Concurrent radiotherapy and intrathecal methotrexate for treating leptomeningeal metastasis from solid tumors with adverse prognostic factors: A prospective and single-arm study

Zhenyu Pan1, Guozi Yang1, Hua He2, Gang Zhao3, Tingting Yuan4, Yu Li1, Weiyan Shi3, Pengxiang Gao1, Lihua Dong1 and Yunqian Li3

1 Department of Radiation-Oncology, The First Hospital of Jilin University, Changchun 130021, China
2 Cancer Center, The First Hospital of Jilin University, Changchun 130021, China
3 Department of Neuro-Oncological Surgery, The First Hospital of Jilin University, Changchun 130021, China
4 Department of Radiology, The First Hospital of Jilin University, Changchun 130021, China

The prognosis of leptomeningeal metastasis (LM) from solid tumors is extremely poor, especially for patients with adverse prognostic factors. In this phase II clinical trial, we evaluated the efficacy and safety of intrathecal chemotherapy (IC) combined with concomitant involved-field radiotherapy (IF-RT) for treating LM from solid tumors with adverse prognostic factors. Fifty-nine patients with LM from various solid tumors were enrolled between May 2010 and December 2014. Concurrent therapy consisted of concomitant IC (methotrexate 12.5–15 mg and dexamethasone 5 mg, weekly) and IF-RT (whole brain and/or spinal canal RT, 40 Gy/20f). For patients with low Karnofsky performance status (KPS) score and radiotherapy intolerance, induction IC (1–3 times) was given before concurrent therapy. Thirty-eight patients (64.4%) received subsequent treatments. All patients were followed up at least 6 months after LM diagnosis or until death. Primary endpoint evaluated was clinical response rate. Secondary endpoints were overall survival (OS) and safety. The pathological types included lung cancer (n = 42), breast cancer (n = 11) and others (n = 6). Median KPS score was 40 (range 20–70). Fifty-one patients (86.4%) completed concurrent therapy. The overall response rate was 86.4% (51/59). OS ranged from 0.4 to 36.7 months (median 6.5 months), and 1-year-survival rate was 21.3%. Treatment-related adverse events mainly included acute meningitis, chronic-delayed encephalopathy, radiculitis, myelosuppression and mucositis. Twelve patients (20.3%) had grade III–V toxic reactions. We concluded that IC combined with concomitant IF-RT, with significant efficacy and acceptable toxicity, may be an optimal therapeutic option for treatment of LM from solid tumors with adverse prognostic factors. LM, in which cancer cells spread to membranes enveloping the brain and spinal cord, is a devastating complication of solid cancers. Existing LM therapies center on IC. In this prospective clinical study, the authors combined intrathecal methotrexate with involved-field radiotherapy in a concomitant regimen, showing that the approach can potentially improve quality of life for patients with adverse prognostic factors. Concurrent radiotherapy-bolstered IC by contributing to prolonged remission of neurological symptoms and increasing OS. The findings suggest that the concomitant regimen could be an optimal treatment option for LM.

Leptomeningeal metastasis (LM) is a lethal complication of solid tumors. Despite specific treatment, the median overall survival (OS) is limited to 2–3 months and the 1-year-survival rate is <15% worldwide.1 Several factors are associated with poor prognosis of LM, such as Karnofsky performance status (KPS) score of < 60, multiple and severe neurologic deficits, bulky central nervous system (CNS) disease, encephalopathy and extensive systemic disease with few treatment options.2–6 For these patients, LM-specific treatment is ineffective and the prognosis is extremely poor.3,4,7–10 Palliative treatment is
What’s new?
Leptomeningeal metastasis (LM), in which cancer cells spread to membranes enveloping the brain and spinal cord, is a devastating complication of solid cancers. Existing LM therapies center on intrathecal chemotherapy (IC). In this prospective clinical study, the authors combined intrathecal methotrexate with involved-field radiotherapy in a concomitant regimen, showing that the approach can potentially improve quality of life for patients with adverse prognostic factors. Concurrent radiotherapy bolstered IC by contributing to prolonged remission of neurological symptoms and increasing overall survival. The findings suggest that the concomitant regimen could be an optimal treatment option for LM.

Material and Methods
Patients
LM patients admitted to our hospital from May 2010 to December 2014 were enrolled. LM diagnosis was ascertained according to the NCCN guidelines and previous literatures (Supporting Information 1). Patients met with any of the following criteria were sufficient to the diagnosis: positive CSF cytology; MRI scans indicating LM or based on the comprehensive analysis of CSF cytology, neuroimaging findings and other clinical features, including malignant tumor history, nervous system symptoms and conventional CSF examination.

The inclusion criteria were: (i) those aged >18 years and confirmed diagnosis of LM; (ii) those confirmed with solid tumors excluding hematological malignancies (e.g., leukemia and lymphoma) and primary brain tumors; (iii) those with at least one poor prognostic factor, including KPS of <60, severe and multiple neurological deficits (those with two or more groups of neurological symptoms/signs or severe neurological symptoms/signs mainly distributed in three domains including cerebral hemisphere, cranial nerve and the existing nerve roots affecting the life quality), encephalopathy, extensive systemic disease with few treatment options (the patients with active systemic disease, and showed tolerance to the systemic therapy including chemotherapy and target therapy), and bulky brain metastasis (brain parenchyma metastatic lesions with a diameter of >2 cm).

The exclusion criteria were: (i) those with severe hepatic or renal insufficiency, leucocyte count of <2.5 × 10^11, and platelet count of <6.0 × 10^9; (ii) received cranial radiotherapy within 6
months; (iii) received systemic chemotherapy within 2 weeks, or molecular target therapy within 1 month and (iv) with poor tolerance of treatment. Written informed consent was obtained from each patient. All procedures were compliant with the Declaration of Helsinki. The study protocols were approved by the Ethic Committee of The First Hospital of Jilin University. This clinical trial was registered in the Chinese Clinical Trial Registry (ID: ChiCTR-OOC-14005403).

**Treatment plan**

The study schema is provided in Figure 1. The regimen of concomitant therapy consisted of IC via lumbar punctures (MTX 12.5–15 mg, plus dexamethasone 5 mg, once per week, 4 weeks in total) and IF-RT. Radiotherapy consisted of fractionated, conformal radiation given at a daily dose of 2 Gy. The planning volume consisted of sites of symptomatic disease, bulky disease observed on MRI, including the whole brain and basis cranii received 40 Gy in 20 fractions and/or segment of spinal canal received 40–50 Gy (the above segments of the first lumbar vertebra were given 40 Gy in 20 fractions; the first lumbar vertebra and the inferior segments were given 40/50 Gy in 20 fractions). Patients with KPS of ≤40 and irradiation intolerance were required to receive induction IC (MTX 12.5–15 mg, plus dexamethasone 5 mg, twice per week). Then these patients were allowed to receive concomitant therapy upon neurologic improvement and radiotherapy tolerance. Supporting therapy was given to patients with low KPS score.

Subsequent treatment was recommended after concomitant therapy. Consolidation IC (MTX 12.5–15 mg, plus dexamethasone 5 mg) was recommended once per week. The total cycles of IC including the induction therapy, concomitant therapy and consolidation therapy should be <8 times within 2 months. Maintenance IC (MTX 12.5–15 mg, plus dexamethasone 5 mg) was recommended once per month after concomitant therapy and/or consolidation therapy to patients with stable systemic disease or longer expected survival. The patients with active systemic disease were proposed to systemic therapy (chemotherapy or molecular target therapy) according to the NCCN guidelines of related tumors.

**Clinical evaluation and follow-up**

Nowadays, it is lack of standardization with respect to response criteria. Neuroimaging and CSF cytology have been used for the diagnosis and even evaluation of LM, however, these techniques do have their limitations. In this study, we established the criteria of evaluation for clinical response based on improvement of neurologic symptoms/signs and changes of KPS. The clinical response was evaluated by at least two experienced neuro-oncologists. The evaluation consists of five layers, including complete response (CR), obvious response (OR), partial response (PR), stable disease (SD) and progressive disease (PD); Table 1. Clinical evaluation was performed once per week from the beginning of LM-related therapy, till 4 weeks later after concomitant

![Figure 1. Protocol schema. IC: intrathecal chemotherapy; RT: radiation therapy; KPS: Karnofsky performance status; MTX: methotrexate; DXM: dexamethasone.](image)

**Table 1. Criteria of clinical response evaluation**

| Neurological symptoms and signs | KPS score |
|---------------------------------|-----------|
| Complete response               | Almost normal neurological examination. Mild cranial nerve symptoms including tinnitus or blurred vision may exist. GCS score of 15. | ≥90 |
| Obvious response                | Significant neurologic improvement. No severe symptoms/signs, such as severe headache, somnolence, mental status. Dizziness, confusion, mild headache, cranial nerve paralysis or radiculitis may exist. GCS ≥12. | ≥70 or elevation of ≥30 compared with the baseline level. |
| Partial response                | Partial neurological improvement. Still with headache or other mild/moderate symptoms/signs. GCS ≥9. | 50–70 or elevation of 10–20 compared with the baseline level. |
| Stable disease                  | No visible neurological improvement. | Elevation of ≤10 compared with the baseline level. |
| Progressive disease             | Deteriorative neurological symptoms and signs. | Decrease of KPS compared to the baseline level. |

Two conditions both of neurological symptoms/signs and KPS must be satisfied synchronously. KPS: Karnofsky performance status score; GCS: Glasgow coma scale.
therapy. Clinical response was defined as continuous presence of CR, OR or PR within an interval of at least 1 week. SD and PD were defined as ineffective.

The following parameters were determined before treatment: general health conditions, KPS score, neurological conditions, Glasgow coma scale, full blood count and multichannel biochemical profile. Imaging examination was used to evaluate systemic disease. Toxicity was evaluated by physical examination, neurological examination, CSF examination, full blood count and multichannel biochemical profile monitoring weekly. CSF cytology was performed once per week. Survival time was recorded since the date of LM diagnosis. All patients were followed up until death or July 31, 2015. Adverse events (AEs) were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). Events of grade 3–5 were defined as moderate and severe adverse events.

Statistical analysis
The primary endpoint was clinical response rate. The secondary endpoints were OS and safety. SPSS 17.0 software was used for data analysis. Survival analysis was performed using the Kaplan–Meier method. Log-Rank test was used to compare the survival time of patients. Univariate and multivariate Cox regression analysis were carried out to determine the risk factors of OS. $\chi^2$ test and Fisher exact test were used to evaluate the difference of clinical response rate and OS between patients with various features. $p < 0.05$ demonstrated significant difference.

Results
Patient characteristics
Fifty-nine patients (male: 27, female: 32, aged 31–72 years, median 55 years) were enrolled in this study. Patients’ characteristics were showing in Table 2. The flow chart of the treatment was shown in Supporting Information 2.

Adverse prognostic factors were identified in all patients, including KPS of < 60 ($n = 46$), severe and multiple neurological deficits ($n = 39$), encephalopathy ($n = 4$), extensive systemic disease with few treatment options ($n = 15$) and bulky brain metastasis ($n = 32$).

Treatment and efficacy
Twenty-nine patients received radiotherapy within 3 days after the first IC. Thirty patients with KPS score of < 40 received induction IC prior to radiotherapy, including 20 (66.7%)...
received for once, 8 (26.7%) for twice and 2 (6.7%) for thrice, respectively. Three (5.1%) critically ill patients died with no response to the induction IC. Fifty-six patients received concomitant therapy, among whom 51 (86.4%) accomplished the concomitant therapy, including 4 with temporary cessation (3–10 days) due to severe bone marrow depression (white blood cell number of <1.5 × 10^9/L), or platelet number of <45 × 10^9/L) and severe mucous reaction. Five patients (8.5%) quit the treatment after receiving 2–3 weeks of concomitant therapy for personal reasons. Fifty-one patients (86%) received whole brain radiotherapy. Twenty patients (34%) received partial spinal irradiation, among whom 2 received cervical spinal irradiation and 3 received thoracic spinal irradiation, and 18 received lumbosacral spinal irradiation. Fifteen (25%) received both whole brain irradiation and partial spinal field irradiation. Forty-two (71%) received supportive treatment.

Neurological remission was generally achieved after the first week of the concomitant therapy, and the clinical response was commonly achieved 2–4 weeks later. The overall clinical response rate was 86.4%, including CR (14, 23.7%), OR (29, 49.1%) and PR (8, 13.6%). Five patients (8.5%) had SD and three (5.1%) had PD. We also evaluated the clinical response rate based on pathological types, and the response rates were 87.5% (28/32) for nonsmall cell lung cancer (NSCLC), 90% (9/10) for small cell lung cancer (SCLC), 72.7% (8/11) for breast cancer and 100% (6/6) for the other tumors. No statistical difference was observed in the response rate based on pathological types, and the response rates were 86.4% (including CR (14, 23.7%), OR (29, 49.1%) and PR (8, 13.6%)). Five patients (8.5%) had SD and three (5.1%) had PD. We also evaluated the clinical response rate based on pathological types, and the response rates were 87.5% (28/32) for nonsmall cell lung cancer (NSCLC), 90% (9/10) for small cell lung cancer (SCLC), 72.7% (8/11) for breast cancer and 100% (6/6) for the other tumors. No statistical difference was observed in the response rate of the patients with various primaries (p = 0.568). No statistical difference was observed in the survival of the patients with various primaries (p = 0.110).

Table 3. Clinical response rate and overall survival of patients with various pathological features

|          | NSCLC (n = 32) | SCLC (n = 10) | Breast cancer (n = 11) | Others (n = 6) |
|----------|----------------|--------------|-----------------------|--------------|
| CR       | 8              | 3            | 2                     | 1            |
| OR       | 15             | 5            | 5                     | 4            |
| PR       | 5              | 1            | 1                     | 1            |
| SD       | 3              | 1            | 1                     | 0            |
| PD       | 1              | 0            | 2                     | 0            |
| Effective| 28             | 9            | 8                     | 6            |
| Noneffective| 4       | 1            | 3                     | 0            |
| Median OS (months) | 6.7 | 4.5 | 5.4 | 11 |

No statistical difference was observed in the response of the patients with various primaries (p = 0.568). No statistical difference was observed in the survival of the patients with various primaries (p = 0.110).

The clinical response (CR, OR, PR or noneffective) was correlated to the patients’ survival (p = 0.006). Significant OS extension was observed in the patients with clinical response to the treatment (p = 0.009).

Implantation metastases of intra-spinal canal were observed at month 2–11 in four patients following cranial radiotherapy and concomitant intrathecal MTX. Thus, spinal radiotherapy was performed subsequently. Fifteen patients presented recurrent neurologic symptoms mainly manifested as headache 2–9 months after concomitant therapy and other initial antitumor treatment. Among these patients, 9 received supportive treatment and died in a short time. For the other 6 patients, symptomatic improvement was obtained in 3 patients received further intrathecal MTX and 3 received second-line IC (cytosine arabinoside, 50 mg, dexamethasone, 5 mg). Particularly, one patient with breast cancer accomplished 8 times of induction, concomitant and consolidation IC, as well as subsequent 8 times of maintenance IC (once per month). Afterward, the patient received IC every 2–3 months to attenuate recurrent headache. Up to now, the patient had received 30 times of IC in total with a survival of up to 36.7 months despite a mild short-term memory loss and a KPS score of 80.

Follow-up and outcomes

All the patients were followed up for 0.4–36.7 months until July 31, 2015. The median OS was 6.5 months. One-year survival rate was 21.3%, and two-year survival rate was 6.1%. Fifty-three patients were dead. Forty-eight (90.6%) died from cancer progression, among whom 22 (41.5%) died wholly from LM, 10 (18.6%) wholly from systemic disease. The remaining patients died from delayed treatment-related neurotoxicity (2, 3.8%) and noncancer diseases (3, 5.7%).

According to the criteria of evaluation of clinical response (Table 1), fourteen patients showed CR (OS: 3.5–36.7 months, median: 8.4 months), and OR was noticed in 29 patients (OS: 1.4–17.2 months, median: 6.8 months). PR was noticed in 8 patients (OS: 2.4–13 months, median: 4.9 months). Five patients had SD (OS: 1.5–18.5 months, median: 3.2 months), and three had PD (OS: 0.4–0.6 months, median: 0.4 months). In total, response was observed in 51 patients (OS: 1.4–36.7 months, median: 6.8 months), and SD and PD was observed in 8 patients (OS: 0.4–18.5 months, median: 2.8 months, Table 4). Significant extension in OS was observed in the patients with clinical response.

Table 4. Clinical response rate and the patients’ survival

|          | N     | OS (months) | Median OS (months) |
|----------|-------|-------------|--------------------|
| CR       | 14    | 3.5–36      | 8.4                |
| OR       | 29    | 1.4–17.2    | 6.8                |
| PR       | 8     | 2.4–13      | 4.9                |
| SD       | 5     | 1.5–18.5    | 3.2                |
| PD       | 3     | 0.4–0.6     | 0.4                |
| Effective| 51    | 1.5–36.7    | 6.8                |
| Noneffective| 8    | 0.4–18.5    | 2.8                |

The clinical response (CR, OR, PR or noneffective) was correlated to the patients’ survival (p = 0.006). Significant OS extension was observed in the patients with clinical response to the treatment (p = 0.009).
Table 5. Mainly adverse events

| Variables | N (%) |
|-----------|-------|
| Acute cerebral meningitis | 1 (2%) |
| I–II degree | 0 |
| III–IV degree | 0 |
| V degree | 1 (2%) |
| Chronic encephalopathy | 3 (5%) |
| I–II degree | 1 (2%) |
| III–IV degree | 1 (2%) |
| V degree | 1 (2%) |
| Radiculitis | 16 (27%) |
| I–II degree | 9 (15%) |
| III–IV degree | 7 (12%) |
| V degree | 0 |
| Bone marrow depression | 13 (22%) |
| I–II degree | 5 (8%) |
| III–IV degree | 8 (14%) |
| V degree | 0 |
| Mucositis | 12 (20%) |
| I–II degree | 10 (17%) |
| III–IV degree | 2 (3%) |
| V degree | 0 |
| Leukodystrophy (n = 44) | 30 (68%) |
| I degree | 15 (50%) |
| II degree | 7 (23%) |
| III degree | 8 (27%) |
| Encephalopathy | 11 (19%) |
| II–III degree | 9 (15%) |
| IV degree | 1 (2%) |
| V degree | 1 (2%) |
| Moderate and severe toxicity | 12 (20%) |
| Treatment-related death | 2 (3%) |
| Death of adverse events during concurrent therapy | 0 |

(p = 0.009, Table 4). The status of clinical response (CR, OR, PR or noneffective) had significant correlation with the OS (p = 0.006, Table 4). The median OS for the patients with breast cancer, NSCLC, SCLC and others was 5.4 months, 6.7 months, 4.5 months and 9 months, respectively. No statistical difference was observed in the OS of patients with various pathologic types (p = 0.110, Table 3).

On univariate analysis (Supporting Information 3) OS was not influenced by gender (p = 0.331), age (p = 0.324), severe and multiple neurological deficits (p = 0.395), bulky CNS disease (p = 0.800), KPS < 40 (p = 0.997) and KPS < 60 (p = 0.309), systemic disease progression (p = 0.288) and primary lung cancer (p = 0.142), and hypoglycorrhachia (p = 0.153), respectively. The cytology was turned to be negative in 15 patients (27%), which showed no protective effects against the OS (p = 0.988). Significant OS benefits were observed in patients with clinical response (p = 0.013), and accomplishing the concomitant therapy (p = 0.016). Besides, extensive systemic disease with few treatment options caused significant adverse effects on the OS (p = 0.009). Multivariate analysis revealed extensive systemic disease with few treatment options (p = 0.005) and primary lung cancer (p = 0.033) were the adverse prognostic factors. In addition, KPS of < 60 (p = 0.107) or severe and multiple neurological deficits (p = 0.110) caused no significant effects on prognosis (Supporting Information 3).

Safety and toxicity

The major toxicities and side effects were radiotherapy-related injuries to skin and mucosa, bone-marrow depression, MTX-induced mucosal injuries, lumbar radiculitis, as well as acute/chronic neurotoxicity (Table 5). Mild or moderate skin reaction and hair loss occurred in all the patients undergoing brain radiotherapy. In addition, radiotherapy-related mild and moderate otitis media was observed in 13 patients. Bone marrow depression was mainly occurred at Week 3 and 4 during concomitant therapy, which was manifested as decreased white blood cell count (n = 12) and platelet count (n = 5). Twelve patients (20.3%) showed MTX-induced mucosal injuries. Among them, five patients received intravenous injection of leucovorin (100 mg, b. i. d.). Eleven patients showed mild or moderate mucosal injuries. Only one patient showed severe mucosal injury (grade IV) manifested as oral mucosal ulcer 2 days after the fourth intrathecal MTX. One week later, this patient showed mucosanguineous stool and mucosal swelling of the perineal region. The symptoms were attenuated after intravenous injection of leucovorin (100 mg, b. i. d.), and gargling with leucovorin (5%) as well as hip-bath. Sixteen patients with radiculitis mainly presented regional numbness of the gluteal region and lower extremities. Among these patients, 9 with mild symptoms were alleviated spontaneously without interfering quality of life. However, several patients showed moderate (n = 5) and severe radiculitis (n = 2), which persistently affected sleeping and walking. No patient showed lumbar puncture-induced purulent meningitis.

Three patients (5.1%) showed severe neurotoxicity, including 1 with acute neurotoxicity manifested as chemical arachnoiditis and 2 with delayed neurotoxicity manifested as encephalopathy. Among these patients, 2 died finally due to deterioration of neurotoxicity. For the patient with acute neurotoxicity, the symptoms were presented at 5.5 months after concomitant therapy, and were manifested as progressively severe headache accompanied by stiff neck, vomiting, seizure, ablesia and photophobia. This patient showed remarkable increase in CSF protein (1.41 g/L, normal range 0.15–0.45 g/L). The patient had received 13 times of IC in total, and also received systemic chemotherapy (Docetaxel and cisplatin) during the consolidation and maintenance IC. Brain MRI showed no new lesions or cerebral apoplexy, but showed grade I...
leukoencephalopathy. For the 2 patients with delayed neurotoxicity, it happened in 6 months and 16 months following concomitant therapy, respectively. Main manifestations were progressive cognitive disorder, mental obtundation, lower motor neuron weakness and dysphagia. Leukoencephalopathy (grade III) was confirmed by neuro-radiologic examination presenting severe cerebral atrophy, increase in subarachnoid space and other features.

Leukoencephalopathy refers to a type of delayed and chronic neurotoxicity evaluated by neuroimaging examination. As regular cranial MRI was not compulsory in this study, it was hard to precisely evaluate leukoencephalopathy. A total of 44 patients received cranial MRI/CT within 1–24 months after concomitant therapy, 30 of whom showed leukoencephalopathy (Table 5). Besides 3 patients with severe neurotoxicity mentioned above, no significant CNS symptoms were noticed except for mild or moderate encephalopathy (grade II–III) mainly manifested as short-term memory loss and depression or dullness of mind in 9 patients. Nineteen patients underwent MRI scan over 6 months after concomitant therapy, and all of them were confirmed with leukoencephalopathy.

In this study, about half the patients showed a Glasgow coma scale of less than 14 upon the diagnosis of LM. As the patients’ conditions were severe, it was hard to perform the cognitive evaluation. Due to the absence of baseline, regular cognitive evaluation was not designed. Patients with typically delayed encephalopathy manifested as cognitive disturbance, confusion and other typical symptoms could be ascertained as adverse effects, and minimum mental state examination (MMSE) was performed for the evaluation. Regular MMSE was not designed as the OS of LM patients was too short.

**Discussion**

In this single-arm and prospective clinical study, we confirmed IF-RT combined with concomitant intrathecal MTX could improve the quality of life and neurological symptoms of LM patients from solid tumors with adverse prognostic factors. Meanwhile, the neurotoxicity was not as severe as expected. The median OS and one-year survival rate was obviously higher than the historical reports. This treatment regimen improved the prognosis of LM patients from solid tumors with adverse prognostic factors for the first time.

LM patients with poor conditions may achieve clinical improvement after IC, however, the neurologic symptoms commonly relapse within a short time.\(^\text{24,26}\) Such situation was also proved by our clinical experiences. In this study, concomitant radiotherapy contributed to a long-term neurologic remission and extension of OS. This regimen provides lots of advantages: (i) MTX is a type of antimeabolic antitumor drug that inhibits the metabolism of folic acid. Cancer cells at S phase and G1/S phase are sensitive to MTX, while those at G1, G2 and M phase are sensitive to irradiation. Thus, radiotherapy and MTX mediate synergetic effects for different phases of the cell cycle. (ii) MTX is also involved in radiosensitizing effect.\(^\text{27}\) (iii) Radiotherapy is indicated to relieve CSF flow block and reestablish normal CSF, which subsequently improves the diffusion of drugs in CSF and attenuates the neurotoxicity induced by CFS flow blocks and drug accumulation.\(^\text{28,21}\) (iv) The simultaneous modality of radiotherapy and IC, rather than the administration of each treatment sequentially, can also shorten the total time of LM-related treatment. After controlling CNS involvement, systemic therapy could be administered promptly. Thus, it is appropriate for the comprehensive treatment of the patients with active systemic disease.

LM patients from solid tumors showed similar outcomes (median OS is 2–3 months approximately) and clinical features.\(^\text{1}\) To our knowledge, lots of previous studies enrolled patients with various solid tumors\(^\text{2,17,24,29–32}\) despite the prognosis of LM from breast cancer was satisfactory.\(^\text{33}\) Therefore, patients with different primaries were enrolled in this study. After all, patients with various tumors showed no statistical difference in the clinical response and OS in this study. We concluded that the concomitant therapeutic modality could be effective for LM from various solid tumors.

Although induction IT showed no marked impact on the OS and clinical response rate, it was applied to the critical patients to alleviating severe conditions temporarily. Upon short-term attenuation of symptoms, the concomitant radiotherapy should be performed subsequently. In this study, 3 patients with severe conditions and lower KPS (20 score) died from LM progression even though induction IC had been given. Consequently, whether concomitant therapy could be administered in those with poor conditions is depended on the response to induction IC. In line with the previous studies,\(^\text{24,34}\) the response to initial IC is one of the key points for the prognosis of critical LM patients. The patients with neurological remission and improved KPS ordinarily indicate better prognosis. The one-dimensional response evaluation criteria in solid tumors (RECIST) are not appropriate for the evaluation of LM as the neuroimaging features of LM commonly are not measurable at least as defined by current brain tumor response criteria.\(^\text{1}\) Moreover, a prior autopsy study revealed that changes in MRI findings might not accurately represent the changes in actual degree of leptomeningeal lesion burden.\(^\text{35}\) To date, CSF cytological clearance rates and symptomatic improvement have been commonly used for clinical evaluation.\(^\text{17,29,30,37}\) However, the presence or absence of CSF cytology did not appear to influence survival.\(^\text{25}\) Besides, false negative testing of CSF cytology is common. Indeed, our study revealed that CSF cytological clearance showed no correlation with either clinical response rate \((p = 0.423)\) or OS \((p = 0.988)\). Thus, CSF cytology may not be a suitable choice for the evaluation. Previously, changes of neurologic symptoms/signs were solely used to assess the clinical response.\(^\text{38}\) The clinical evaluation based on changes of neurologic symptoms/signs was performed every 2 weeks or before each cycle of therapy in several studies.\(^\text{26,29,31}\) Transient neurological symptoms related with supportive treatment or AEs might be misconstrued as clinical improvement or...
progression. Thus, it should be necessary to define a span of time to identify the effectiveness of treatment. In one study, it was defined that clinical status persisting >4 weeks could serve as a criterion of evaluation.26 Considering the survival of LM patients with adverse prognostic factors was extremely short, continuous CR, OR or PR for two times of evaluation within an interval for at least 1 week was set as a criterion for effectiveness in this study. Data analysis revealed the clinical response (CR, OR, PR or noneffective) was correlated with the patients’ survival \((p = 0.006, \text{Table } 4)\), which indicated this method was effective for the evaluation of prognosis.

Recurrence was inevitable even though presence of CSF cytological clearance, as it was difficult to eradicate the tumor cells in CSF thoroughly. According to the NCCN guidelines, maintenance IC was mostly recommended to the clinically stable patients. The patients received maintenance IC usually showed stable disease or longer expected survival that caused absence of randomness in this study. However, maintenance IC was still effective in improving neurologic symptoms of the patients with recurrent disease following the concurrent therapy. Of note, all of 3 patients with severe neurotoxicity (grade IV–V) received many times of IC (12–13 times) and concomitant systemic therapy with consolidation/maintenance IC during the subsequent treatment. Thus, for the patients with active systemic disease and needed systemic therapy, it should be deliberated to decide whether simultaneous systemic therapy should be given during the regimen of IC.

To date, the efficacy of systemic therapy for LM from solid tumors is uncertain. Blood–brain and blood–CSF barriers limit penetration of most systemically administered anticancer agents into CNS. Thus, CSF exposure to most cytotoxic agents is <5% of the plasma concentration, and it is rarely used for the primary treatment of LM.1 Further- more, it has been reported that systemic chemotherapy provided no additional benefits over the combination of IC and radiotherapy.39 Nevertheless, most LM patients showed active systemic disease that was considered as the main cause of death.5 For these patients, systemic therapy was necessary.40–44 However, partial patients showed poor tolerance to systemic therapy due to low KPS and fatal CNS involvement. Thus, it is crucial to select an appropriate time for the systemic therapy. In a previous study, Park et al. 40 suggested further systemic therapy (chemotherapy or target therapy) after IC conferred survival benefits. In this study, the regimen shortened the total time of LM-related treatment. After controlling CNS involvement, systemic chemotherapy could be given to the patients with active systemic disease promptly. Despite no obvious survival benefits in the patients received systemic therapy \((p = 0.296)\), active systemic disease showed no influence on OS either \((p = 0.288)\). However, extensive systemic disease with few treatment options was an adverse prognostic factor \((p = 0.006)\). It seemed that systemic therapy improved the prognosis of the LM patients with active systemic disease. However, it was hard to confirm whether systemic therapy could cause benefits to the CNS dissemination.

In line with the previous studies,4,5 multivariate analysis revealed lung cancer was a risk factor for poor prognosis \((p = 0.033)\), which might be attributed to the poor prognosis of SCLC patients (mean OS: 4.5 months). According to the univariate analysis, the survival of SCLC patients was inferior to NSCLC \((p = 0.082)\). Moreover, the clinical response rate of SCLC patients was up to 90%, however, half of them (50%) died from progressive systemic disease in a short time. Above all, as a risk factor, lung cancer might be related with the progression of the systemic disease rather than invalidness for the regimen of the concurrent therapy. Based on the multivariate and univariate analysis, the prognosis is worse for those with systemic disease progression with few treatment options. Despite no benefits in the OS in these patients following concomitant therapy, significant improvement was noticed in their neurologic function and quality of life.

It was difficult to ascertain a time span for MRI examination as the survival time of LM patients with poor prognostic factors was extremely short. Therefore, regular MRI was not compulsory in this study. A total of 44 patients received cranial MRI scan after concomitant therapy, among whom a higher incidence (68%) of leukoencephalopathy was noticed. Consistent with the previous studies,23,45,46 most of the patients with leukoencephalopathy were asymptomatic, and mainly presented in patients aged < 60 years or received high dose chemotherapy. In this study, leukoencephalopathy was mainly observed in the patients with survival time of \(\geq 6\) months. Thus, the incidence of leukoencephalopathy was inclined to increase in patients with longer survival, but severe neurological deficit was seldom observed.

Indeed, there were limitations in this study. The concurrent therapy was designed as the mainstay of this study, and classical regimen of IC (including induction IC, consolidation IC and maintenance IC) was not compulsory. Thus, patients received various cycles of IC, which might affect the outcomes slightly. Additionally, LM is a lethal complication of malignancy. The design of clinical trial and the patients’ prognosis could be affected by many aspects, such as general status of patients, status of extra-CNS disease and other anticancer treatment. The subsequent therapy, including consolidation/maintenance IC or systemic therapy, might have potential influence on the outcomes, especially the delayed neurotoxicity and patients’ survival. Furthermore, LM patients usually present with pleomorphic and subtle neurological signs affecting the CNS, and sometimes it is difficult to differentiate from those caused by the adverse effects of cancer treatment. Thus, it is hard to evaluate the treatment related neurotoxicity (e.g., cognitive disturbance) precisely. In this study, approximately half the patients showed a Glasgow coma scale of less than 14 upon the diagnosis of LM. Due to severe conditions of these patients, it was hard to perform the cognitive evaluation before treatment. Because of the absence of baseline, regularly cognitive evaluation was not designed in this study. Despite the inevitable limitations, the patients received comprehensive treatment based on the concurrent therapy as...
a mainstay achieved higher clinical response rate and obvious survival benefit than histological reports.

In conclusion, this study provides important information about the regimen of the concurrent therapy with significant efficacy and acceptable toxicity that may serve as an optimal therapeutic option for treatment of LM from solid tumors with adverse prognostic factors. The evaluation criteria based on the neurologic improvement and KPS changes are appropriate for the response assessment of LM-related treatment.

References

1. Le Rhun E, Taillibert S, Chamberlain MC. Carcinomatous meningitis: leptomeningeal metastases in solid tumors. Surg Neurol Int 2013; 4:265
2. Chamberlain MC. Combined modality treatment of leptomeningeal gliomatosis. Neurosurgery 2003; 52:324–30.
3. Chamberlain MC, Tsoa-Wei D, Groshen S. Neuroplastic meningitis-related encephalopathy: prognostic significance. Neurology 2004; 63:2199–61.
4. Chamberlain MC, Glantz MJ, Groves MD, et al. Diagnostic tools for neuroplastic meningitis: detecting disease, identifying patient risk, and determining benefit of treatment. Semin Oncol 2009; 36:535–45.
5. Taillibert S, Laigle-Donadey F, Chodkiewicz C, et al. Leptomeningeal metastases from solid malignancy: a review. J Neurooncol 2005; 75:85–99.
6. Chamberlain MC, Johnston SK, Glantz MJ. Neuroplastic meningitis-related prognostic significance of the Karnofsky performance status. Arch Neurol 2009; 66:274–8.
7. Brem SS, Bierman PJ, Black P, et al. Central nervous system cancers: clinical practice guidelines in oncology. J Natl Compr Canc Netw 2005; 3:644–90.
8. Chamberlain MC, Kormanik PA. Prognostic significance of 111Indium-DTPA CSF flow studies in leptomeningeal metastases. Neurology 1996; 46: 1674–7.
9. Chamberlain MC, Kormanik PA. Prognostic significance of coexistent bulky metastatic central nervous system disease in patients with leptomeningeal metastases. Arch Neurol 1997; 54:1364–8.
10. Chamberlain M. Leptomeningeal metastases: a review of evaluation and treatment. J Neuro Oncol 1998; 37:271–84.
11. Gani C, Müller A-C, Eckert F, et al. Outcome after whole brain radiotherapy alone in intracranial leptomeningeal carcinomatosis from solid tumors. Strahlen Onkol 2012; 188:148–53.
12. Morris PG, Reiner AS, Zebren OB, et al. Leptomeningeal metastasis from non-small cell lung cancer: survival and the impact of whole brain radiotherapy. J Thorac Oncol 2012; 7:382–5.
13. Clarke JL, Perez HR, Jacks LM, et al. Leptomeningeal metastases in the MRI era. Neurology 2010; 74:1449–54.
14. Chamberlain M, Soffietti R, Raijer J, et al. Leptomeningeal metastasis: a response assessment in neuro-oncology critical review of endpoints and response criteria of published randomized clinical trials. Neuro-Oncology 2014; 16:1176–85.
15. Glantz MJ, Lafollette S, Jaeckle K, et al. Randomized trial of a slow-release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. J Clin Oncol 1999; 17:3110–16.
16. Cole BFL, Glantz MJ, Jaeckle KA, et al. Quality-of-life-adjusted survival comparison of sustained-release cytosine arabinoside versus intrathecal methotrexate for treatment of solid tumor neuroplastic meningitis. Cancer 2003; 97:3033–68.
17. Glantz MJ, Jaeckle KA, Chamberlain MC, et al. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neuroplastic meningitis from solid tumors. Clin Cancer Res 1999; 5:3394–402.
18. Groves MD. Leptomeningeal metastasis: still a challenge. ASCO Educational Book. 2008. 80–87.
19. Chamberlain MC. Neuroplastic meningitis. J Clin Oncol 2005; 23:3605–17.
20. Blasberg RG, de Leval D, Fenstermacher JD. Intrathecal chemotherapy: brain tissue profiles after ventriculocisternal perfusion. J Pharmacol Exp Ther 1975; 195:73–83.
21. Chamberlain MC, Kormanik P, Jaeckle KA, et al. 111Indium-diethylentriamine pentaacetic acid CSF flow studies predict distribution of intrathecally administered chemotherapy and outcome in patients with leptomeningeal metastases. Neurology 1999; 52:214.
22. Novak LJ. Radiotherapy of the central nervous system in acute leukemia. Hematol Oncol 1989; 11:87–104.
23. Bleyer WA. Current status of intrathecal chemotherapy for human meningeal neoplasms. Natl Cancer Inst Monogr 1977; 46:171–8.
24. Hitchins RN, Bell DR, Woods RL, et al. A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. J Clin Oncol 1987; 5:1655–62.
25. Chamberlain MC, SK J. Neuroplastic meningitis: survival as a function of cerebrospinal fluid cytol- ogy. Cancer 2009; 115:1941–6.
26. Vedrine L, Artru P, Tournigand C, et al. Menin- geal carcinomatosis in gastric cancer. Gastroon- cereol Clin Bicoll 2001; 25:422–4.
27. Kim A, Lee J-E, Jang W-S, et al. A combination of methotrexate and irradiation promotes cell death in NK/T-cell lymphoma cells via down-regulation of NF-κB signaling. Leuk Res 2012; 36: 350–57.
28. Wassefstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. Cancer 1982; 49:759–72.
29. Grossman SA, Finkelstein DM, Rudkescel JC, et al. Randomized prospective comparison of intrathecal methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. J Clin Oncol 1993; 11:561–9.
30. Shapiro WR, Schmid M, Glantz M, et al. A randomized phase III/IV study to determine bene- fit and safety of cytarine liposome injection for treatment of neoplastic meningitis. J Clin Oncol 2006; 24:1528s.
31. Groves MD, Glantz MJ, Chamberlain MC, et al. A multicenter phase II trial of intrathecal topotecan in patients with meningeal malignancies. Neuro-Oncology 2008; 10:208–15.
32. Chamberlain MC, Wei-Tao DD, Groshen S. A phase 2 trial of intra-CSF etoposide in the treat- ment of neoplastic meningitis. Cancer 2006; 106: 2021–7.
33. Scott BJ, Oberheim-Bush NA, Kesari S. Leptomeningeal metastasis in breast cancer—a systematic review. Oncotarget 2016; 7: 3740–47.
34. Sause WT, Crowley J, Eyer HJ, et al. Whole brain irradiation and intrathecal methotrexate in the treatment of solid tumor leptomeningeal metastases—a southwest oncology group study. J Neurooncol 1988; 6:107–12.
35. Bussani R, Cova M, Pozzi-Mucelli R, et al. Extensive metastatic leptomeningeal melanomatosis as the first clinical sign of a cutaneous melanoma: morphological correlations between magnetic res- onance imaging and autopsy findings. A case report. Hum Pathol 2003; 34:625–8.
36. Jackman DM, Cioffi A, Jacobs L, et al. A phase 1 trial of high dose gefitinib for patients with leptomeningeal metastases from non-small cell lung cancer. Oncotarget 2015; 6:6527–36.
37. Scott BJ, van Vugt VA, Rush T, et al. Concurrent intrathecal methotrexate and liposomal cytarabine for leptomeningeal metastasis from solid tumors: a retrospective cohort study. J Neurooncol 2014; 119:361–8.
38. Boogerd W, van den Bent MJ, et al. The relevance of intrathecal chemotherapy for leptomeningeal metastasis in breast cancer: a randomized study. Eur J Cancer 2004; 40:2726–33.
39. Chamberlain MC, Kormanik P. Carcinoma men- ingitis secondary to non-small cell lung cancer: combined modality therapy. Arch Neurol 1998; 55:506–12.
40. Park IH, Kim YJ, Lee J-O, et al. Clinical outcome of leptomeningeal metastasis in patients with non-small cell lung cancer in the modern chemotherapy era. Lung Cancer 2012; 76:387–92.
41. Boogerd W, Hart AAM, van der Sande JJ, et al. Meningeal carcinomatosis in breast cancer. Prog- nostic factors and influence of treatment. Cancer 1991; 67:1685–95.
42. Fizazi K, Asselain B, Vincent-Salomon A, et al. Meningeal carcinomatosis in patients with breast carcinoma: clinical features, prognostic factors, and results of a high-dose intrathecal methotrex- ate regimen. Cancer 1996; 77:1315–23.
43. Grant R, Naylor B, Greenberg HS, et al. Clinical outcome in aggressively treated meningeal carci- nomatosis. Arch Neurol 1994; 51:457–61.
44. Siegal T, Lossos A, Pfeffer MR. Leptomeningeal metastases analysis of 31 patients with sustained off-therapy response following combined- modality therapy. Neurology 1994; 44:1463–3.
45. Kerr JZ, Berg S, Blaney SM. Intrathecal chemo- therapy. Crit Rev Oncol Hematol 2001; 37:227–36.
46. Kim YJ, Kim ST, Nam D-H, et al. Leukoencephalopathy and disseminated necrotizing leu- koencephalopathy following intrathecal methotrexate chemotherapy and radiation therapy for central nerve system lymphoma or leukemia. J Korean Neur surg Soc 2011; 50:304–10.