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EGFR 돌연변이가 있는 폐암환자의 뇌연수막전이 치료에서 전신치료의 역할

The role of systemic treatment in the *EGFR*-mutant lung cancer patients with leptomeningeal metastasis

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Abstract

The role of systemic treatment in the *EGFR*-mutant lung cancer patients with leptomeningeal metastasis

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Objectives: Leptomeningeal metastasis (LM), still an area of unmet need, has frequently been observed in patients with epidermal growth factor receptor (*EGFR*)-mutant non-small cell lung cancer (NSCLC). We explored the treatment modalities associated with a better outcome in patients with LM from *EGFR*-mutant NSCLC.

Materials 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 analyzed in patients with EGFR tyrosine kinase inhibitor (TKI) exposure before LM.

Results: In our patient cohort with *EGFR*-mutant NSCLC (n = 631), 17.4% (n = 110) developed LM, and 90 patients with an exposure to TKI before LM were included in our analysis. Median post-LM survival of these 90 patients was 4.6 months (95% confidence interval, [CI], 2.8-6.4 months). Post-LM survival was not significantly different between the groups with and without intrathecal (IT) chemotherapy (P = 0.838) or whole brain

radiotherapy/involved-field radiotherapy (WBRT/IFRT; *P* = 0.612). In contrast, post-LM survival was significantly longer with TKI after LM than without TKI after LM, with a median of 15.0 months (95% CI, 7.1-23.0 months) *vs.* 3.0 months (95% CI, 2.4-3.7 months; *P* = 0.001), respectively. Pemetrexed after LM also was predictive of post-LM survival, with a median of 18.5 months (95% CI, 3.0-34.1 months) *vs*. 3.6 months (95% CI, 2.5-4.7 months; *P* = 0.010) for the pemetrexed group vs. no-pemetrexed group, respectively. In the multivariate analyses, no TKI use after LM and no pemetrexed use after LM were independently associated with poor post-LM survival with a hazard ratio of 2.8 (95% CI, 1.4-5.9; *P* = 0.005) and 2.6 (95% CI, 1.0-6.4; *P* = 0.040), respectively.

Conclusion: Effective systemic treatment, such as TKI and pemetrexed, after LM was independently associated with a longer post-LM survival in *EGFR*-mutant NSCLC patients with TKI use before LM. Local therapies including IT chemotherapy and WBRT/IFRT were not associated with survival benefit in this setting.

Keywords: Leptomeningeal metastasis; Epidermal growth factor receptor; Non-small cell lung cancer; Pemetrexed

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1. 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 with 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) While the use of EGFR TKIs has consistently been shown to correlate with a survival benefit, the role of cytotoxic chemotherapy, intrathecal (IT) chemotherapy, or whole brain radiotherapy (WBRT) in this setting has been rather conflicting.

We explored the treatment modalities associated with better survival after the diagnosis of LM in patients with *EGFR*-mutant NSCLC.

2. Materials and Methods

2.1. Patient selection and data gathering

We retrospectively reviewed a consecutive database of 2,002 patients with advanced NSCLC treated with EGFR TKIs between July 2006 and October 2016 at Seoul National University Hospital (SNUH), from which 631 patients were identified to have sensitizing *EGFR* mutations. Of these, patients without LM were excluded, as did patients without exposure to TKI before LM. We limited our main survival analysis to patients previously treated with TKI because these represent majority of patients with LM from *EGFR*-mutant lung cancer and likely exhibit different susceptibility to treatment and prognosis.

Advanced NSCLC was defined as 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 on gadolinium enhanced T1-weighted magnetic resonance imaging (MRI).

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 before and/or 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.

2.2. 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 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 <0.05 in the univariable analyses were subsequently entered to a multivariable model. All *P* values were two-sided, and *P* <0.05 were considered statistically significant. SPSS software version 23 (IBM Co., Armonk, NY, USA) was used for all analyses. The study protocol was reviewed and approved by the SNUH's Institutional Review Board (approval number: H1712-151-911).

3. Results

3.1. Clinical characteristics

Of the patients with *EGFR*-mutant NSCLC treated with EGFR TKIs, 17.4% developed LM (110 out of 631 cases). Among them, 90 patients with an exposure to TKI before LM were eligible for our analysis (Fig. 1).

Table 1 shows the baseline characteristics of the included patients with the majority being women (54.4%), neversmokers (57.8%), and having a histology of adenocarcinoma (94.4%). More than half (61.1%) of the patients exhibited an ECOG PS of 2-4 at the diagnosis of LM. LM was diagnosed with both cytologic and radiologic evidence in 71 patients (78.9%).

Table 2 shows treatments before the detection of LM. The median time from the initial diagnosis of lung cancer to the development of LM was 18.1 months (range, 1.4-91.9 months). Parenchymal brain metastases were noted prior to the detection of LM in 50 (55.6%) cases. Nineteen patients (21.1%) had received WBRT before the diagnosis of LM. Extra-cranial disease status was progressive at LM presentation in 27 patients (30.0%). As for systemic chemotherapy before LM, pemetrexed was used in 26 patients (28.9%), gefitinib was used in 77 patients (85.6%), and the median line of previous chemotherapy was 2 (range, 1-8).

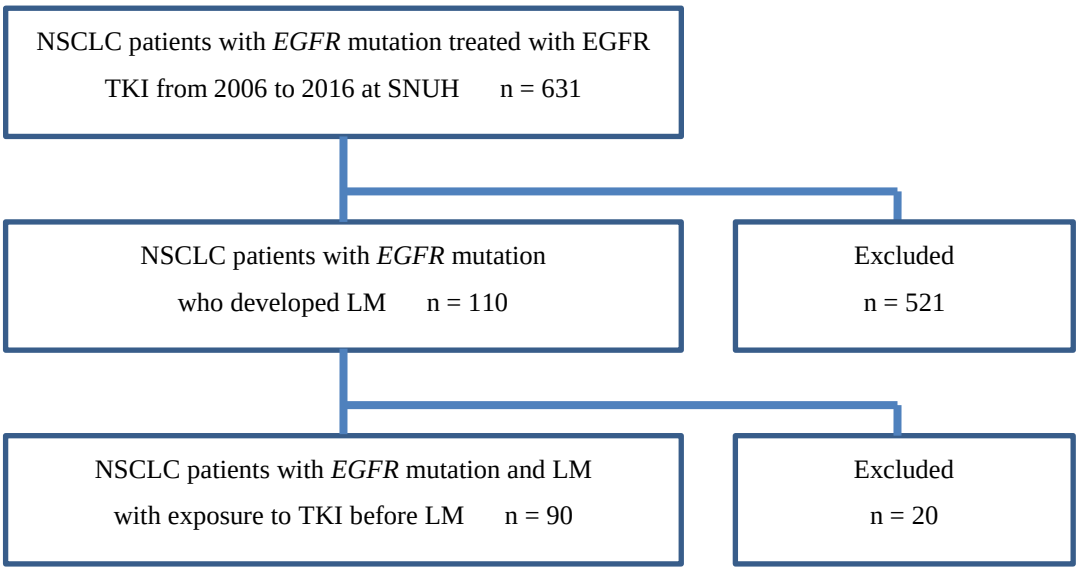

Figure 1. Patient selection

Abbreviations: NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; SNUH, Seoul National University Hospital; LM, leptomeningeal metastasis

Table 1. Baseline characteristics.

Characteristics		**n = 90**
Age at diagnosis in years, median (range)		60 (39-84)
Sex, n (%)	Male	41 (45.6%)
	Female	49 (54.4%)
Stage of disease at initial lung cancer diagnosis, n (%)	Stage I-III	18 (20.0%)
	Stage IV	72 (80.0%)
Smoking status, n (%)	Ex- or current smoker	36 (40.0%)
	Never-smoker	52 (57.8%)
	Unknown	2 (2.2%)
Histology, n (%)	Adenocarcinoma	85 (94.4%)
	Non-adenocarcinoma	5 (5.6%)
***EGFR* mutation status, n (%)**	Exon 19 deletion	47 (52.2%)
	Exon 21 L858R	43 (47.8%)
ECOG performance status at the diagnosis of LM	0-1	33 (36.7%)
	2-4	55 (61.1%)
	Unknown	2 (2.2%)
Diagnostic modality	CSF cytology	12 (13.3%)
	Brain MRI	7 (7.8%)
	Both	71 (78.9%)

Abbreviations: EGFR, epidermal growth receptor; LM, leptomeningeal metastasis; ECOG, Eastern Cooperative Oncology Group; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging

Table 2. Treatments before the detection of leptomeningeal metastasis.

Features		n = 90
Time from the initial diagnosis to development of LM in months, median (range)		18.1 (1.4-91.9)
Detection of brain parenchymal metastases	Before LM	50 (55.6%)
	Concurrent with LM	23 (25.6%)
	No	17 (18.9%)
Radiotherapy to the brain before LM, n (%)	WBRT	19 (21.1%)
	SRS	19 (21.1%)
	Both	2 (2.2%)
	No	50 (55.6%)
Extracranial disease status at diagnosis of LM	Progressive	27 (30.0%)
	Non-progressive	62 (68.9%)
	Not evaluable	1 (1.1%)
Cytotoxic agents before LM, n (%)	Pemetrexed	26 (28.9%)
	Gemcitabine	45 (50.0%)
	Taxane	22 (24.4%)
TKI before LM, n (%)	Gefitinib	77 (85.6%)
	Erlotinib	11 (12.2%)
	Gefitinib-erlotinib	2 (2.2%)
Previous lines of systemic chemotherapy before LM, median (range)		2 (1-8)

Abbreviations: EGFR, epidermal growth receptor; LM, leptomeningeal metastasis; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor

3.2. Treatment

The treatment modalities used for LM are shown in Table 3. Seventy-one patients (78.9%) received IT chemotherapy, and the majority (71.1%, n = 64) of them was treated with IT methotrexate. WBRT was given after LM diagnosis in 32 patients (35.6%), whereas 2 patients (2.2%) underwent involved-filed RT (IFRT) for LM. Among the 37 patients (41.1%) who received any systemic therapy after the development of LM, pemetrexed, taxane, and EGFR TKIs were used in 15 patients (16.7%), 5 patients (5.6%), and 25 patients (27.8%), respectively. Osimertinib was used in 8 patients (8.9%), all of whom had the T790M mutation verified on their repeat biopsies.

Table 3. Treatments after the detection of leptomeningeal metastasis.

Treatment modalities		**n = 90**
Intrathecal therapy for LM	Yes	71 (78.9%)
	No	19 (21.1%)
Intrathecal drugs	Methotrexate	64 (71.1%)
	Methotrexate, hydrocortisone, and cytarabine	6 (6.7%)
	Either of the above and thiotepa	1 (1.1%)
Radiotherapy to the brain after LM, n (%)	WBRT	32 (35.6%)
	IFRT	2 (2.2%)
	No	56 (62.2%)
Systemic therapy after LM	Yes	37 (41.1%)
	No	53 (58.9%)
Pemetrexed use after LM	Yes	15 (16.7%)
	No	75 (83.3%)
Taxane use after LM	Yes	5 (5.6%)
	No	85 (94.4%)
TKI sequence after LM diagnosis	Rechallenge of the same TKI	8 (8.9%)
	Switch from gefitinib to erlotinib	9 (10.0%)
	Switch to osimertinib	8 (8.9%)
	No	65 (72.2%)

Abbreviations: LM, leptomeningeal metastasis; WBRT, whole brain radiotherapy; IFRT, involved-filed radiotherapy; TKI, tyrosine kinase inhibitor

3.3. Comparison of survival after leptomeningeal metastasis

The total population with LM previously treated with TKI exhibited a median post-LM survival of 4.6 months (95% CI, 2.8-6.4 months; Fig. 2).

When the patients were grouped by treatment factors, post-LM survival was not significantly different between the groups with and without IT chemotherapy ($P = 0.838$; Fig. 3A), WBRT/IFRT ($P = 0.612$; Fig. 3B), or taxane use ($P = 0.485$; Fig. 3C).

In contrast, post-LM survival was significantly longer with pemetrexed after LM than without pemetrexed after LM, with a median of 18.5 months (95% CI, 3.0-34.1 months) vs. 3.6 months (95% CI, 2.5-4.7 months), respectively ($P = 0.010$; Fig. 3D). TKI use after LM also was predictive of survival after the diagnosis of LM, with a median of 15.0 months (95% CI, 7.1-23.0 months) vs. 3.0 months (95% CI, 2.4-3.7 months) for the TKI group vs. no-TKI group, respectively ($P = 0.001$; Fig. 3E). Fig. 3F compared post-LM survival by different sequences of TKI use.

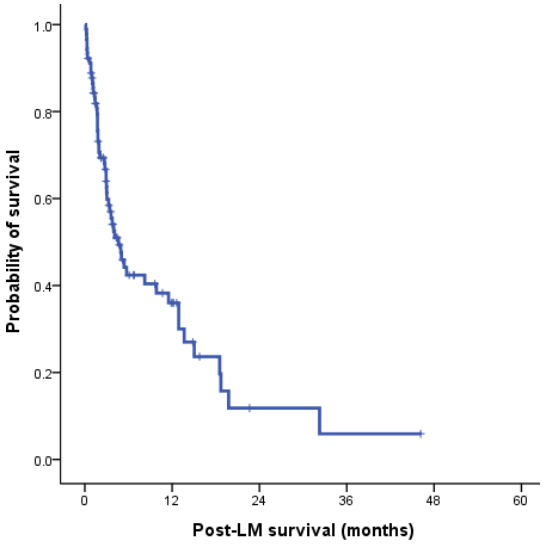

Figure 2. Survival after leptomeningeal metastasis (post-LM survival) in overall population.

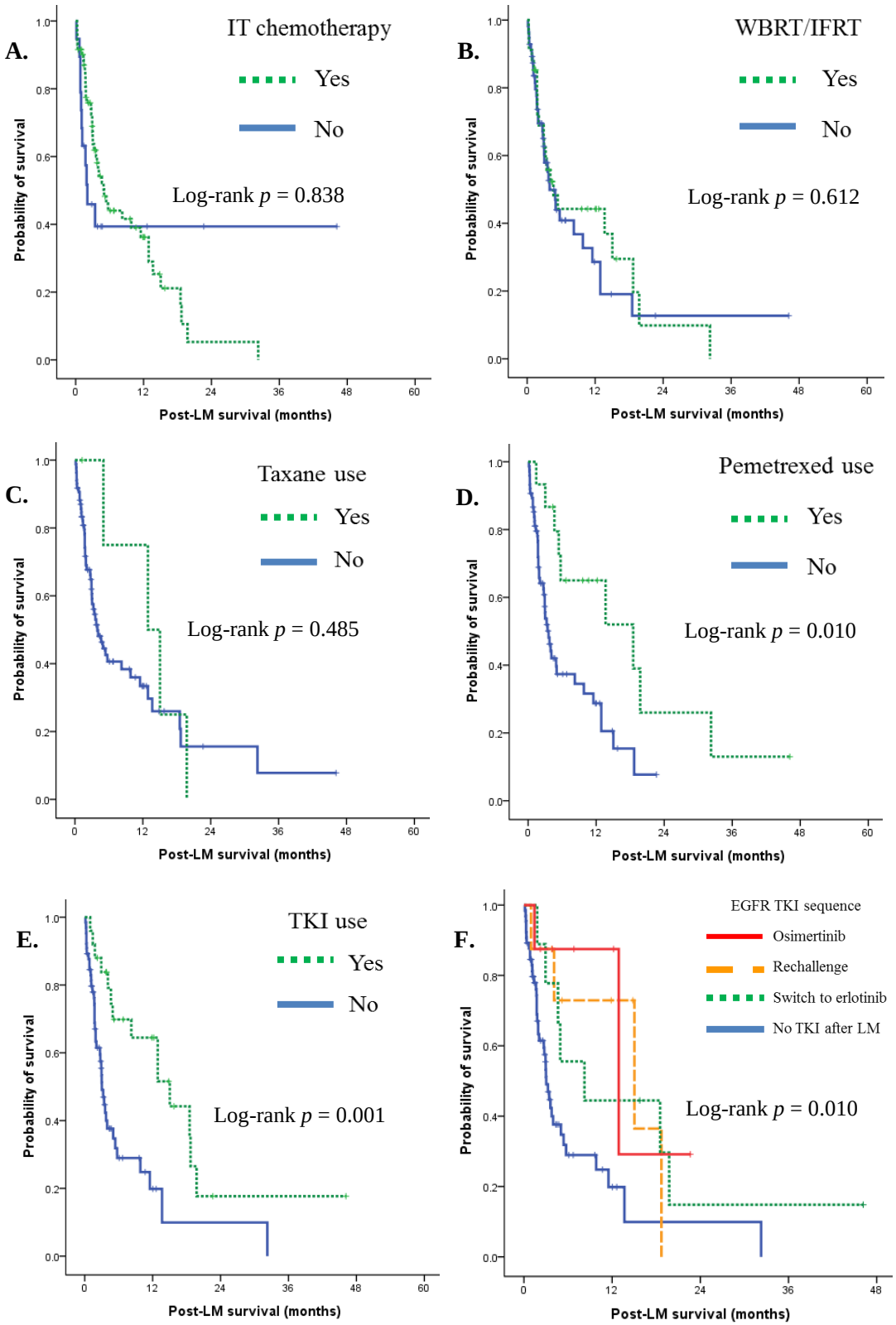

Figure 3. Comparison of survival after leptomeningeal metastasis (post-LM survival). (A) By intrathecal (IT) chemotherapy use. (B) By whole brain radiotherapy (WBRT) or involved-field radiotherapy (IFRT) use. (C) By taxane use. (D) By pemetrexed use. (E) By tyrosine kinase inhibitor (TKI) use. (F) By different strategies of TKI use.

3.4. Prognostic factor analysis for survival

Of the clinical and treatment-related variables, the followings were good prognostic factors for post-LM survival in the univariable analyses of patients with TKI exposure before LM: younger age, ECOG PS of 0-1, pemetrexed use after LM, and TKI use after LM. In the multivariable analyses, pemetrexed use after LM and TKI use after LM were independent prognostic factors for prolonged post-LM survival with a hazard ratio (HR) of 2.6 (95% CI, 1.0-6.4; $P = 0.040$) and 2.8 (95% CI, 1.4-5.9; $P = 0.005$), respectively (Table 4).

Table 4. Prognostic factor analysis for survival after the detection of leptomeningeal metastasis.

Parameters		n	Univariable analysis Hazard ratio (95% CI)	*P*	Multivariable analysis Hazard ratio (95% CI)	*P*
Age		90	1.0 (1.0-1.1)	0.027	1.0 (1.0-1.0)	0.396
Sex	Female	49	1			
	Male	41	1.5 (0.9-2.5)	0.161		
ECOG PS at LM	0-1	33	1		1	
	2-4	55	2.4 (1.3-4.3)	0.003	1.7 (0.9-3.4)	0.105
Brain parenchymal metastases	Absent	17	1			
	Present	73	0.9 (0.4-1.8)	0.755		
WBRT before LM	No	69	1			
	Yes	21	0.9 (0.5-1.6)	0.665		
Extracranial disease status at LM	Non-progressive	62	1			
	Progressive	27	0.9 (0.5-1.7)	0.756		
Intrathecal therapy for LM	Yes	71	1			
	No	19	1.1 (0.5-2.1)	0.839		
WBRT/IFRT after LM	Yes	34	1			
	No	56	1.2 (0.7-2.0)	0.613		
Pemetrexed use after LM	Yes	15	1		1	
	No	75	2.7 (1.2-5.8)	0.013	2.6 (1.0-6.3)	0.040
TKI use after LM	Yes	25	1		1	
	No	65	2.9 (1.5-5.5)	0.001	2.8 (1.4-5.9)	0.005
Taxane use after LM	Yes	5	1			
	No	85	1.4 (0.5-4.0)	0.489		

Abbreviations: EGFR, epidermal growth receptor; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; LM, leptomeningeal metastasis; WBRT, whole brain radiotherapy; IFRT, involved-filed radiotherapy; TKI, tyrosine kinase inhibitor

3.5 Subgroup analysis

Among 62 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 ($P = 0.020$; Fig. 4A) and with TKI use after LM than without TKI use after LM ($P = 0.008$; Fig. 4B). In the group of 27 patients whose extra-cranial disease was progressive when LM was diagnosed, no significant improvement in survival was observed with either treatment modality (Fig. 4C-D).

When the survival analyses were limited to 59 patients without pemetrexed exposure before LM, pemetrexed use after LM was predictive of survival after the diagnosis of LM ($P = 0.011$; Fig. 3E). Pemetrexed had not been rechallenged in 26 patients with pemetrexed exposure before LM.

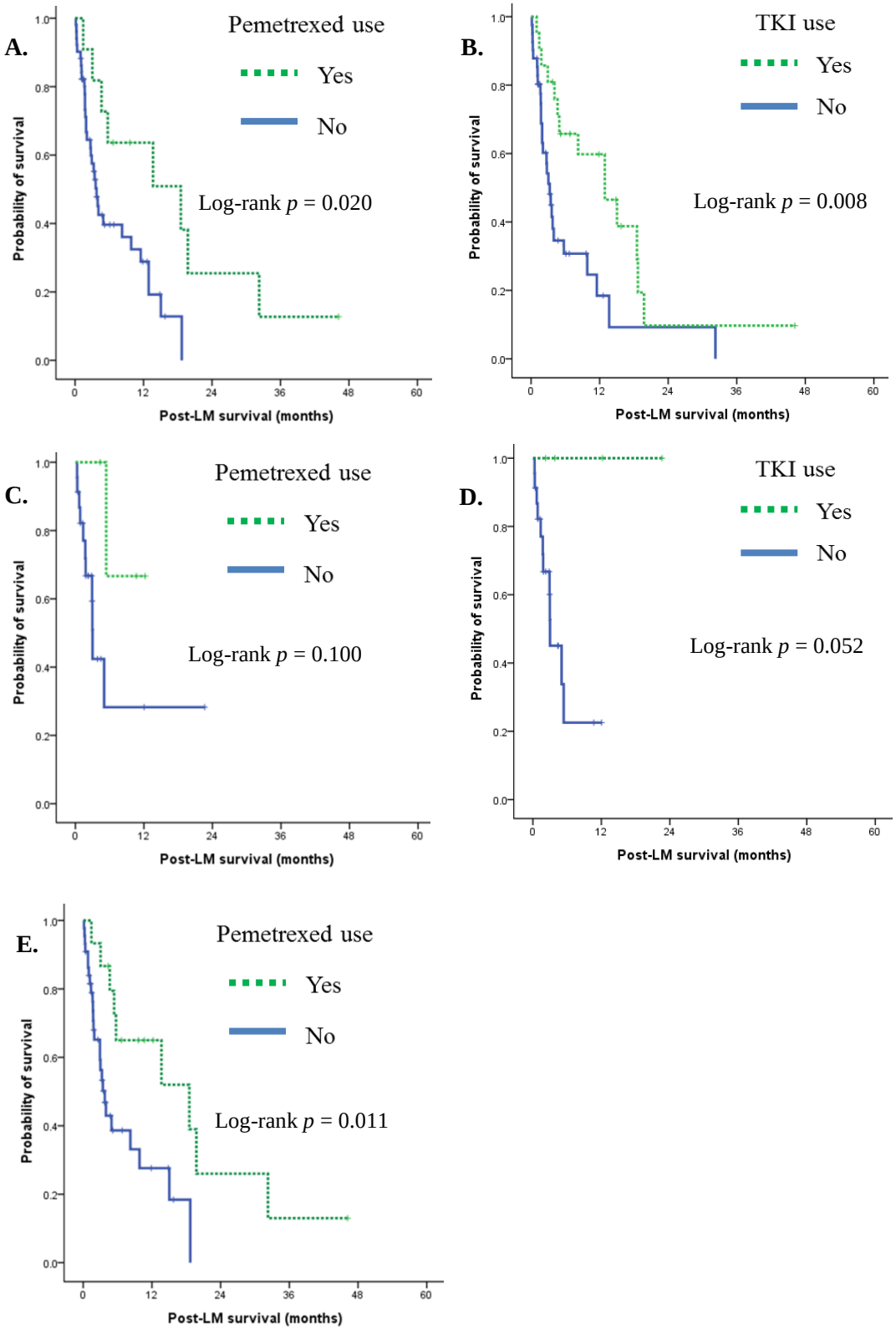

Figure 4. Comparison of survival after leptomeningeal metastasis (post-LM survival) within specified subgroups. In patients with non-progressive extracranial disease, (A) by pemetrexed use and (B) by tyrosine kinase inhibitor (TKI) use. In patients with progressive extracranial disease, (C) by pemetrexed use and (D) by TKI use. (E) By pemetrexed use in patients without prior exposure to pemetrexed

4. Discussion

In this study, we found that effective systemic treatment, such as EGFR TKI and pemetrexed, after LM was independently associated with a longer post-LM survival in *EGFR*-mutant NSCLC patients previously treated with EGFR TKI. 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, 10) 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,(11, 12) 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 (BBB) into the CSF (13-15) and even metastatic tropism of *EGFR*-mutant lung cancer to the CNS.(5, 16)

The median post-LM survival of 4.6 months in the patients with LM from *EGFR*-mutant NSCLC is shorter than that of 8.7 months from the most recent report by Li et al. (6) This discrepancy presumably resulted from a higher proportion of patients with symptomatic LM, a poor PS, and fewer TKI use for LM in our cohort than in that of the aforementioned study. In addition, patients without TKI exposure before LM were excluded from our analysis in contrast to that of Li et al. As EGFR TKI use after LM has been consistently associated with prolonged post-LM survival in the patients with *EGFR*-mutant NSCLC,(6, 10) patients without TKI exposure before LM were likely more sensitive to effective systemic treatment including EGFR TKIs, thereby exhibiting a better prognosis.

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.(17, 18) Despite CNS penetration of less than 5% of its plasma concentration,(19, 20) 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 30-40% either alone or in combination with a platinum agent, not only in the treatment-naïve patients but also in previously treated patients.(21-26) The safety profile of pemetrexed was acceptable for fragile patients like those with CNS metastases.(23)

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 pemetrexed's effect was even comparable to that of EGFR TKI use, while IT chemotherapy, WBRT, and taxanes lacked clinical relevance in terms of survival benefit. Because pemetrexed is one of the main systemic agents against NSCLC, one may argue that patients with exposure to pemetrexed before LM would have a worse prognosis than those without it, and have selectively been included in no-pemetrexed after LM group. In a subgroup without exposure to pemetrexed before LM, however, patients with pemetrexed after LM was still associated with better post-LM survival than their counterpart.

It is currently unclear whether TKI and pemetrexed after LM exert their 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 and 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 and pemetrexed use after LM than without them in cases with progressive extracranial disease at LM as well, but limited survival and number of cases rendered the results inconclusive. We 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 LM who had been asymptomatic underrepresented in our cohort. Second, we did not fully evaluate different strategies of TKI use after LM in patients with prior TKI exposure, because each approach was adopted by small number of patients. Nevertheless, osimertinib, one of the strategies adopted, has a higher penetration across the BBB than that of 1st generation EGFR TKIs and showed efficacy in the treatment of patients with LM from pretreated *EGFR*-mutant NSCLC.(27, 28) Third, pemetrexed had never been rechallenged in our patient cohort. This is largely because rechallenge of the previously used cytotoxic agent is not covered by the Korean National Helath Insurance and there had been a lack of data on antitumor efficacy of pemetrexed in the face of LM.

Despite these limitations, we found pemetrexed to be a potentially active drug in LM for the first time, in addition to TKI. Pemetrexed as well as TKI have 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 due to their poor general condition and limited life expectancy, our study is noteworthy despite its retrospective nature.

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

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요약

EGFR 돌연변이가 있는 폐암환자의 뇌연수막전이 치료에서 전신치료의 역할

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목표: 뇌연수막전이는 EGFR 돌연변이가 있는 폐암 환자들에서 비교적 흔하게 관찰되는 합병증들 중 하나이다. 본 연구에서는 EGFR 돌연변이가 있는 폐암에서 발생한 뇌연수막전이 환자들에서 양호한 예후와 연관되는 치료 방법을 모색해보고자 하였다.

방법: 서울대학교병원에서 2006년부터 2016년까지 치료받은, EGFR 돌연변이가 있는 폐암에서 발생한 뇌연수막전이 환자들의 의무기록을 후향적으로 검토하였다. 주요 지표로서 뇌연수막전이 발생후의 생존기간을, 뇌연수막전이 발생전 EGFR 티로신인산화효소 억제제 치료를 받은 환자들에서 분석하였다.

결과: EGFR 돌연변이가 있는 폐암 환자들 631명 중, 17.4% (110명)에서 뇌연수막 전이가 발생하였고, 이들중 이전 EGFR 티로신인산화효소 억제제 치료력이 있는 환자들이 90명이였다. 뇌연수막전이 발생후의 생존기간의 중앙값은 4.6 개월 (95% 신뢰구간, 2.8-6.4개월)이였다. 뇌연수막전이 발생후의 생존기간은 척수강내 항암치료 여

부나, 전뇌방사선치료 혹은 침범부위 국소방사선치료 여부와는 유의한 상관관계를 보이지 않았다 (각각 $P = 0.838$, $P = 0.612$). 반면, 뇌연수막전이 발생후 EGFR 티로신인산화효소 억제제나 페메트렉시드를 사용한 환자들은 사용하지 않은 환자들에 비해 뇌연수막전이 발생후의 생존기간의 중앙값이 각각 15.0 개월 (95% 신뢰구간, 7.1−23.0 개월) 대 3.0 개월 (95% 신뢰구간, 2.4−3.7 개월; $P = 0.001$), 18.5 개월 (95% 신뢰구간, 3.0−34.1 개월) 대 3.6 개월 (95% 신뢰구간, 2.5−4.7 개월; $P = 0.010$)로 유의하게 길었다. 다변량 분석에서 뇌연수막전이 발생후 EGFR 티로신인산화효소 억제제 사용과 페메트렉시드 사용이 각각 미사용에 비해, 위험도 2.8 (95% 신뢰구간, 1.4−5.9; $P = 0.005$)과 2.6 (95% CI, 1.0−6.4; $P = 0.040$)으로, 불량한 뇌연수막전이 발생후의 생존기간과 연관되었다.

결론: 이전에 EGFR 티로신인산화효소 억제제로 치료받은 EGFR 돌연변이가 있는 폐암 환자들에서 뇌연수막전이 발생후 티로신인산화효소 억제제나 페메트렉시드 사용은 양호한 뇌연수막전이 발생후 생존기간과 독립적인 연관성을 나타냈다. 이에 대해서는 추후 전향적 연구를 통한 검증이 필요하다.

주요어: 뇌연수막전이; EGFR; 비소세포폐암; 페메트렉시드

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