an approved Stanford University School of Medicine Institutional Review Board Protocol. Identified cases had pathology proven NSCLC with either positive CSF for malignant or atypical cells or LM enhancement by MRI with gadolinium contrast in the appropriate clinical context (NSCLC diagnosis with no other apparent cause of LM). Medical records were reviewed for patient demographics, pathologic characteristics, treatment regimens and clinical outcomes. Patients where molecular testing was not available, but whose tumor demonstrated radiographic response to an EGFR-TKI were defined as having “suspected” EGFR activating mutations. Known or suspected EGFR activating mutations was used since many patients in this analysis were treated with an EGFR-TKI before EGFR mutation testing to select for EGFR-TKI therapy became standard of care. Patients were considered to receive modern systemic treatment for LM if they received pemetrexed, bevacizumab and/or a tyrosine kinase inhibitor (either erlotinib, gefitinib or crizotinib) for treatment of LM.

Retrospective, landmark analyses were performed to estimate survival from the time of LM diagnosis using Kaplan-Meier method. A two sided p-value of < 0.05 was considered significant. Overall survival from development of LM and from development of initial metastatic disease was examined. Treatment for LM was defined as therapy given for LM after diagnosis as noted in the medical record. Time to LM was calculated as the time of metastatic diagnosis on imaging to time to development of LM. A limited cox-regression was performed to estimate hazard ratios (HR) of factors hypothesized to impact survival with LM. The proportionalhazards assumption was checked using Schoenfeld residuals and was found to be valid for all factors in the forms presented. Statistical analyses were performed using SAS Enterprise Guide v4.3 (Cary, NC).

Results:

The demographics and molecular alterations of the thirty identified NSCLC patients diagnosed with LM are presented in tables 1 and 2. Table 3 summarizes the treatments these patients received. Patients had a median survival of 6 months from time of LM diagnosis (95% CI 3–12 months, Figure 1a). Patients who received modern systemic treatment for

their LM (defined as either a erlotinib, gefitinib, pemetrexed, bevacizumab or crizotinib) had a prolonged survival with LM compared to patients who did not receive these treatments (Fig 1b, $p=0.003$ logrank). All patients in this cohort had adenocarcinoma histology. Mean time to development of LM from initial diagnosis of metastatic lung adenocarcinoma was lengthy at 16.4 months (95% CI: 11.3 – 21.5 months). A univariate cox-regression of pertinent factors thought to be associated with prolonged survival with LM highlights that patients diagnosed with LM at metastatic diagnosis (HR 0.063, $p=0.008$) or who received modern systemic treatment for LM (HR 0.24, $p=0.007$) had the best overall survival with LM (Table 4). Patient characteristics comparing groups who received or did not receive modern systemic treatment for LM are highlighted in Table 5. Forty-three percent of patients who did not receive modern systemic treatment received other older chemotherapy regimens and 71% received whole brain radiotherapy for LM.

Discussion:

In this single institution, retrospective analysis we observed a lengthy median survival with LM of 6 months, which compares favorably to previously published median overall survivals with LM⁴. Other recent retrospective analysis of patients with LM in the modern treatment era show similar results in an Asian patient population⁵. Our results in a US patient population provide further evidence (albeit retrospective) that clinical outcomes of NSCLC patients with LM may be improving.

The population with LM described in this analysis (Tables 1 and 2) is not the typical metastatic NSCLC population (even for lung adenocarcinoma) with high percentages of women, Asian ethnicity, non-smokers and patients with known or suspected oncogenic driver mutations. This may be partly reflective of the lung cancer population seen at our institution or may represent a population more prone to develop LM. A recently published trial of NSCLC patients with CNS metastases treated with erlotinib and concurrent whole brain radiotherapy, where a high percentage (50%) of enrolled patients had tumors with EGFR-activating mutations, also supports the hypothesis that certain lung adenocarcinoma subtypes and populations may be more predisposed to developing CNS metastases.²⁰ Patients who developed LM after initial diagnosis of metastatic lung cancer had a prolonged time to development of LM (mean 16.4 months (95% CI: 11.3 – 21.5 months)), suggesting that LM may be a late complication of advanced NSCLC in many patients and thus may occur more frequently in patient populations that often do well with treatment for long periods of time (women, non-smokers, patients with EGFR and ALK driver mutations). A similar analysis from Korea showed a prolonged time to development of LM in metastatic patients with lung cancers harboring EGFR activating mutations and treated with EGFR-TKI (mean time to LM > 21 months)²¹.

In patients who had LM at the time of diagnosis of metastatic disease, median survival with LM was particularly lengthy at 18 months. A recent analysis of another institutions experience with LM correlated intrathecal treatment (IT) of LM with increased overall survival. Only two patients in our cohort were treated with IT chemotherapy, limiting our analysis of outcomes for this treatment modality⁴. Another study from Korea showed WBRT or systemic chemotherapy was associated with improved overall survival in NSCLC patients

with LM⁵. Analysis of our cohort also suggests that patients who received systemic treatment for LM, especially with modern or targeted therapy did well with a decreased hazard of death that was statistically significant. These differences in survival comparing patients who received modern systemic therapy with those who did not could be biased due to the retrospective nature of our study, but the magnitude of the effect is noteworthy. Confounding by performance status between does not account for these differences as 56% of patients who received modern systemic therapy had Zubrod PS > 1 compared to 50% for patients who did not receive these modern therapies (Table 5). There were some differences in frequency between these treatment groups in regarding whole brain radiotherapy or suspected EGFR activating mutations, but Cox Regression did not show that they affected overall survival, though the sample size of this retrospective analysis was too small to reach a definitive conclusion (Tables 4, 5). Many of the patients who did not receive modern systemic therapy for LM received whole brain radiotherapy (71%) or older chemotherapies (43%). Multivariate analysis was not performed due to the small sample size of patients analyzed.

Conclusion:

Prospective clinical trials are difficult in this patient population. Thus, we must rely on retrospective analyses like this one and others that are limited by small sample size and biases that include: selection, lead and length time bias. Nevertheless, we see a striking lengthening of survival in patients with LM compared to historical controls, particularly in patients with LM at diagnosis who received systemic treatment and patients with LM who received modern treatment regimens—including systemic therapies with CNS activity. Thus the magnitude of the effect we observed in this retrospective analysis suggests that systemic therapy, particularly with modern agents in not heavily pretreated patients can have good survival outcomes compared with the historically poor outcomes of this uncommon complication of non-small cell lung cancer.

Clinical Practice Points:

Leptomeningeal carcinomatosis in NSCLC has historically indicated a poor prognosis. Compared to historical controls this retrospective study suggests that prognosis for these patients may be improving. Patients with LM who are naïve to treatment at the time of LM diagnosis may preferentially benefit from systemic treatment. Modern systemic treatments may be improving patient outcomes in this difficult to treat patient population.

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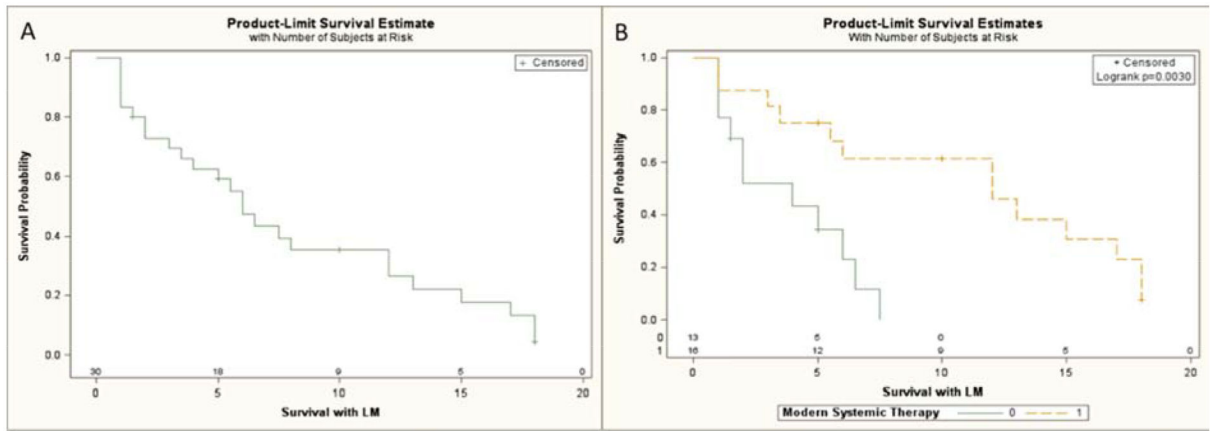


Figure 1: Overall Survival from: A) Time of LM Diagnosis of Patients Diagnosed with Leptomeningeal Carcinomatosis. B) Time of LM Diagnosis of Patients Who Received Modern Systemic Therapy for LM (Orange) Compared to Patients Who Did Not Receive Modern Systemic Therapy for LM (Green).

Table 1:

Clinical and Tumor Characteristics of NSCLC Patients Diagnosed with Leptomeningeal Carcinomatosis.

Patient Characteristic	Percent (Number/Total)
Number of Patients	30
Adenocarcinoma Histology	100% (30/30)
Women	67% (20/30)
Age (Mean)	58
Stage IV at NSCLC Diagnosis	73% (22/30)
Current or Former Smoker	30% (9/30)
LM Disease at Time of Metastatic Presentation	27% (8/30)
Diagnosis by MRI	97% (29/30)
Diagnosis by Lumbar Puncture	33% (10/30)
ECOG PS at LM Diagnosis	
- ECOG PS 0-1	46% (14/30)
- ECOG PS 2	54% (16/30)
Neurologic Symptoms	70% (21/30)
Brain metastases	
- Prior to LM Diagnosis	50% (11/22)
- At Diagnosis of LM	73% (22/30)
Race	
- Asian	53% (16/30)
- White	37% (11/30)
- Hispanic	7% (2/30)
- Not Known	3% (1/30)

Table 2:

Molecular Alterations Present in Tumor of Patients with LM. a. Suspected EGFR activating mutations defined as a patient who had a documented response to gefitinib or erlotinib on imaging in the absence of EGFR mutation testing.

Molecular Alteration	Percent (number/total)
- K-ras mutation	7% (2/30)
- Known or Suspected EGFR activating mutation ^a	43% (13/30)
- ALK translocation	7% (2/30)
- EGFR Exon 20 insertion/PI3K mutation	3% (1/30)
- None/Unknown	40% (12/30)

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Table 3:

Treatment Received in NSCLC Patients Diagnoses with LM.

Treatment	Percent (Number/Total)
Whole Brain Radiotherapy	
- Before LM	10% (3/22)
- At/During LM	63% (19/30)
Intrathecal Chemotherapy	7% (2/30)
Chemotherapy or TKI for LM	70% (21/30)
Pemetrexed or TKI or Bevacizumab at/during LM diagnosis	53% (16/30)
Pemetrexed or TKI or Bevacizumab prior to LM diagnosis	82% (18/22)
Pemetrexed or TKI or Bevacizumab at any Point in Treatment	87% (26/30)

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Table 4:

Cox-Regression of Pertinent Factors Associated With Survival With LM. a) Modern systemic treatment includes patients who received pemetrexed, bevacizumab and/or a tyrosine kinase inhibitor (either erlotinib, gefitinib or crizotinib for treatment of LM). b) Suspected EGFR activating mutations were patients who had a response to an EGFR-TKI, by imaging but were not formally tested for an EGFR activating mutation.

Variable	HR	95% CI	p-value	Number/Total
LM at Diagnosis	0.062	(0.008–0.492)	0.008	8/30
Any Systemic Treatment for LM	0.415	(0.162–1.066)	0.068	21/30
Modern Systemic Treatment for LM ^a	0.24	(0.087–0.69)	0.007	16/30
Whole Brain Radiation Treatment for LM	0.93	(0.391–2.251)	0.87	19/30
Known Or Suspected EGFR Activating Mutations ^b	0.99	(0.445–2.186)	0.97	13/30

Table 5:

Clinical and Tumor Characteristics of NSCLC Patients Whether Patients Received Modern Systemic Treatment for LM. Modern systemic treatment includes patients who received pemetrexed, bevacizumab and/or a tyrosine kinase inhibitor (either erlotinib, gefitinib or crizotinib) for treatment of LM.

Patient Characteristic	Modern Systemic Treatment (N=16)	No Modern Systemic Treatment (N=14)
Women	62% (10/16)	71% (10/14)
Age (Mean)	54	60
Current or Former Smoker	25% (4/16)	50% (5/14)
ECOG PS at LM Diagnosis		
- ECOG PS 0-1	44% (7/16)	50% (7/14)
- ECOG PS 2	56% (9/16)	50% (7/14)
Whole Brain Radiotherapy	56% (9/16)	71% (10/14)
Systemic Therapy for LM	100% (16/16)	43% (6/14)
Known of Suspected EGFR activating mutation	56% (9/16)	29% (4/14)