Salvage Treatment with Intracerebrospinal Fluid Thiotepa in Patients with Leptomeningeal Metastasis After Failure of Methotrexate-based Treatment

KYOUNG-MIN CHO1,4*, YU JUNG KIM1*, SE HYUN KIM1, JIN WON KIM1, JEONG-OK LEE1, JUNG HO HAN2, KEUN-WOOK LEE1, JEE HYUN KIM1, CHAE-YONG KIM2, SOO-MEE BANG1, IN-AH KIM3, JAE SUNG KIM3 and JONG-SEOK LEE1

Departments of 1Internal Medicine, 2Neurosurgery, and 3Radiation Oncology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; 4Department of Internal Medicine, School of Medicine, Kyung Hee University, Seoul, Republic of Korea

Abstract. Aim: To evaluate the efficacy of intracerebrospinal fluid (intra-CSF) thiotepa in patients with leptomeningeal metastasis (LM) after failure of a methotrexate-based treatment. Patients and Methods: We retrospectively reviewed the medical records of patients with LM who received 10 mg of intra-CSF thiotepa twice a week. Results: Out of 40 patients, 25 were females (63%), and 31 (78%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2. Fourteen out of the 30 evaluable patients (47%) had a cytological response to intra-CSF thiotepa. The median overall survival (OS) after treatment with thiotepa was 19.4 weeks (95% confidence interval (CI)=15.3-23.5). Grade 3 toxicities were thrombocytopenia (N=2), bacterial meningitis (N=2), and pneumonia (N=1). According to a multivariate analysis, an ECOG PS ≥2 (hazard ratio (HR)=5.11, 95% CI=1.39-18.80, p=0.014), clinical improvement (HR=0.09, 95% CI=0.03-0.29, p<0.001), and radiation for LM after intra-CSF thiotepa (HR=0.33, 95% CI=0.11-0.97, p=0.043) were independently associated with survival. Conclusion: Intra-CSF thiotepa seems to be a meaningful salvage treatment for patients with LM whose disease progresses after a methotrexate-based treatment.

*These Authors contributed equally to this study.

Correspondence to: Professor Jong-Seok Lee, MD, Ph.D., Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, 166 Gumi-ro, Bundang-gu, Seongnam, Gyeonggi-do, 463-707, Korea. Tel: +82 317877003, e-mail: jslee0918@gmail.com

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Patients and Methods

Patients. All patients who were treated for LM at the Seoul National University Bundang Hospital between 2008 and 2013 were retrospectively reviewed. A total of 40 patients with cytologically-proven LM treated with second- or third-line intra-CSF thiotepa were identified (Figure 1). We did not include patients with radiological evidence of LM that was not confirmed by positive CSF cytology in this study. All 40 patients were previously treated with intra-CSF methotrexate, methotrexate in combination with cytarabine, or both of the regimens. Intra-CSF methotrexate and intra-CSF methotrexate plus cytarabine are the most commonly used first- or second-line regimens at our institution. The protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (approval number: B-1305-204-116).

Treatment and evaluation. Patients were treated with 10 mg of intra-CSF thiotepa twice every week. Patients whose CSF was free of malignant cells for three consecutive measurements received thiotepa once weekly as a maintenance treatment. The concurrent administration of radiation therapy or systemic chemotherapy were determined at the discretion of the attending medical oncologist.

The clinical response was divided into three categories: improved, stable, or deteriorated. Clinical improvement was defined as improvements in terms of neurological symptoms and/or Eastern Cooperative Oncology Group performance status (ECOG PS). Patients with clinical improvement were considered clinical responders. Patients were considered 'stable' when the neurological symptoms or ECOG PS were constant. A cytological response was defined as complete clearing of all malignant cells from the CSF. Persistent positive cytology for more than 4 weeks, the reappearance of malignant cells in CSF, new or worsening neurological deficits, or a decline in the ECOG PS were considered progressive disease. An objective systemic response to systemic chemotherapy was assessed by the Response Evaluation Criteria in Solid Tumors (11). Adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 were reviewed based on the oncologists' medical records and laboratory test results (12).

Statistical methods. Time to progression (TTP) was calculated from the starting date of intra-CSF thiotepa treatment to the date of documented disease progression. Overall survival (OS) was calculated from the date of LM diagnosis or of starting intra-CSF thiotepa treatment to the date of death or last follow-up. The TTP and OS were analyzed using the Kaplan–Meier method. A univariate analysis was performed using the Cox proportional hazard regression analysis. The age, sex, and variables with a p-value of less than 0.1 by univariate analysis were included in the multivariate analysis. A stepwise regression analysis was performed using the Cox proportional hazard model to identify independent prognostic factors. Two-sided p-values of less than 0.05 were considered significant and the confidence intervals (CIs) were calculated at the 95% confidence level. All statistical analyses were performed with the IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Patients' characteristics. The patients' characteristics are summarized in Table I. The median age was 54.5 years (range=31-70 years). Of the 40 patients, 25 (63%) were female, and 31 (78%) had an ECOG PS ≥2. The majority of patients had adenocarcinoma (85%), and the primary cancer types were lung cancer (70%), breast cancer (15%), stomach cancer (10%), and lymphoma (5%). Ten patients (25%) had LM at the time of initial diagnosis of metastatic cancer. Headache (60%) was the most common neurological symptom. Eleven patients (28%) showed features of encephalopathy and 16 (40%) had fixed neurological deficits such as cranial nerve palsy or paraplegia. Radiological evidence of hydrocephalus was present in 15 patients (38%). Prior to starting intra-CSF thiotepa treatment, 10 patients (25%) received intra-CSF methotrexate as a first-line treatment, 18 (45%) received methotrexate in combination with cytarabine (45%), and 12 (30%) received first-line methotrexate followed by second-line methotrexate plus cytarabine. Most of the patients (95%) received intra-CSF chemotherapy via an Ommaya reservoir. Twenty patients (50%) received whole-brain radiation therapy, two (5%) received spinal radiation therapy, and two (5%) received both in order to control the symptoms of LM. Thirteen patients (33%) were diagnosed with brain metastases before LM diagnosis, eight (20%) received a concurrent diagnosis, and two (5%) received this diagnosis after the diagnosis of LM.

Prior to starting intra-CSF thiotepa treatment, 21 patients (53%) had controlled extra-CNS disease. The patients were treated with a median of two different regimens (range=0-6) of systemic chemotherapy before starting intra-CSF thiotepa. Twenty-six patients (65%) received systemic chemotherapy after being diagnosed with LM, and 20 (50%) received systemic chemotherapy after starting intra-CSF thiotepa. Nine patients (23%) received radiation for LM after starting thiotepa.

Intra-CSF thiotepa treatment. In terms of clinical response, 16 patients (40%) improved after administration of intra-CSF thiotepa, nine (23%) remained stable, and 15 (38%) deteriorated. Fourteen out of 30 evaluable patients (47%) had a cytological response to intra-CSF thiotepa. The cytological response was not evaluable in 10 patients; therapy for five out of these patients was changed to intra-CSF thiotepa due to clinical deterioration but they had negative CSF cytology after methotrexate-based intra-CSF chemotherapy, three were transferred to another hospital, and two refused further treatment. Among the four patients (10%) who stopped methotrexate-based intra-CSF chemotherapy due to methotrexate toxicity rather than disease progression, two achieved a cytological response. Eleven out of 14 cytological responders did not achieve a cytological response to previous methotrexate-based intra-CSF chemotherapy. These 11 patients were switched to thiotepa due to persistent positive cytology ranging from 2 to 7 weeks after previous intra-CSF chemotherapy despite clinical improvement (N=6), clinical deterioration (N=3), or methotrexate toxicity (N=2).
The treatment-related toxicities were generally mild. Grade 3 thrombocytopenia was observed in two patients. Seven other patients had grade 3 or 4 neutropenia and/or thrombocytopenia that were definitely related to the concurrent cytotoxic chemotherapy. The documented grade 3 non-hematological toxicities were fatigue (N=1), bacterial meningitis (N=2), and pneumonia (N=1).

Survival and prognostic factors. The median TTP after intra-CSF thiotepa was 8.0 weeks (95% CI=16.8-43.2). The median OS after the diagnosis of LM was 30.0 weeks (95% CI=16.8-43.2) and the median OS after treatment with intra-CSF thiotepa was 19.4 weeks (95% CI=15.3-23.5; Figure 2a). Overall, 10 patients (25%) lived longer than 6 months after intra-CSF thiotepa, and five (13%) longer than 1 year. Of the five long-term survivors, four had non-small cell lung cancer (NSCLC), and one had breast cancer. Notably, three patients with NSCLC had an epidermal growth factor receptor (EGFR) mutation and were treated with EGFR tyrosine kinase inhibitors (TKIs) (erlotinib, n=2; gefitinib, n=1) together with intra-CSF thiotepa. The median OS after intra-CSF thiotepa in these three patients was 31.9+, 32.1+, and 37.3 months. The median OS in patients with an ECOG PS of 0 or 1 was longer than that of patients with an ECOG PS of 2-4 (46.3 vs. 13.1 weeks, p<0.001; Figure 2b). The survival of patients who showed clinical improvement or stabilization was better than that of patients with clinical deterioration (46.3 vs. 18.0 vs. 6.4 weeks, p<0.001; Figure 2c). Fourteen patients who showed a cytological response lived longer than non-responders or inevaluable patients (39.3 vs. 11.0 weeks, p=0.001; Figure 2d). The survival of patients who received further systemic chemotherapy together with intra-CSF thiotepa was also better (37.0 vs. 9.4 weeks, p<0.001; Figure 2d).

### Table I. Patients’ characteristics at the time of intra-cerebrospinal fluid (CSF) thiotepa treatment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
</tr>
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<tbody>
<tr>
<td>Age, median (years)</td>
<td>54.5 (range=31-70)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 15 (38) Female 25 (63)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0-1 9 (23) 2 12 (30) 3 12 (30) 4 7 (18)</td>
</tr>
<tr>
<td>Primary cancer type</td>
<td>Lung 28 (70) Breast 6 (15) Gastric 4 (10) Lymphoma 2 (5)</td>
</tr>
<tr>
<td>Neurological symptoms and signs of LM</td>
<td>Headache 24 (60) Altered mentality 11 (28) Dizziness 10 (25) Cranial nerve palsy 9 (23) Extremity weakness 8 (20)</td>
</tr>
<tr>
<td>Brain metastasis</td>
<td>Diagnosed before LM diagnosis 13 (33) Concurrent diagnosis 8 (20) Diagnosed after LM diagnosis 2 (5) None 17 (43)</td>
</tr>
<tr>
<td>Ommaya reservoir</td>
<td>38 (95)</td>
</tr>
<tr>
<td>Previous intra-CSF chemotherapy</td>
<td>MTX single 10 (25) MTX in combination with cytarabine 18 (45) Both 12 (30)</td>
</tr>
<tr>
<td>Radiation for LM</td>
<td>WBRT 20 (50) Spine radiation 2 (5) Both 2 (5)</td>
</tr>
<tr>
<td>Radiation for LM after intra-CSF thiotepa</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Systemic chemotherapy lines before intra-CSF thiotepa</td>
<td>Median 2 (range=0-6)</td>
</tr>
<tr>
<td>Systemic chemotherapy after LM diagnosis</td>
<td>PR 8/26 (31) SD 11/26 (42) PD 5/26 (19) Not evaluable 2/26 (8)</td>
</tr>
<tr>
<td>Systemic chemotherapy after intra-CSF thiotepa</td>
<td>PR 20/40 (50) SD 8/20 (40) PD 3/20 (15) Not evaluable 5/20 (20)</td>
</tr>
</tbody>
</table>

CNS, Central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; IT, intrathecal; LM, leptomeningeal metastasis; No., number; PD, progressive disease; PR, partial response; SD, stable disease.
Figure 2. Kaplan–Meier curve for overall survival after intrathecal thiotepa treatment (a), and according to Eastern Cooperative Oncology Group performance status (b), clinical response (c), cytological response (d), and systemic chemotherapy (e).
weeks, p<0.001; Figure 2e). All nine patients with ECOG PS 0 or 1 received systemic chemotherapy, while 11 out of 31 patients (36%) with ECOG PS 3 or 4 received further systemic chemotherapy (p=0.001).

According to the univariate Cox proportional hazard regression analysis, a poor ECOG PS (p=0.001), encephalopathy (p=0.010), and uncontrolled extra-CNS disease (p=0.010) were significantly associated with a poor OS after intra-CSF thiotepa treatment, while a clinical response (p<0.001), cytological response (p=0.008), radiation for LM after intra-CSF thiotepa (p=0.013), and systemic chemotherapy after intra-CSF thiotepa (p=0.001) were associated with a better OS (Table II). A stepwise multivariate analysis which included age, sex, and variables with a p-value of less than 0.1 by univariate analysis showed that an ECOG PS ≥2 (hazard ratio (HR)=5.11, 95% CI=1.39-18.80, p=0.014), clinical improvement after intra-CSF thiotepa (HR=0.09, 95% CI=0.03-0.29, p<0.001), and radiation for LM after intra-CSF thiotepa (HR=0.33, 95% CI=0.11-0.97, p=0.043) were independently associated with survival after thiotepa treatment (Table III).

### Discussion

Although widely used as a standard treatment for patients with LM, many aspects of intra-CSF chemotherapy remain unclear. In particular, the optimal treatment after failure of first-line intra-CSF chemotherapy is not known. Additionally,
the efficacy and role of intra-CSF thiotepa is not well established. In this retrospective study, we found that intra-CSF thiotepa treatment was feasible as a second- or third-line treatment after the failure of methotrexate-based regimens with considerable efficacy and acceptable toxicities.

In Table IV, we summarize the currently available studies using single-agent intra-CSF thiotepa for the treatment of LM in adults (6, 7, 9, 10). Briefly, previous studies showed clinical response rates of 26-70%, cytological response rates of 44-50%, and a median OS of 14.1-19.3 weeks after treatment with intra-CSF thiotepa. It would be impossible to draw any conclusion from these studies, as all examined a small number of patients in different clinical settings, and a standard definition or criteria regarding a “clinical response” is lacking. However, the results of our study were quite similar to those of the largest study reported to date by Comte et al., in terms of the cytological response and OS (10). Nevertheless, that study included 66 patients with breast cancer, while the majority of patients in our study had lung cancer (70%).

Two recent studies have also shown the efficacy of intra-CSF thiotepa in a second-line setting (9, 10). One study analyzed the outcome of second-line intra-CSF thiotepa in 24 patients with breast cancer after the failure of first-line intra-CSF liposomal cytarabine (9). That study used a treatment schedule similar to that of our study, 10 mg of intra-CSF thiotepa twice weekly. Clinical response was defined as an improvement or stabilization of LM-related neurological deficits on two consecutive studies. Accordingly, 82% of patients showed a clinical response in this study. In our study, we considered patients with a definite improvement in the ECOG PS or neurological symptoms to have a clinical response, and the clinical response rate was 40%. Additionally, 23% of patients had stable disease in our study. In the second study, 50 out of 66 patients with breast cancer received intra-CSF thiotepa as a second-line treatment following intra-CSF methotrexate treatment (10). The outcome of second-line therapy was not specified in that study, but clinical improvement was observed in 17 out of 53 evaluable patients (32%) as a whole. Together with these studies, our study may support the use of thiotepa as second-line intra-CSF chemotherapy.

Unlike the above-mentioned two studies of patients with breast cancer, most patients in our study had NSCLC (N=26), and 30% of patients received intra-CSF thiotepa as a third-line treatment. Despite these poor prognostic factors, our patients had a relatively good median survival of 19.4 weeks (95% CI=15.3-23.5 weeks) after treatment with intra-CSF thiotepa. This apparently longer survival may be explained by a selection bias in part, as fewer than one-fourth of patients with LM who were treated with intra-CSF treatment received intra-CSF thiotepa in our study (Figure 1). The median OS after the diagnosis of LM was also relatively longer in our patient cohort, which was 30.0 weeks (95% CI=16.8-43.2 weeks). Five patients (13%) lived longer than a year after thiotepa treatment. Notably, three out of five long-term survivors had EGFR-mutation positive NSCLC and were treated concurrently with EGFR TKIs. This observation is in accordance with recent studies reporting a subset of patients with LM with long-term survival in NSCLC treated with modern chemotherapeutic agents, especially EGFR TKIs (13-16). At present, the contribution of intra-CSF thiotepa treatment to the apparent survival improvement in these patients remains uncertain, while it is undeniable that EGFR TKIs might have conferred a major effect. However, only five patients in our study received EGFR TKI together with intra-CSF thiotepa, and two other patients who lived more than a year had received aggressive combined treatment with radiation, intra-CSF chemotherapy, and systemic chemotherapy without any molecularly-targeted agent. As intra-CSF chemotherapy, radiation therapy, and systemic chemotherapy (including EGFR TKIs) have all been reported as independent prognostic factors in previous studies (14, 15), we assume that multimodality treatment with intra-CSF thiotepa, radiation, and systemic chemotherapy contributed to the numerically improved survival in our study. High tolerability to intra-CSF thiotepa might also have contributed to the successful administration of concurrent systemic chemotherapy. However, further studies are definitely needed to determine the optimal combination and duration of intra-CSF chemotherapy and systemic chemotherapy. For monoclonal antibodies such as trastuzumab or rituximab, concomitant administration with conventional intra-CSF chemotherapeutic agents via an Ommaya reservoir might be feasible (17, 18).
According to the multivariate analysis, poor ECOG PS (≥2) was a poor prognostic factor (HR=5.11) for survival, while clinical improvement after intra-CSF thiotepa (HR=0.09) and radiation for LM after intra-CSF thiotepa treatment (HR=0.33) were favorable prognostic factors. The presence of encephalopathy and concurrent administration of systemic chemotherapy were highly significant according to the univariate analysis but they were not included in the final multivariate analysis because of high co-linearity with ECOG PS. In fact, all patients who had a good ECOG PS received concurrent systemic chemotherapy in our study.

Even less is known about the toxicities of intra-CSF thiotepa. In a randomized study conducted by the ECOG that compared intra-CSF methotrexate and thiotepa, toxicities were more common in the methotrexate arm but the two therapies did not statistically differ in terms of life-threatening complications, probably due to a small number of patients in each group (7). The study reported one death from bacterial meningitis, two grade 4 hematological toxicities, and one transient respiratory arrest immediately after thiotepa administration. Additionally, patients on methotrexate treatment experienced significantly more neurological toxicities, skin/mucous membrane complications, and marginally significantly more vomiting than those on thiotepa. Recent retrospective studies have not reported toxicities related to intra-CSF thiotepa (9, 10). In our study, two patients developed grade 3 thrombocytopenia that was not related to concurrent systemic chemotherapy. Three patients developed a significant infection (two bacterial meningitis, one pneumonia) that were possibly related to intra-CSF thiotepa. Three patients who were switched to intra-CSF thiotepa from methotrexate-based treatment due to grade 3 nausea and vomiting did not experience nausea and vomiting after intra-CSF thiotepa treatment (data not shown).

In conclusion, our study showed that salvage intra-CSF thiotepa treatment after the failure of methotrexate-based treatment may have clinical benefit in patients with LM with acceptable toxicities. Although oncologists should carefully weigh the risks and benefits of aggressive treatment in patients with LM who are near the end of life, our study suggests that combined modality treatment with intra-CSF thiotepa, radiation and systemic chemotherapy might improve the clinical outcome, especially in patients with good ECOG PS and clinical response after intra-CSF thiotepa treatment.

Conflicts of Interest

The Authors have declared no conflicts of interest with regard to this study.

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