Original Study

Pemetrexed in the Treatment of Leptomeningeal Metastasis in Patients With *EGFR*-mutant Lung Cancer

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Abstract

The role of pemetrexed in the treatment of leptomeningeal metastasis (LM) was examined retrospectively in 110 patients with *EGFR*-mutant lung cancer. Pemetrexed use after LM was independently associated with a survival benefit for patients with LM.

Introduction: Leptomeningeal metastasis (LM), still an area of unmet need, has frequently been observed in patients with *EGFR*-mutant non–small-cell lung cancer (NSCLC). Because the antitumor efficacy of systemic cytotoxic agents against LM is unclear, we explored the role of pemetrexed in the treatment of patients with LM from *EGFR*-mutant NSCLC. **Patients and Methods:** We retrospectively reviewed the medical records of patients with LM from *EGFR*-mutant NSCLC treated between 2006 and 2016. Post-LM survival was evaluated as well as clinical factors. **Results:** In our patient cohort with *EGFR*-mutant NSCLC (n = 631), 17.4% (n = 110) developed LM. Their median post-LM survival was 5.7 months (95% confidence interval, [CI], 0.0-12.0 months). Post-LM survival was significantly longer with pemetrexed use after LM (median, 13.7 months; 95% CI, 4.1-23.2 months) than without pemetrexed use after LM (median, 4.0 months; 95% CI, 2.2-5.7 months; $P = .008$). In the multivariate analyses, no pemetrexed use after LM (vs. use) and no EGFR tyrosine kinase inhibitor use after LM (vs. use) were independently associated with a poor post-LM survival with a hazard ratio of 3.1 (95% CI, 1.5-6.3; $P = .002$) and 3.0 (95% CI, 1.6-5.8; $P = .001$), respectively. **Conclusion:** Pemetrexed use after LM was independently associated with a longer post-LM survival in patients with *EGFR*-mutant NSCLC with LM. Prospective studies are warranted to validate this finding.

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Introduction

Leptomeningeal metastasis (LM) develops as cancer cells disseminate to the leptomeninges and cerebrospinal fluid (CSF) within the subarachnoid space. It is a severe complication of advanced cancer, leading to clinical deterioration and limited survival in affected individuals. It has only a few therapeutic options with modest efficacy.[1,2] Although LM can complicate the course of any type of malignancies, non–small-cell lung cancer (NSCLC) has been the most common primary cancer developing LM.[3,4]

In patients with advanced NSCLC, patients whose tumors have activating mutations in epidermal growth factor receptor (*EGFR*) genes have been observed to have a higher incidence of LM than those with *EGFR*-wild type tumors.[5,6] The central nervous system (CNS) is a frequent site of disease progression after an initial response to EGFR tyrosine kinase inhibitors (TKIs).[7,8]

Several retrospective studies have suggested that a good performance status (PS) at the diagnosis of LM and EGFR TKI therapy after the diagnosis of LM were associated with prolonged survival in this population with EGFR-mutant NSCLC.[9] Although the use of EGFR TKIs has consistently been shown to correlate with a survival benefit, the role of cytotoxic chemotherapy in this setting has not been fully evaluated.

Recently, pemetrexed, a cytotoxic drug with multiple targets in folate metabolism, has been suggested to confer CNS activity based

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on several retrospective and phase II studies on cases with brain metastases from NSCLC.[10-15] Its role in the treatment of LM, however, remains unclear. We explored the role of pemetrexed in the treatment of patients with *EGFR*-mutant NSCLC and LM.

Patients and Methods

Patient Selection and Data Gathering

We retrospectively reviewed a consecutive database of 2002 patients with advanced NSCLC treated with EGFR TKIs between July 2006 and October 2016 at Seoul National University Hospital, from which 631 patients were identified to have sensitizing *EGFR* mutations.

Advanced NSCLC was defined as stage IIIB or IV or recurrent disease after curative surgery. EGFR TKIs were specified as gefitinib, erlotinib, and osimertinib, and sensitizing *EGFR* mutations were specified as exon 19 deletion and exon 21 L858R.

LM was diagnosed by the presence of malignant cells on the CSF cytology and/or consistent neuroimaging findings, characterized by enhancing subarachnoid nodules in gadolinium enhanced T1-weighted magnetic resonance imaging. Presentation of LM was classified as either synchronous or metachronous depending on whether LM was diagnosed within or after 6 months of the diagnosis of advanced NSCLC, respectively. Cytologic negative conversion was defined as an absence of malignant cells from the CSF for 3 or more consecutive times in cases whose previous CSF cytology was positive.

Intrathecal (IT) chemotherapy was delivered by either an Ommaya reservoir or a lumbar puncture twice weekly. Methotrexate monotherapy was given at a dose of 15 mg, and thiotepa monotherapy was administered at a dose of 10 mg, respectively. As a combination, methotrexate, hydrocortisone, and cytarabine were dosed at 15 mg, 15 mg/m^2, and 30 mg/m^2, respectively. Systemic therapy after LM consisted of cytotoxic chemotherapy such as docetaxel, weekly paclitaxel, paclitaxel with carboplatin, and pemetrexed, as well as TKIs including gefitinib, erlotinib, and osimertinib.

Statistical Analysis

Post-LM survival was defined as the time from the date of LM detection to the date of death by any cause or last follow-up. Survival curves were plotted using the Kaplan-Meier method and compared with the log-rank test. Cox proportional hazard regression models were applied to identify prognostic factors for post-LM survival, in which variables with a P value of $< .05$ in the univariate analyses were subsequently entered into a multivariate model. All P values were 2-sided, and $P < .05$ was considered statistically significant. SPSS software version 23 (IBM Co., Armonk, NY) was used for all analyses. The study protocol was reviewed and approved by the Institutional Review Board at Seoul National University Hospital (approval number: H1712-151-911).

Results

Clinical Characteristics of the Patients

Of the patients with *EGFR*-mutant NSCLC treated with EGFR TKIs, 17.4% (110 out of 631 cases) developed LM. Table 1 shows the baseline characteristics of the included patients with the majority being women (58.2%), never-smokers (62.6%), and having a histology of adenocarcinoma (94.5%).

Table 1 Baseline Patient Characteristics

Characteristics	N = 110, n (%)
Median age at diagnosis, y (range)	59 (39-84)
Gender	
Male	46 (41.8)
Female	64 (58.2)
Stage of disease at initial lung cancer diagnosis	
Stage I-III	22 (20.0)
Stage IV	88 (80.0)
Smoking status	
Ex- or current smoker	40 (37.4)
Never-smoker	67 (62.6)
Histology	
Adenocarcinoma	104 (94.5)
Non-adenocarcinoma	6 (5.5)
***EGFR* mutation status**	
Exon 19 deletion	60 (54.5)
Exon 21 L858R	50 (45.5)

Abbreviations: EGFR = epidermal growth receptor; LM = leptomeningeal metastasis; NSCLC = non–small-cell lung cancer.

Table 2 shows the clinical characteristics at LM presentation of the study population. The median time from the initial diagnosis of lung cancer to the development of LM was 14.4 months (range, 0.0-91.9 months). LM occurred synchronously with the initial presentation of lung cancer in 16 (14.5%) patients. More than one-half (64.5%) of the patients exhibited an Eastern Cooperative Oncology Group (ECOG) PS of 2 to 4 at the diagnosis of LM. LM was diagnosed with both cytologic and radiologic evidence in 87 (79.1%) patients. Parenchymal brain metastases were noted prior to the detection of LM in 52 (47.3%) cases. Twenty (18.2%) patients had received whole brain radiotherapy (WBRT) before the diagnosis of LM. Extra-cranial disease status was progressive at LM presentation in 42 (38.2%) patients. As for systemic chemotherapy before LM, gefitinib was used in 77 (70.0%) patients, and the median lines of previous chemotherapy were 2 (range, 0-8).

Treatment Modalities of the Patients

The treatment modalities used for LM are shown in Table 3. Ninety (81.8%) patients received IT chemotherapy, and the majority (71.8%; n = 79) of them were treated with IT methotrexate. WBRT was given after LM diagnosis in 42 (38.2%) patients, whereas 4 (3.6%) patients underwent involved-field radiotherapy (IFRT) for LM. Among the 57 (51.8%) patients who received any systemic therapy after the development of LM, pemetrexed, taxane, and EGFR TKIs were used in 19 (17.3%) patients, 6 (5.5%) patients, and 44 (40.0%) patients, respectively. Osimertinib was used in 8 (7.3%) patients, all of whom had the T790M mutation verified on their repeat biopsies. Cytologic clearance of malignant cells was observed in the CSF of 19 (17.3%) patients.

Post-LM Survival

The total population with LM exhibited a median post-LM survival of 5.7 months (95% CI, 0.0-12.0 months) (Figure 1).

Table 2 Clinical Features at the Presentation of Leptomeningeal Metastasis

Features	N = 110, n (%)
Median time from the initial diagnosis to development of LM, mo (range)	14.4 (0.0-91.9)
Presentation of LM	
Synchronous	16 (14.5)
Metachronous	94 (85.5)
ECOG performance status at diagnosis of LM	
0-1	36 (32.7)
2-4	71 (64.5)
Unknown	3 (2.7)
Diagnostic modality	
CSF cytology	14 (12.7)
Brain MRI	9 (8.2)
Both	87 (79.1)
Detection of brain parenchymal metastases	
Before LM	52 (47.3)
Concurrent with LM	33 (30.0)
No	25 (22.7)
Radiotherapy to the brain before LM	
WBRT	20 (18.2)
SRS	19 (17.3)
Both	3 (2.7)
No	68 (61.8)
Extracranial disease status at diagnosis of LM	
Progressive	42 (38.2)
Non-progressive	67 (60.9)
Not evaluable	1 (0.9)
TKI before LM	
Gefitinib	77 (70.0)
Erlotinib	11 (10.0)
Gefitinib-erlotinib	2 (1.8)
None	20 (18.2)
Median previous lines of systemic chemotherapy before LM (range)	2 (0-8)

Abbreviations: CSF = cerebrospinal fluid; ECOG = Eastern Cooperative Oncology Group; LM = leptomeningeal metastasis; MRI = magnetic resonance imaging; SRS = stereotactic radiosurgery; TKI = tyrosine kinase inhibitor; WBRT = whole brain radiotherapy.

Table 3 Treatments for Leptomeningeal Metastasis

Treatment Modalities	N = 110, n (%)
Intrathecal therapy for LM	
Yes	90 (81.8)
No	20 (18.2)
Intrathecal drugs	
Methotrexate	79 (71.8)
Methotrexate, hydrocortisone, and cytarabine	9 (8.2)
Either of the above and thiotepa	2 (1.8)
Radiotherapy to the brain after LM	
WBRT	42 (38.2)
Involved-field radiotherapy	4 (3.6)
No	64 (58.2)
Systemic therapy after LM	
Yes	57 (51.8)
No	53 (48.2)
Pemetrexed use after LM	
Yes	19 (17.3)
No	91 (82.7)
Taxane use after LM	
Yes	6 (5.5)
No	104 (94.5)
TKI after LM diagnosis	
Gefitinib	19 (17.3)
Erlotinib	13 (11.8)
Osimertinib	8 (7.3)
Gefitinib-erlotinib or erlotinib-gefitinib	4 (3.6)
No	66 (60.0)

Abbreviations: LM = leptomeningeal metastasis; TKI = tyrosine kinase inhibitor; WBRT = whole brain radiotherapy.

When the patients were grouped by treatment factors, post-LM survival was not significantly different between the groups with and without IT chemotherapy ($P = .475$) (Figure 2A), WBRT/IFRT ($P = .550$) (Figure 2B), cytologic negative conversion ($P = .588$) (see Supplemental Figure 1A in the online version), or taxane use after LM ($P = .898$) (see Supplemental Figure 1B in the online version).

In contrast, post-LM survival was significantly longer with pemetrexed use after LM than without pemetrexed use after LM, with a median of 13.7 months (95% CI, 4.1-23.2 months) versus 4.0 months (95% CI, 2.2-5.7 months), respectively ($P = .008$) (Figure 2C). TKI use after LM also was predictive of survival after the diagnosis of LM, with a median of 16.9 months (95% CI, 10.4-23.4 months) versus 3.0 months (95% CI, 2.4-3.7 months) for the TKI group versus the no-TKI group, respectively ($P < .001$) (Figure 2D).

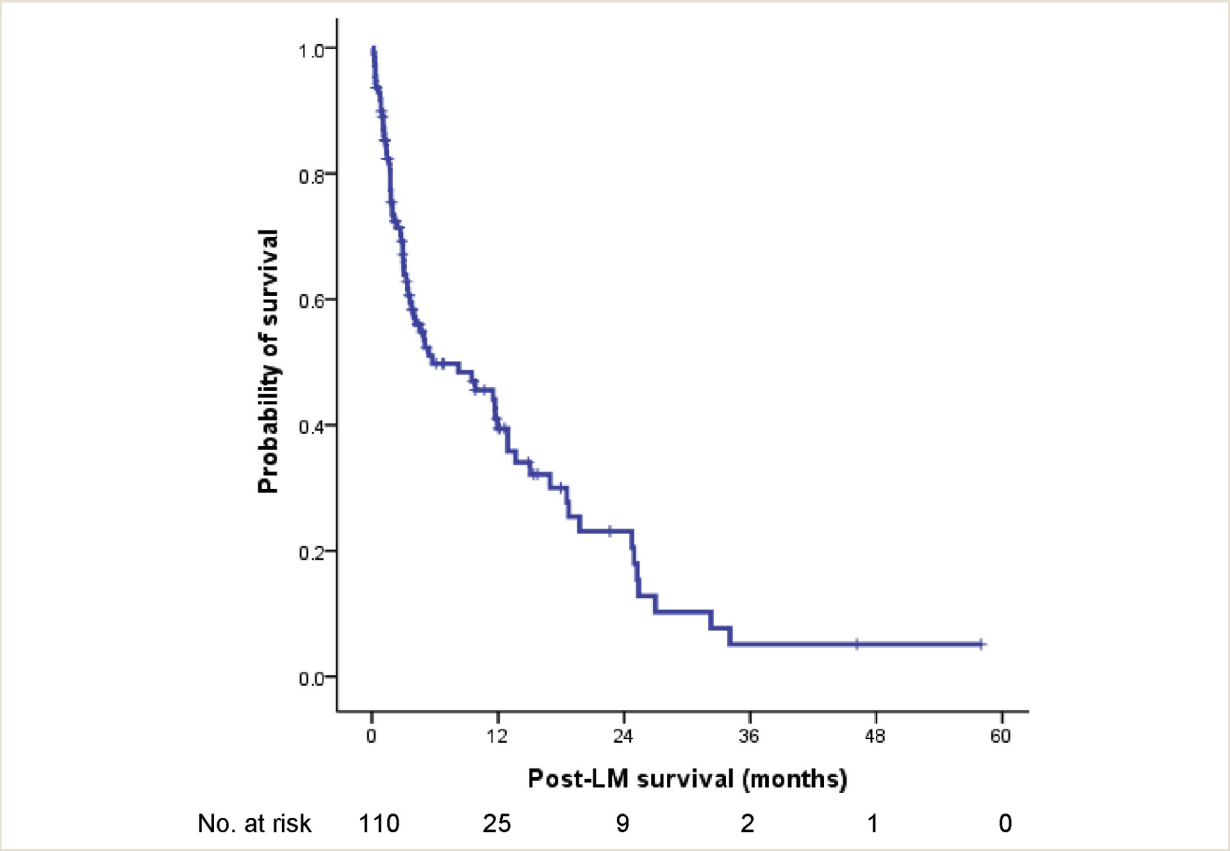
Prognostic Factor Analysis for Post-LM Survival

Of the clinical and treatment-related variables, the following were good prognostic factors for post-LM survival in the univariate analyses: synchronous presentation of LM, no TKI use before LM, pemetrexed use after LM, and TKI use after LM. In the multivariate analyses, pemetrexed use after LM and TKI use after LM were independent prognostic factors for prolonged post-LM survival with a hazard ratio of 3.1 (95% CI, 1.5-6.3; $P = .002$) and 3.0 (95% CI, 1.6-5.8; $P = .001$), respectively (Table 4).

Subgroup Analysis

Among 67 patients whose extra-cranial disease status was non-progressive at the time of LM detection, post-LM survival was significantly longer with pemetrexed after LM than without pemetrexed after LM ($P = .012$) (see Supplemental Figure 2D in the online version) and with TKI use after LM than without TKI

Figure 1 Survival From the Diagnosis of LM (Post-LM Survival)



Abbreviation: LM = leptomeningeal metastasis.

use after LM ($P = .008$) (see Supplemental Figure 2E in the online version). In the group of 42 patients whose extra-cranial disease was progressive when LM was diagnosed, significant improvement in survival was observed with TKI use after LM ($P = .008$) (see Supplemental Figure 3 in the online version).

Discussion

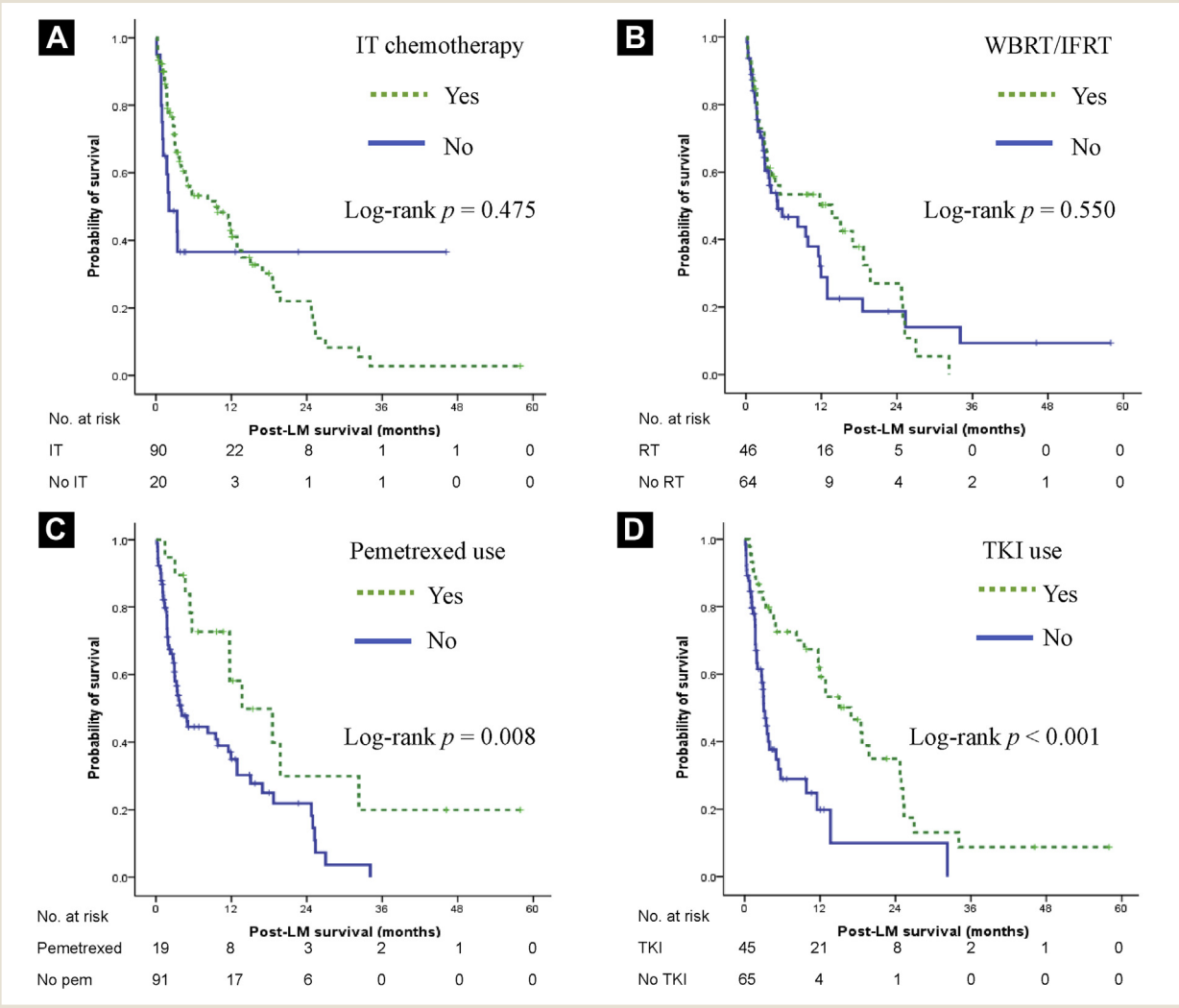
In this study, we found that pemetrexed use after LM was independently associated with a longer post-LM survival in patients with *EGFR*-mutant NSCLC with LM, along with TKI use after LM. This finding suggests a potential anti-tumor activity of pemetrexed for patients with *EGFR*-mutant NSCLC with LM. Local therapies including IT chemotherapy and WBRT/IFRT were not associated with survival benefit in this setting.

LM developed in 17.4% of our patient cohort of *EGFR*-mutant lung cancer. This was similar to findings from previous studies showing a higher incidence of LM and longer post-LM survival in patients with *EGFR*-mutant NSCLC than in those with molecularly unselected NSCLC.[6,16] Several factors were suggested to explain the predisposition of *EGFR*-mutant NSCLC to LM. One explanation comes from their extended survival enabled by the use of EGFR TKIs,[17,18] which likely increases the risk of cancer cells reaching the CNS. Other possible reasons are the poor penetration of the first-generation EGFR TKIs across the blood brain barrier into the CSF[19-21] and even the metastatic tropism of *EGFR*-mutant lung cancer to the CNS.[5,22]

The median post-LM survival of 5.7 months in our work is shorter than that of 8.7 months as reported by Li et al.[6] In addition, the previous study has found PS as a significant prognostic factor for post-LM survival, although it did not confer a significant effect on survival in our study. These discrepancies at least in part resulted from a higher proportion of patients with symptomatic LM (100.0% vs. 75.4%) and a poor PS (PS 2-4, 64.5% vs. 43.2%) and less TKI use for LM (40.0% vs. 80.7%) in our cohort than in that of the aforementioned study. Of note, the former study did not explore the role of systemic therapies other than TKIs in this setting, but the apparent association between PS and survival may have been confounded by indication bias. Namely, preserved PS likely indicated the patient condition for which an effective cytotoxic agent can be considered, as suitability to cytotoxic chemotherapy generally requires more preserved condition than that of TKI does.

A novel finding of the current study is the potential role of pemetrexed in the treatment of LM. Pemetrexed is used as one of the standard systemic chemotherapy regimens either in conjunction with cisplatin or as a monotherapy for patients with NSCLC of non-squamous histology.[23,24] Despite CNS penetration of less than

Figure 2 A, Post-LM Survival by IT Chemotherapy Use. B, Post-LM Survival by WBRT or IFRT Use. C, Post-LM Survival by Pemetrexed Use. D, Post-LM Survival by TKI Use



Abbreviations: IFRT = involved-field radiotherapy; IT = intrathecal; LM = leptomeningeal metastasis; TKI = tyrosine kinase inhibitor; WBRT = whole brain radiotherapy.

5% of its plasma concentration,[25,26] the intracranial antitumor activity of pemetrexed was shown in several small studies on patients with brain metastases from NSCLC. In these studies, the intracranial response rate of the drug was as high as 30% to 40% either alone or in combination with a platinum agent, not only in the treatment-naive patients but also in previously treated patients.[10-15] The safety profile of pemetrexed was acceptable for fragile patients like those with CNS metastases.[12]

Although the activity of pemetrexed against LM cannot be extrapolated from this anecdotal evidence of its therapeutic effect on brain parenchymal metastases, data have been scarce on the role of systemic cytotoxic drugs in LM. Notably, a recent retrospective analysis correlated "modern systemic therapies" including pemetrexed, bevacizumab, and TKIs with improved post-LM survival in patients with LM from NSCLC, but their small sample size (n = 30) and grouping with other agents made it difficult to assess the effect of an individual agent.[27] In this context, our analysis was the first to demonstrate an association between pemetrexed use after LM and a better post-LM survival in patients with *EGFR*-mutant NSCLC. The magnitude of its effect was even comparable to that of EGFR TKI use after LM, whereas IT chemotherapy, WBRT, and taxanes lacked clinical activity in terms of survival benefit.

It is currently unclear whether TKI or pemetrexed after LM exerts its positive effect on post-LM survival via intracranial or systemic control. When stratified by extracranial disease status at the detection of LM, post-LM survival continued to be better with TKI use or pemetrexed use after LM than without them in patients with non-progressive extracranial disease, supporting a role of intracranial control. We observed a trend of better post-LM survival with TKI use or pemetrexed use after LM than without them in patients with progressive extracranial disease at LM as well, but limited survival and number of the cases rendered the results inconclusive. We

Table 4 Prognostic Factor Analysis for Survival After Leptomeningeal Metastasis Diagnosis

Parameters	N	Univariate Analysis		Multivariate Analysis	
		Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Age	110	1.0 (1.0-1.1)	.070		
Gender					
Female	64	1			
Male	46	1.5 (0.9-2.4)	.103		
Presentation of LM					
Synchronous	16	1		1	
Metachronous	94	2.0 (1.1-3.9)	.032	1.9 (0.6-6.0)	.281
ECOG PS at LM					
0-1	36	1			
2-4	71	1.6 (1.0-2.7)	.065		
Brain parenchymal metastases					
Absent	25	1			
Present	85	1.3 (0.7-2.2)	.424		
WBRT before LM					
No	87	1			
Yes	23	1.1 (0.6-1.9)	.742		
Extracranial disease status at LM					
Non-progressive	67	1			
Progressive	42	0.7 (0.4-1.1)	.129		
TKI use before LM					
No	20	1		1	
Yes	90	1.8 (1.0-3.3)	.044	0.8 (0.3-2.4)	.678
Intrathecal therapy for LM					
Yes	90	1			
No	20	1.3 (0.7-2.3)	.477		
WBRT/IFRT after LM					
Yes	46	1			
No	64	1.2 (0.7-1.9)	.551		
Pemetrexed use after LM					
Yes	19	1		1	
No	91	2.4 (1.2-4.6)	.010	3.1 (1.5-6.3)	.002
TKI use after LM					
Yes	45	1		1	
No	65	2.8 (1.7-4.8)	.000	3.0 (1.6-5.8)	.001
Taxane use after LM					
Yes	6	1			
No	104	1.1 (0.4-2.7)	.898		
Cytologic negative conversion					
Yes	19	1			
No	87	1.2 (0.7-2.1)	.590		

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; IFRT = involved-field radiotherapy; LM = leptomeningeal metastasis; TKI = tyrosine kinase inhibitor; WBRT = whole brain radiotherapy.

suppose that whether intracranial or extracranial, these activities are probably not mutually exclusive to each other.

Our study has several limitations. First, this is a retrospective study with potential selection bias. In our usual clinical practice, we perform a CSF exam and CNS imaging when neurologic symptoms suggestive of LM are present. This could have left a few patients with asymptomatic LM underrepresented in our cohort. Second, this analysis did not fully evaluate the efficacy of third-generation EGFR TKIs against LM, because the majority of the included patients had been treated before the third-generation EGFR TKIs were available. Nevertheless, they are expected to be promising therapeutic alternatives for this patient population, in that osimertinib and AZD3759 have a higher penetration across the blood brain barrier than that of first-generation EGFR TKIs and showed efficacy in the treatment of patients with LM from pretreated *EGFR*-mutant NSCLC.[28-30] Third, the current study did not address the combination of pemetrexed with bevacizumab with or without platinum, because this combination was not covered by the Korean National Health Insurance. The addition of bevacizumab to standard chemotherapy demonstrated promising results for treatment-naive non-squamous NSCLC,[31,32] although its role in the setting of active CNS disease has yet to be elucidated.

Despite these limitations, we found pemetrexed to be a potentially active drug in LM for the first time. Pemetrexed has a manageable toxicity profile and can be administered safely to fragile patients with LM. Because conducting prospective trials on patients with LM has been difficult owing to their poor general condition and limited life expectancy, our study is noteworthy despite its retrospective nature.

Conclusion

In conclusion, pemetrexed use after LM was independently associated with prolonged post-LM survival in our patient cohort with *EGFR*-mutant NSCLC. A future prospective study is warranted to validate this finding.

Clinical Practice Points

- LM is frequent in patients with *EGFR*-mutant lung cancer.
- We explored the role of pemetrexed for the treatment of LM in 110 patients with *EGFR*-mutant lung cancer.
- Pemetrexed use after LM was independently associated with a survival benefit for patients with LM.
- Pemetrexed may be effective for the treatment of patients with *EGFR*-mutant NSCLC and LM.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2019.03.005.

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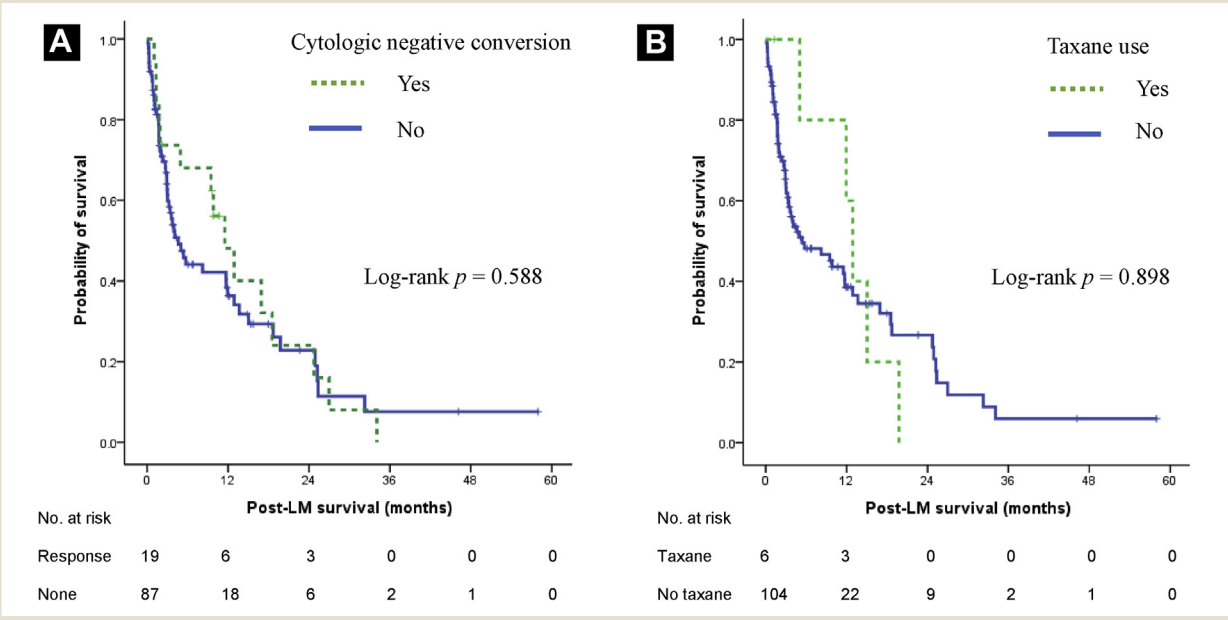
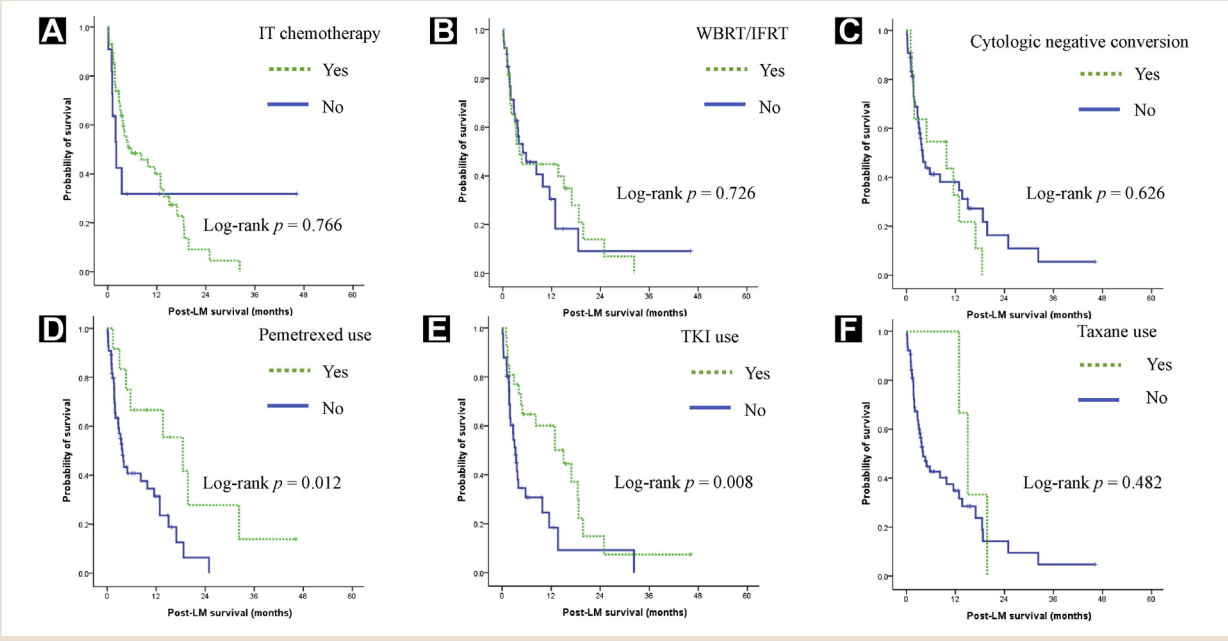
Supplemental Figure 1 A, Post-LM Survival by Presence or Absence of Cytologic Negative Conversion. B, Post-LM Survival by Taxane Use



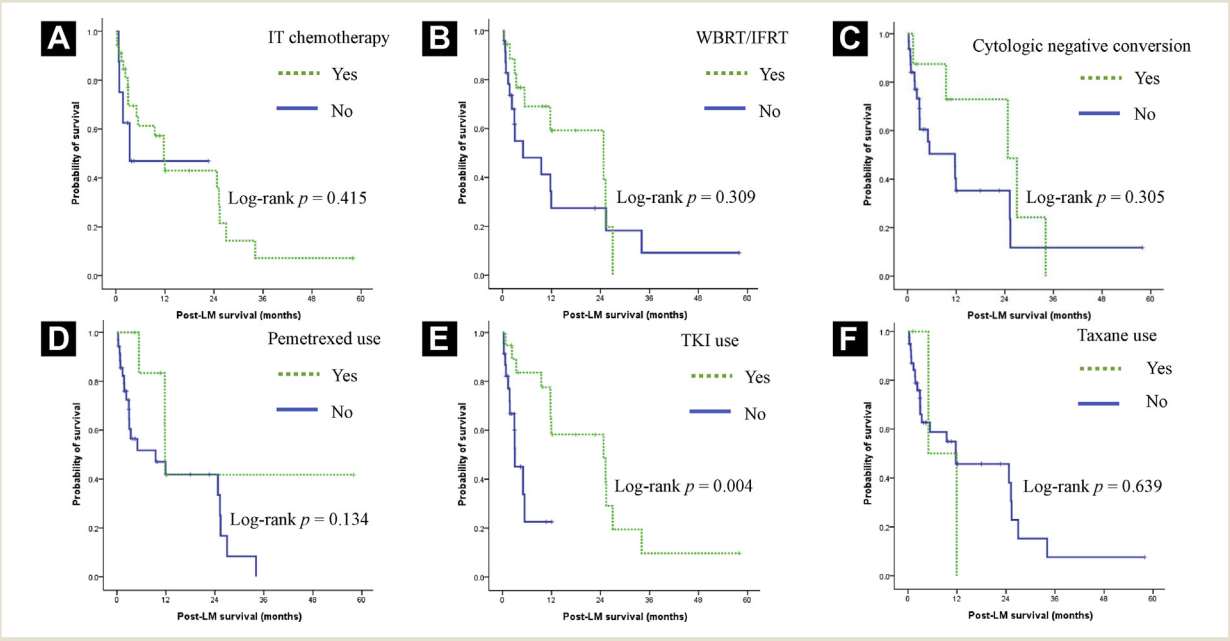
Abbreviation: LM = leptomeningeal metastasis.

Supplemental Figure 2 Comparison of Post-LM Survival in Patients With Non-progressive Extracranial Disease at LM (n = 67). A, By IT Chemotherapy Use. B, By WBRT or IFRT Use. C, By Cytologic Negative Conversion. D, By Pemetrexed Use. E, By TKI Use. F, By Taxane Use



Abbreviations: IFRT = involved-field radiotherapy; IT = intrathecal; LM = leptomeningeal metastasis; TKI = tyrosine kinase inhibitor; WBRT = whole brain radiotherapy.

Supplemental Figure 3 Comparison of Post-LM Survival in Patients With Progressive Extracranial Disease at LM (n = 42). A, By IT Chemotherapy Use. B, By WBRT or IFRT Use. C, By Cytologic Negative Conversion. D, By Pemetrexed Use. E, By TKI Use. F, By taxane Use



Abbreviations: IFRT = involved-field radiotherapy; IT = intrathecal; LM = leptomeningeal metastasis; TKI = tyrosine kinase inhibitor; WBRT = whole brain radiotherapy.