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의학석사 학위논문

**Impact of Multimodality Approach for
Patients with Leptomeningeal Metastases
from Solid Tumor**

고형암에서 발생한 뇌수막 전이 환자에
대한 병용 치료법의 영향

2014년 2월

서울대학교 대학원
의과대학 임상외과학과
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권진이

Impact of Multimodality Approach for Patients with Leptomeningeal Metastases from Solid Tumor

지도 교수 지 의 규

이 논문을 의학석사 학위논문으로 제출함

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서울대학교 대학원
의과대학 임상외과학과
권진이

권진이의 의학석사 학위논문을 인준함

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위원장 _____ (인)

부위원장 _____ (인)

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ABSTRACT

Purpose: To identify the prognostic factors and define the role of multimodality approach for patients with leptomeningeal metastases (LM) from solid tumor.

Materials and Methods: Medical records of 80 patients diagnosed with LM from solid tumor from January 1, 2004 to May 31, 2011 were retrospectively reviewed. Most frequent site of origin was lung (59%) followed by breast (25%) and stomach (16%). Median age was 54 years. Forty-nine female and 31 male were included. Two thirds of patients were ECOG class 1 or 2. Most patients were treated with intrathecal chemotherapy (IT-CTx) and whole brain RT (WBRT), 90% and 67.5%, respectively. Systemic chemotherapy (Sys-CTx) was offered to 33.8%. Patients treated with single, dual, and triple modality were 32.5%, 43.8%, and 23.8%, respectively.

Results: Median survival was 2.7 months and 1 year survival rate was 11.3%. Multivariate analysis showed that negative CSF cytology ($P < 0.001$), fewer regimen of CTx prior to LM ($P = 0.026$), WBRT ($P = 0.01$), Sys-CTx ($P < 0.001$), and combined modality treatment ($P < 0.001$) had statistically significance on survival.

NSCLC subgroup analysis showed that negative CSF cytology, target agent (EGFR-TKI) and CMT had significant impact on survival. Median survival of patients with treatment including target agent was 10.1 months.

Conclusions: Unlike previous reports, no factors among the characteristics of patients and symptoms at the time of presenting LM affected survival, and survival of patients with NSCLC was comparable to breast. Furthermore, CMT significantly improved survival outcome for all patients and use of target agent for NSCLC patients. Role of radiotherapy in conjunction with

target agent needs to be validated in future studies.

Keywords: leptomeningeal metastases, prognostic factor, solid tumor

Student number: 2012-22680

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INTRODUCTION

Leptomeningeal metastasis (LM) is dissemination of malignant tumor cell into the subarachnoid spaces. Typically, LM presents with advanced stage. But it may be the first manifestation of cancer for 6-21% of the patients (1). LM occurs 5-8% among all cancer patients. According to autopsy data, the incidence is estimated at 19%, and 40% of them had negative cerebrospinal fluid (CSF) cytology prior to death (2). Recently, the incidence of LM is increasing. Despite lengthened survival of cancer patients with improvement in chemotherapeutic agents, intracranial area still remains sanctuary due to blood brain barrier (BBB). Moreover, advanced diagnostic capability for LM contributes to the increase in the detection rate (3,4).

It is well-known that LM carries dismal prognosis. Even though patients surviving longer than 1 or 2 years are occasionally observed, most patients succumbed to disease only 3 to 4 months after the diagnosis (5). Many studies have proposed various prognostic factors to predict the response to therapy or patients' survival. But there is no consensual prognostic marker. Recently, novel chemotherapy agents or immunotherapy were added for the treatment of LM to more traditional treatments including intra-thecal chemotherapy (IT-CTx), radiotherapy (RT) and systemic chemotherapy (Sys-CTx) (6–8). However, there is no gold standard treatment as prospective randomized study is lacking. Multimodality treatment is recommended only for patients with breast primary among various solid tumors according to current NCCN guideline (9). Therefore, the purpose of this study was to identify the factors affecting survival in patients with LM from solid tumors and define the role of multimodality approach.

MATERIALS AND METHODS

Among patients treated at Seoul National University Hospital from January 2004 to March 2011, 82 patients met following eligibility criteria; (1) histological verification of primary solid tumor and (2) presence of malignant cell in cytologic evaluation of CSF, or demonstration of findings consistent with LM on brain or spine magnetic resonance imaging (MRI). After the Institutional Review Board's approval, retrospective review of patient medical records was conducted to gather demographics, treatment patterns, and clinical outcomes. Two patients were excluded from further analysis after review of medical records. One patient was diagnosed with sepsis simultaneously and expired prior to treatment of LM due to sepsis. The other patient was lost to follow up immediately after the diagnosis of LM.

Clinical profiles

Patient characteristics are summarized in Table 1. Median age at diagnosis was 54-years (range: 27-78 years). Forty-nine patients (61.3%) were female and 31 (38.8%) were male. About one-third of the patients had an ECOG performance status class of 0 or 1 at the time of diagnosis of LM (29 patients, 36.3%). The most frequent site of primary tumor was lung (47 patients, 58.8%) followed by breast (20patients, 25%) and stomach (13 patients, 16.3%). Most patients (75 patients, 93.8%) had distant metastasis prior to the diagnosis of LM. Forty-nine patients (61.3%) were treated with multiple chemotherapy regimens.

Table 1. Patient characteristics

Variable	N (%)	
Age	Median : 54 years	
	Range : 27-78 years	
Gender	Male	31 (38.8)
	Female	49 (61.3)
ECOG score	0	2 (2.5)
	1	27 (33.8)
	2	19 (23.8)
	3	13 (16.3)
	4	5 (6.3)
Primary site	NSCLC	37 (46.3)
	SCLC	10 (12.5)
	Breast	21 (25.0)
	Stomach	13 (16.3)
DM prior to diagnosis of LM	Yes	75 (93.8)
	No	5 (6.3)
Regimen. of prior CTx	Median : 2	
	Range : 0-7	
	0	4 (5.0)
	1	27 (33.8)
	2	14 (17.5)
	3	15 (18.8)
	4	12 (15.0)
≥ 5	8 (10.1)	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; DM = distant metastasis; LM = leptomeningeal metastasis; CTx = Chemotherapy

Presenting symptoms of LM were categorized into three subgroups; symptoms suggestive of the involvement of the cerebrum, spinal cord or cranial nerve (Table 2). Among cerebral involvement symptoms (62 patients, 77.5%), headache was most common with 43 patients (53.8%) followed by nausea or vomiting in 28 patients (35.0%). Among 23 patients (28.8%) presented with spinal involvement symptoms, weakness of extremities was most common manifestation with 13 patients (16.3%) and bowel/bladder dysfunction was second most common symptom with 9 patients (11.3%). Fifteen patients (18.8%) had symptoms of the cranial nerve involvement such as visual disturbance (6 patients, 7.5%) or diplopia (5 patients, 6.3%). Malignant cells in CSF cytology were found in 55 patients (68.8%). Increased opening pressure was observed in less than half of available cases (17 patients, 21.3%). CSF leukocytosis ($WBC \geq 4$) was found in 62 patients (77.5%). Number of patients with elevated protein (>50 mg/dl) and decreased glucose (<60 mg/dl) in CSF were 51 (63.8%) and 45 (56.3%), respectively. Brain MRI was obtained from all patients suspected of LM. Linear, nodular or diffuse leptomeningeal enhancement after administration of gadolinium was considered as positive finding for LM and these findings were shown in 70 patients (87.5%). Spine MR was done for 35 patients with suspected spinal involvement. The evidence of LM was found in 21 cases (26.3%). CSF cytology and MR findings are depicted in table 3.

Table 2. Presenting symptoms

Variable	N (%)
Cerebral symptoms	62 (77.5)
Headache	43 (53.8)
Mental change	9 (11.3)
Gait disturbance	5 (6.3)
Nausea, vomiting	28 (35.0)
Vertigo	11 (13.8)
Loss of consciousness	3 (3.8)
Spinal symptoms	23 (28.8)
Weakness of extremities	13 (16.3)
Parasthesia	6 (7.5)
Back/Neck pain	5 (6.3)
Bowel/bladder dysfunction	9 (11.3)
Cranial symptoms	15 (18.8)
Diplopia	5 (6.3)
Visual disturbance	6 (7.5)
Facial numbness	1 (1.3)
Tinnitus	3 (3.8)
Dysphonia	1 (1.3)

Table 3. CSF profile and MRI findings

Variables		N (%)
Opening pressure (mmHg)	Median 18.5 (range, 3-68)	
	≤ 20	30 (37.5)
	>20	17 (21.3)
WBC	Median 11.0 (range, 0-180)	
	< 4	18 (22.5)
	≥ 4	62 (77.5)
Protein	Median 63.9 (range, 23-2610.2)	
	≤ 50	25 (31.3)
	> 50	51 (63.8)
Glucose	Median 55.0 (range, 11.0-121.0)	
	< 60	45 (56.3)
	≥ 60	31 (38.8)
CSF Cytology	Positive	55 (68.8)
	Negative	22 (27.5)
Brain MRI	Positive	70 (87.5)
	Negative	10 (12.5)
Spinal MRI	Positive	21 (26.3)
	Negative	14 (17.5)

Abbreviations: CSF = cerebrospinal fluid

Treatment patterns

Patterns of treatment are displayed in Table 4. IT-CTx was given to 72 patients (90%). IT-CTx was performed thorough lumbar puncture mainly and ommaya reservoir was used in 4 cases. Methotrexate (15mg) was most commonly administered agent with 57 patients. Triple regimen of methotrexate (15mg), hydrocortisone (15mg/m²) and cytarabine (30mg/m²) was injected in 15 patients. Median number of cycle for IT-CTx was 6. IT-MTx was performed twice per week initially. After two consecutive negative conversions of CSF cytologies, IT-CTx was repeated weekly. For the maintenance chemotherapy, frequency of treatment was tapered to bi-weekly twice, tri-weekly twice, and off treatment.

Radiotherapy for LM was whole brain radiotherapy (WBRT) and/or focal spinal radiotherapy. WBRT was offered to 54 patients. The scheme of 30 Gy / 10 fractions was most commonly applied (70.9%), and additional boost to focal lesion was given in 9 patients (range, 8 - 24 Gy). Spinal radiotherapy was delivered to 14 patients (17.5%). Most common field included lumbar spine (7 patients) followed by sacrum (5 patients). Most frequently applied RT schedule was also 30 Gy over 10 fractions.

Systemic chemotherapy (Sys-CTx) was offered to 27 patients and various regimens were used according to primary tumor type. Sys-CTx included both cytotoxic chemotherapy (19 patients, taxane, platinum, and etc.) and/or target agents (14 patients, epidermal growth factor receptor – tyrosine kinase inhibitor (EGFR-TKI) or tyrosine kinase inhibitor).

Patients were grouped into three according to the number of treatment modalities. Number of patients treated with single treatment modality was 26 (32.5%). IT-CTx was most frequently chosen single modality with 19 patients

(23.8%). Thirty-five patients (43.8%) were treated with dual modalities. Dominant combination was IT-CTx and WBRT with 29 patients (36.3%). Number of patients treated with triple modalities was 19 (23.8%).

Table 4. Treatment patterns

Treatment pattern		N (%)
IT-CTx	Done	72 (90.0)
	Not done	8 (10.0)
Sys-CTx	Done	27 (33.8)
	Not done	53 (66.3)
WBRT	Done	54 (67.5)
	Not done	26 (32.5)
Combined Modality treatment		
	Single modality	26 (32.5)
	IT-CTx only	19 (23.8)
	WBRT only	5 (6.3)
	Sys- CTx only	2 (2.5)
	Double modality	35 (43.8)
	IT-CTx+ WBRT	29 (36.3)
	IT-CTx +Sys- CTx	5 (6.3)
	WBRT + Sys-CTx	1 (1.3)
	Triple modality	19 (23.8)
Spine RT	Done	14 (17.5)
	Not done	66 (82.5)

Abbreviations: IT-CTx = intrathecal chemotherapy; Sys-CTx = Systemic chemotherapy;

WBRT = whole brain radiotherapy; RT = radiotherapy

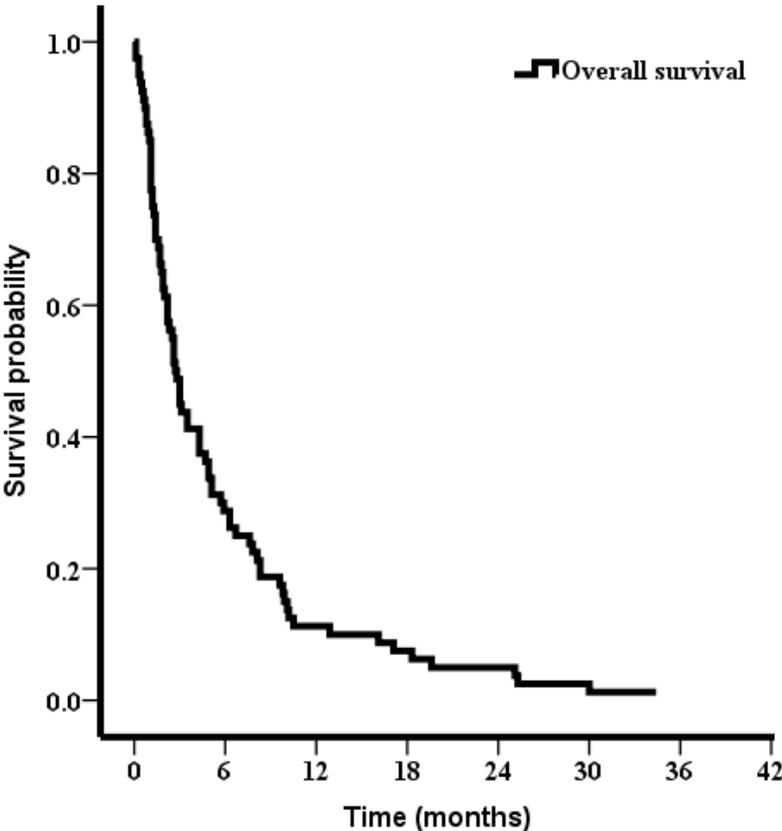
Clinical endpoint and statistical analysis

Endpoint was determined as date of death or last available follow up. Date of diagnosis of primary tumor and LM were defined as the date of histological verification and reported date of CSF cytology or image study, respectively. Overall survival (OS) was calculated from date of diagnosis of LM to the endpoint. Estimated OS was obtained by using the Kaplan-Meier method. Possible prognostic factors including demographics, clinical manifestations, laboratory results, image findings and treatment patterns were analyzed to evaluate the effects on survival. Univariate analyses were done using the Log-rank test and multivariate analyses were performed through the Cox proportional hazards regression analyses. P-value less than 0.05 was considered statistically significant. All statistical analyses were performed by IBM SPSS statistics version 19 (SPSS Inc., an IBM Company, Chicago, Illinois, USA).

RESULTS

Median interval from diagnosis of primary tumor to LM was 15.7 months. Median follow-up duration was 2.6 months. Median survival (MS) was 2.7 months and the 1-year survival rate was 11.3% (Figure 1). Only one patient was alive at the time of analysis.

Fig. 1. Overall survival rate



Results of statistical analyses for OS are summarized in Table 5. Patients who were 65 years old or younger had longer survival (MS; 3.0 mo vs. 1.1 mo, $P = 0.03$). Survival outcomes were not affected by gender, performance status or manifesting symptoms. There was significant difference according to primary site ($P = 0.002$); LM from non-small cell lung cancer (NSCLC) showed most favorable outcomes with MS of 4.3 months whereas LM from small cell lung cancer (SCLC) had worst outcome with 1.4 months of MS. MS of patients with breast cancer and stomach cancer were 2.7 and 1.6 months, respectively. Patients treated with multiple chemotherapy regimen prior to the LM diagnosis had trend toward decreased survival (MS; 2.7 mo vs. 2.8 mo, $P = 0.074$). Among laboratory results, patients with positive CSF cytology had inferior survival (MS; 2.3 mo vs. 6.3 mo, $P = 0.005$), whereas patients with CSF leukocytosis survived longer (MS; 2.8 mo vs. 1.7 mo, $P = 0.004$). There were no relationships between increased opening pressure, CSF protein or glucose level and survival outcome. Identification of LM on neuraxis image study did not affect outcomes, as well.

Table 5. Prognostic factors for survival

Characteristics	N (%)	MS (mo)	P - uni variate	P – multi variate HR (95% CI)
Age				
≤ 65	64 (80)	3.0	0.003	0.493
> 65	16 (20)	1.1		
Gender				
Male	31 (38.8)	2.3	0.337	
Female	49 (61.3)	3.0		
ECOG				
0,1	29 (36.3)	3.5	0.154	
2,3,4	37 (46.3)	2.6		
Cerebral symptoms				
Yes	62 (77.5)	2.6	0.197	
No	18 (22.5)	2.8		
Spinal symptoms				
Yes	23 (28.8)	2.7	0.121	
No	57 (71.3)	2.5		
Cranial nerve symptoms				
Yes	15 (18.8)	2.6	0.620	
No	65 (81.3)	3.0		
Primary site				
Lung (NSC)	37 (46.3)	4.3	0.003	0.104
Lung (SC)	10 (12.5)	1.4		
Breast	20 (25.0)	2.7		
Stomach	13 (16.3)	1.6		
DM prior to LM diagnosis				

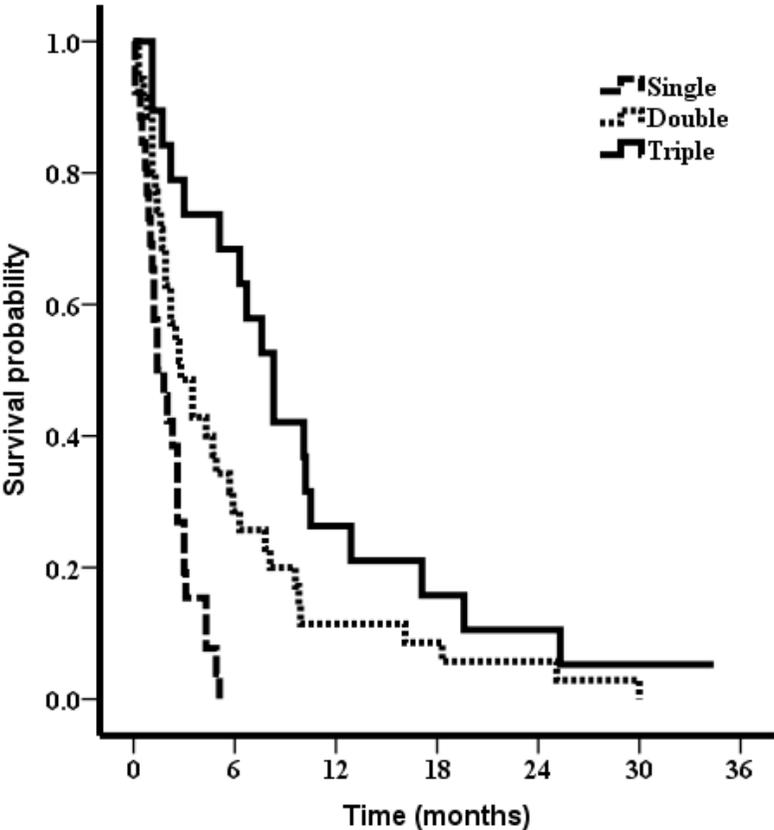
Absent	75 (93.8)	3.0	0.318		
Present	5 (6.3)	2.2			
Prior chemotherapy regimen					
< 2	31 (38.8)	2.8	0.074	0.026	1
≥ 2	49 (61.3)	2.7			1.91 (1.08-3.37)
CSF opening pressure					
≤ 20	30 (37.5)	2.3	0.918		
>20	17 (21.3)	2.7			
CSF WBC					
< 4	18 (22.5)	1.7	0.004	0.263	
≥ 4	62 (77.5)	2.8			
CSF Protein					
≤ 50	25 (31.3)	2.6	0.513		
> 50	51 (63.8)	3.0			
CSF Glucose					
< 60	45 (56.3)	2.5	0.910		
≥ 60	31 (38.8)	4.4			
CSF Cytology					
Positive	55 (68.8)	2.3	0.005	<0.001	3.14 (1.66-5.95)
Negative	22 (27.5)	6.3			1
Brain MRI					
Positive	70 (87.5)	2.7	0.934		
Negative	10 (12.5)	2.2			
Spine MRI					
Positive	21 (26.3)	4.3	0.582		
Negative	14 (17.5)	5.9			
IT-CTx					
Done	72 (90.0)	2.7	0.058	0.861	

Not done	8 (10.0)	2.6			
Sys-CTx					
Done	27 (33.8)	7.6	<0.001	<0.001	0.32 (0.18-0.58)
Not done	53 (66.3)	2.0			1
WBRT					
Done	54 (67.5)	3.5	0.065	0.010	0.47 (0.26-0.83)
Not done	26 (32.5)	2.0			1
Spinal RT					
Done	14 (17.5)	4.3	0.673		
Not done	66 (82.5)	2.6			
Combined modality					
Single	26 (32.5)	1.4	<0.001	<0.001	1
Double	35 (43.8)	2.8		0.013	0.45 (0.24-0.84)
Triple	19 (23.8)	8.3		<0.001	0.20 (0.09-0.44)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; NSC = non-small cell; SC = small cell; DM = distant metastasis; LM = leptomeningeal metastasis; CSF = cerebrospinal fluid; IT-CTx = intrathecal chemotherapy; Sys-CTx = Systemic chemotherapy; WBRT = whole brain radiotherapy; RT = radiotherapy

In respect to treatment modality, Sys-CTx (MS; 7.6 mo vs. 1.9 mo, $P < 0.001$) significantly improved survival outcomes. IT-CTx (MS; 2.7 mo vs. 2.6mo, $P = 0.058$) and WBRT also showed marginally statistically significant impact on survival (MS; 3.5 mo vs. 2.0 mo, $P = 0.065$). Patients treated with combined modality had statistically significant survival prolongation (MS; single, 1.4 mo vs. dual, 2.8 mo vs. triple, 8.3 mo, $P < 0.001$). In multivariate analysis (Table 5), survival outcomes were unfavorable in patients treated with multiple chemotherapy regimen before LM ($P = 0.026$, HR 1.91, 95% CI [1.08-3.37]). CSF cytology-positive group had shorter survival ($P < 0.001$, HR 3.14, 95% CI [1.66-5.95]). Statistically significant survival improvement was shown in patients treated with Sys-CTx group ($P < 0.001$, HR 0.32, 95% CI [0.18-0.58]) and WBRT ($P = 0.01$, HR 0.47, 95% CI [0.26-0.83]). Combined modality treatment (CMT) showed superior survival outcomes ($P < 0.001$), whereas age, primary site, CSF leukocytosis, and IT-CTx lost their statistical significance, when adjusted for other factors (Figure 2).

Fig. 2. Overall survival rate according to combined treatment modality



Subgroup analysis of NSCLC

Subgroup analysis of NSCLC (n = 37) was performed. Table 6 shows the characteristics and analysis of prognostic factors for OS in NSCLC. Factors with favorable outcome were; absence of cranial nerve symptoms (MS; 5.7 mo vs. 2.6 mo, P = 0.036), less Sys-CTx regimen (MS; 8.3 mo vs. 3.5 mo, P = 0.024), CSF leukocytosis (MS; 5.7 mo vs. 3 mo, P = 0.013), negative CSF cytology (MS; 8.3 mo vs. 3.5 mo, P = 0.038), IT-CTx (MS; 5.7 mo vs. 2.6 mo, P = 0.007), Sys-CTx (MS; 10.1 mo vs. 2.8 mo, P < 0.001). Multivariate analysis revealed that CSF cytology and Sys-CTx were statistically significant prognostic factors (CSF cytology, P = 0.028, HR 2.74, 95% CI [1.12-6.73]; Sys-CTx, P = 0.001, HR 0.14, 95% CI [0.05-0.42]).

Table 6. Subgroup analysis of NSCLC

Characteristics	N (%)	MS (mo)	P - uni variate	P - multi variate	HR (95% CI)
Age					
≤ 65	31 (83.8)	4.7	0.266		
> 65	6 (16.2)	1.1			
Gender					
Male	14 (37.8)	3.5	0.942		
Female	23 (62.2)	4.7			
ECOG					
0,1	16 (43.2)	2.6	0.773		
2,3,4	13 (35.1)	4.3			
Cerebral symptoms					
Yes	30 (81.1)	3.5	0.103		
No	7 (18.9)	10.5			
Spinal symptoms					
Yes	9 (24.3)	6.3	0.106		
No	28 (75.7)	4.3			
Cranial nerve symptoms					
Yes	8 (21.6)	5.7	0.036	0.630	
No	29 (78.4)	2.6			
DM prior to LM diagnosis					
Absent	35 (94.6)	2.6	0.773		
Present	2 (5.4)	4.3			
Prior chemotherapy regimen					
< 2	15 (40.5)	8.3	0.024	0.645	
≥ 2	22 (59.5)	3.5			

CSF opening pressure					
≤ 20	13 (35.1)	6.3	0.388		
>20	10 (27.0)	2.6			
CSF WBC					
< 4	8 (21.6)	3.0	0.013	0.394	
≥ 4	29 (78.4)	5.7			
CSF Protein					
≤ 50	12 (32.4)	4.3	0.900		
> 50	24 (64.9)	4.3			
CSF Glucose					
< 60	17 (45.9)	3.5	0.245		
≥ 60	19 (51.4)	4.9			
CSF Cytology					
Positive	23 (62.2)	3.5	0.038	0.028	2.74 (1.12-6.73)
Negative	13 (35.1)	8.3			1
Brain MRI					
Positive	33 (89.2)	4.3	0.652		
Negative	4 (10.8)	3.5			
Spine MRI					
Positive	6 (16.2)	4.3	0.689		
Negative	9 (24.3)	9.6			
IT-CTx					
Done	31 (83.8)	5.7	0.007	0.676	
Not done	6 (16.2)	2.6			
Sys-CTx					
Done	15 (40.5)	10.1	0.001	0.001	0.14 (0.05-0.42)
Not done	22 (59.5)	2.8			1
WBRT					

Done	30 (81.1)	4.7	0.801
Not done	7 (18.9)	2.6	

Spinal RT

Done	2 (5.4)	1.9	0.707
Not done	4 (10.8)	4.3	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; NSCLC = non -small cell lung cancer; DM = distant metastasis; LM = leptomeningeal metastasis; CTx = Chemotherapy; CSF = cerebrospinal fluid; IT-CTx = intrathecal chemotherapy; Sys-CTx = Systemic chemotherapy; WBRT = whole brain radiotherapy; RT = radiotherapy

Unlike other solid tumors, target agents (EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor) were commonly used in NSCLC patients (Table 7). Further analysis was performed on EGFR-TKI and its associated factors. Evaluation of EGFR mutation was performed in 19 patients, and 12 patients (32.4%) had gene mutation. Of the patients without the analysis of EGFR mutation, probability of the mutation was suspected to be high for 13 patients based on two favorable clinical parameters, adenocarcinoma histology and never-smoking history. EGFR-TKI was prescribed to these patients based on this speculation. Detected or suspicious EGFR mutation had no significant impact on survival in univariate analysis ($p = 0.955$). During the entire course of treatment for NSCLC and LM, 28 patients (75.7%) were exposed to EGFR-TKI during course of the treatment and EGFR-TKI exposure was related with marginal prolongation of survival (MS, 4.7 mo vs. 2.8 mo, $p = 0.056$). Nineteen (51.4%) and 13 patients (35.1%) received the EGFR-TKI before and after LM diagnosis, respectively. Patients exposed to EGFR-TKI prior to LM diagnosis had a relatively short survival (MS, 3.5 mo vs. 4.9, $p = 0.034$), whereas, EGFR-TKI after LM diagnosis led to statistically significant improvement in survival (MS, 10.5 mo vs. 3 mo, $p < 0.001$). After adjustment for other factors, the statistical significance of EGFR-TKI use prior to LM diagnosis disappeared ($p = 0.759$). In contrast, statistical significance of EGFR-TKI administration after LM diagnosis remained after multivariate analysis ($p = 0.001$, HR 0.13, 95% CI [0.04-0.44], Fig. 3).

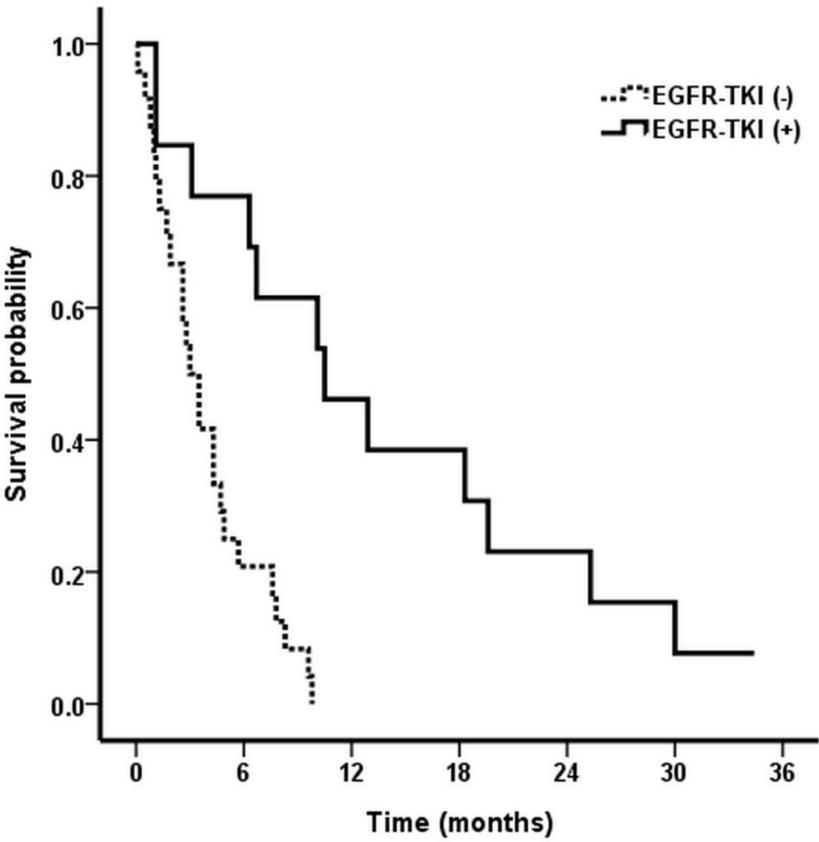
Table 7. EGFR-TKI in NSCLC

Characteristics	N (%)	MS (mo)	P- uni variate	P - multi variate	HR (95% CI)
Suspicious ^a or detected EGFR mutation					
No	12 (32.4)	4.9	0.955		
Yes	25 (67.6)	4.3			
EGFR-TKI during the entire course					
No	9 (24.3)	2.8	0.056		
Yes	28 (75.7)	4.7			
EGFR-TKI exposure prior to LM diagnosis					
No	18 (48.6)	4.9	0.034	0.759	1
Yes	19 (51.4)	3.5			1.16 (0.44-3.04)
EGFR-TKI exposure after LM diagnosis					
No	24 (64.9)	3.0	<0.0001	0.001	1
Yes	13 (35.1)	10.5			0.13 (0.04-0.45)

Abbreviations: NSCLC = non -small cell lung cancer; EGFR-TKI = epidermal growth factor receptor – tyrosine kinase inhibitor; LM = leptomeningeal metastasis

^a Highly suspicious of EGFR mutation, clinically based on adenocarcinoma histology and never-smoking history

Fig. 3. Overall survival according to use of EGFR-TKI after diagnosis of leptomeningeal metastasis in NSCLC



DISCUSSION

Patients with LM, which is the third most common metastatic site of the central nervous system (7), have a poor prognosis with reported MS of 4-6 weeks for untreated patients (1,7,10,11). The proper treatment for LM could not only give palliation of symptoms but also prolongation of survival. But treatment of LM is complicated as standard of care is not established and the role of each treatment modality is not well defined (10). Prognostic factors also have been reported in many literatures, but it is still controversial.

In the current study including 80 patients with LM from various solid tumors, MS was 2.7 months and 1-year survival rate was 11.3%, which is similar to previous reports (1,3,4,8,11,12). Though the difference in MS for primary site was not statistically significant, patients with NSCLC showed the most favorable outcome with a MS of 4.3 months followed by patients with breast cancer in presenting cohort. This is in contrast to previous reports where breast cancer is considered most favorable primary tumor (3,13,14). Reported MS for breast primary ranges from 3 to 7.5 months (11,13,15), whereas that for NSCLC primary is from 1.5 to 5 months (10). Shorter survival of patients with breast primary compared to other series may be related with inclusion of patients with more aggressive tumor biology. The influence of molecular subtype in patients with LM from breast has been reported by Gauthier et al (13,16). In current cohort, proportion of patients without membrane receptor was relatively higher than other studies (13,16). MS of hormonal receptor positive group (7 patients, 35%) was 5.1 months, whereas that for hormonal receptor negative group (12 patients, 60%) was only 1.7 months. Though statistical significance was not found, this may be mere reflection of insufficient number of analyzed patients.

Survival outcomes were significantly affected by positive CSF cytology, exposure to multiple chemotherapy regimens for the primary tumor treatment, administration of Sys-CTx, WBRT and CMT for LM, after adjusting for other possibly related clinical factors. There were no significant effect on survival by performance status, age, presence of symptoms suggesting specific structure involvement, extent of CNS infiltration observed on imaging study, and CSF laboratory findings except for cytology. In the previous studies, performance status was considered as significant prognostic factor (10,13,16). But it is not conclusive because some studies failed to show the significance in multivariate analysis, as in current study (17). As most studies were conducted retrospectively, performance status was estimated by researcher based on medical records in contrast to other variables, such as CSF or image findings and therefore is subject to bias. Boogerd et al (15) reported that age older than 55 years is one of negative prognostic factors, but study by Balm et al (18) and current study showed that age is not a predictive factor. According to manifesting symptoms, Boogerd et al (15) and Balm et al (18) demonstrated that patients with symptoms related to cranial nerve or cerebral involvement had worse prognosis, respectively. But the relationship between symptoms and outcomes was conflicted with each other studies (15,16,19). Although the neuraxis imaging study is one of most important diagnostic tools for LM, it is unclear whether extent of CNS infiltration on imaging study affects the survival. Other studies as well as current study, showed that presence of parenchymal CNS metastases or greater imaging evidence of LM is not indicative of inferior survival (15,16,20).

The meaning of CSF study also has controversies. Boogerd et al (15) reported that patients with CSF glucose of 43mg/dl or less had significantly

short survival in multivariate analysis. They explained that CSF glucose level was decreased because of consumption by circulating tumor cells and impairment of glucose transfer caused by meningeal involvement. They also described that normal CSF protein means the absence of wide spread leakage through involved meninges and found that patients with normal protein level had longer MS. But studies by Park et al (10) and Gauthier et al (16) failed to show its significance. In contrast to current study, malignant tumor cell in CSF at diagnosis was not correlated with survival in the study by Harstad et al (20). These results might reflect the quantitative uncertainty of CSF study. According to Murray et al, even if there is no impairment of CSF flow, level of glucose, protein and malignant cells in CSF specimen might vary at different levels of the neuraxis (21).

Of our cohort, patients treated with two or more regimen of chemotherapy prior to LM showed poor outcome. Gauthier et al (16) also showed that overall survival was independently influenced by the number of prior chemotherapy which reflects chemosensitivity of remaining cancer cells.

In current study, trend toward improved survival for patients undergoing IT-CTx in univariate analysis was lost after multivariate analysis, whereas positive impact of WBRT, Sys-CTx and CMT was sustained. Of note is that there was no difference in performance status of patients according to treatment modality. This means that choice of the treatment was not based on patient's performance status. In the past, IT-CTx was considered as the main treatment modality in LM, whereas the role of Sys-CTx was questioned as intravenously injected CTx agents was thought unavailable to cross BBB (13). Thus, older studies mainly focused on validating the role of IT-CTx (18–20,22,23). Recently, however, the role of IT-CTx has been questioned. In the

study by Boogerd et al (15), survival outcomes of non-IT-CTx treated group were identical to those of IT-CTx group. Park et al (10) and Bokstein et al (24) also showed no significant difference of MS when two groups treated with or without IT-CTx was compared.

Nowadays, the role of Sys-CTx is more emphasized. In patients with LM, disturbed BBB enables Sys-CTx agents to penetrate into the CSF space (13). In concordance with results from current study, other studies also confirmed survival improvement by Sys-CTx in patients with LM from solid tumor (10,13,16). In the study by Glantz (25), high dose Sys-CTx showed significant improvement of survival over IT-CTx (MS, 13.8 mo vs. 2.3 mo). Particularly, in several studies, LM from breast primary seemed to respond to intravenously injected CTx (13,16). Thus, NCCN guideline recommends Sys-CTx to responsive cancer such as breast cancer or lymphoma (9).

However, with introduction of EGFR TKIs in NSCLC, there were many attempts to use it for LM from NSCLC. Most studies showed the favorable outcomes. Park et al (10) and Yi et al (26) demonstrated that Sys-CTx such as EGFR TKIs could enlengthen survival in patients with LM from NSCLC as well. Our results of NSCLC subgroup analysis also showed that EGFR TKI for LM significantly reduced risk of death (HR 0.15, MS 10.1 mo) and MS of EGFR-TKI group was the longest among all subgroups. In contrast to number of regimens prior LM, the prior exposure to EGFR-TKI did not compromised the survival. Gefitinib was mainly used before LM diagnosis, whereas most patients were treated with erlotinib after LM diagnosis. Many previous studies reported that gefitinib does not seem to penetrate the BBB. Thus tumor cells within neuraxis were naive to gefitinib and were not resistant to the EGFR-TKI. In addition, erlotinib seems to penetrate the BBB more readily, making it

more effective for control of the LM lesions (26,27). As for the EGFR mutation, though it was not directly related to the prognosis in the current study, any conclusion should not be drawn, considering small sample size.

On the other hand, radiotherapy for LM has traditionally been limited to bulky disease or site of CSF flow obstruction (9,11). The purpose of these focal RT was to provide symptom palliation. WBRT has been used for LM in limited institutions. Rudnicka et al (13) reported that WBRT prolonged survival in univariate analysis. Though this was not valid in multivariate analysis, they contended that use of WBRT has a positive impact on the quality of life and thus should be included in multimodality treatment for LM. Study by Park et al (10) demonstrated the impact of WBRT on survival in multivariate analysis ($P = 0.032$, Adjusted HR 2.76 [1.09-7.0]). However, recently published largest series in this regard by Patrick et al (28) showed that survival was not improved by WBRT in patients with primary lung cancer ($P = 0.84$). The improvement of survival from WBRT in current study may have been influenced somewhat by combined modality treatment. There were only 5 patients (9.3%) treated with WBRT as sole modality, whereas 21 patients underwent single modality treatment other than WBRT. In contrast, there were only 5 patients who underwent CMT other than WBRT. Thus, distribution of patients receiving WBRT as a component of treatment was skewed in favor of CMT ($P < 0.001$, data not shown). Kim et al (29) also reported survival benefit from addition of chemotherapy to WBRT in patients with LM from breast cancer ($P < 0.001$). They also showed that chemotherapy after WBRT was the most powerful prognostic factors for survival in the multivariate analysis, stressing the importance of combined modality management. It should also be noted that in current study, role of radiotherapy

in conjunction with EGFR-TKI could not be sought, as there were no patients exposed to both modalities.

Aforementioned improved treatment outcomes from Sys-CTx and RT suggest the need of CMT for LM (13,23). Even though performance status did not affect survival in this study, CMT might not be feasible to compromised patients. Thus other factors to select the patient more suitable for CMT for LM should be studied in the future to improve the survival of these patients with dismal prognosis.

In current study, estimated survival curve is relatively reliable because all patients included were not censored. However, as it was retrospective study, it is not free from inherent limitations. There is also limitation stemming from limited number of patients included for analysis.

CONCLUSION

Unlike previous studies, no factors among the characteristics of patients and symptoms at the time of diagnosis of LM affected survival including performance status. Survival in patients with primary NSCLC was comparable to that in patients with primary breast cancer. Furthermore, survival improvement was significant with combined modality treatment including Sys-CTx and WBRT over single modality treatment. Thus, multimodality treatment should be sought for patients with feasible performance to tolerate treatment and those with not only breast primary but also NSCLC primary tumors. In addition, use of EGFR-TKI after LM diagnosis significantly improved survival for NSCLC patients. Further study is warranted to define the role of EGFR-TKI in conjunction with radiotherapy.

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국문 초록

고형암에서 발생한 뇌수막 전이 환자에 대한 병용치료법의 영향

목적: 본 연구에서는 고형암에서 발생한 뇌수막 전이 환자에서의 예후 인자와 병용치료법의 역할을 밝히고자 하였다.

대상환자 및 방법: 2004 년 1 월부터 2011 년 5 월까지 서울대학교 병원에서 고형암에서 발생한 뇌수막 전이를 진단받은 환자 80 명의 의무기록을 후향적으로 조사하였다. 가장 흔한 원발 병소는 폐였고(59%), 그 다음으로 유방과(25%) 위(16%) 순으로 많이 포함되었다. 환자들의 중앙나이는 54 세였고, 49 명의 여환과 31 명의 남환이 포함되었다. 환자의 2/3 가 ECOG class 1 이거나 2 로 평가 되었다. 대부분의 환자들은 경막 내 항암화학요법과(90%) 전뇌 방사선치료를(67.5%) 시행 받았다. 전신 항암화학 요법은 33.8%에서 시행되었다. 단일치료만을 받은 환자, 두 가지 치료법을 병용한 환자, 그리고 세가지 치료법을 병용한 환자는 각각 32.5%, 43.8% 그리고 23.8%였다.

결과: 중앙 생존기간은 2.7 개월, 1 년 생존률은 11.3%였다. 생존에 대한 다변량 분석 결과, 뇌척수액 세포검사상 종양세포가 관찰되지 않는 경우 ($P < 0.001$), 뇌수막 전이 이전에 사용된 항암화학요법의 개수가 적은 경우 ($P = 0.026$), 전뇌 방사선치료 ($P = 0.01$), 전신 항암화학요법 ($P < .001$), 그리고 병용치료법 (P

< 0.001)이 시행될 경우 통계적으로 유의하게 생존률을 향상시키는 것을 확인할 수 있었다.

비소세포암 환자군에 대한 하위 분석에서는, 역시 뇌척수액 검사상 종양세포가 관찰되지 않거나, 표적치료제를 사용한 경우, 혹은 병용치료법이 시행될 경우 생존률이 유의하게 증가하였다. 특히 표적치료제를 포함하여 치료 받은 환자들의 중앙 생존기간은 10.1개월이었다.

결론: 기존 연구들과 달리, 환자의 특성과 뇌수막 전이 발현 당시의 증상 중 생존에 영향을 미치는 인자는 확인할 수 없었고, 원발암이 비소세포암종인 환자들의 생존률이 유방암환자의 생존률에 비할 만 하였다. 또한, 병용치료법이 전체 환자, 또한 표적치료제의 사용이 비소세포성 폐암 환자에서 유의하게 생존률을 향상시키는 것을 확인할 수 있었다. 방사선 치료와 표적 치료제와의 병용 효과에 대해서는 향후 추가 연구가 필요하겠다.

주요어 : 뇌수막전이, 예후인자, 병용치료법

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