

Intrathecal pemetrexed combined with involved-field radiotherapy as a first-line intra-CSF therapy for leptomeningeal metastases from solid tumors: a phase I/II study

Zhenyu Pan*, Guozi Yang*, Hua He, Jiuwei Cui, Wei Li, Tingting Yuan, Kunzhi Chen, Tongchao Jiang, Pengxiang Gao, Yanan Sun, Xiaofeng Cong, Zhi Li, Yongxiang Wang, Xiaochuan Pang, Yuanyuan Song and Gang Zhao 

Abstract

Purpose: A phase I/II study of intrathecal pemetrexed (IP) combined with involved-field radiotherapy (IFRT) was performed to determine feasibility, safety, and antitumor activity for leptomeningeal metastases (LM) from solid tumors.

Methods: Participants first received induction IP administration, followed by concomitant radiotherapy within 3 days. The concomitant regimen consisted of IP (pemetrexed 10 mg, dexamethasone 5 mg, once per week, 4 times in 4 weeks) and IFRT (40 Gy in 20 fractions). Six participants were recruited to assess feasibility in phase I, and then 28 patients were recruited further. All patients were assessed to investigate safety, efficacy, and outcomes.

Results: Between April 2018 and December 2018, 34 patients (male: 15; female: 19; median age: 56 years) were enrolled, including non-small-cell lung cancer (21), small-cell lung cancer (5), breast cancer (4), and others (4). Thirty-two patients received concurrent therapy and 25 (74%) patients completed the treatment. Major adverse events (AEs) consisted of myelosuppression, the elevation of hepatic aminotransferases, and radiculitis. Total AEs rate was 53% (18/34), including 6 (18%) patients with grade 3 and 1 (3%) with grade 4 AEs. The response rate was 68% (23/34). The median overall survival was 5.5 (0.3–16.6) months. Median neurological progression-free survival (NPFs) was 3.5 (0.3–15.2) months. Six-month NPFs rate was 47%. One-year survival rate was 21.6%.

Conclusion: IP at a 10 mg dose on a schedule of 1–2 times per week presented good efficacy and safety in CSF. The concomitant regimen is an efficacious therapeutic option for LM patients with solid tumors.

Trial Registration: This study (IPLM) was registered at <https://register.clinicaltrials.gov> [ClinicalTrials.gov identifier: NCT03507244].

Keywords: leptomeningeal metastases, pemetrexed, intrathecal chemotherapy, radiotherapy, solid tumor

Received: 31 December 2019; revised manuscript accepted: 21 May 2020.

Introduction

Intrathecal chemotherapy is one of the mainstay treatment options for leptomeningeal metastases (LM).¹ Owing to the limited number of

agents available for intrathecal chemotherapy, it is crucial to find a novel agent with efficacy and safety. Pemetrexed, a multitargeted antifolate agent, has demonstrated antitumor activity

Ther Adv Med Oncol

2020, Vol. 12: 1–14

DOI: 10.1177/
1758835920937953

© The Author(s), 2020.
Article reuse guidelines:
[sagepub.com/journals-](https://sagepub.com/journals-permissions)
[permissions](https://sagepub.com/journals-permissions)

Correspondence to:

Gang Zhao
Department of Neuro-
Oncological Surgery, The
First Hospital of Jilin
University, 71 Xinmin
Street, Changchun,
130021, China
gzhao@jlu.edu.cn

Yuanyuan Song
Department of Clinical
Laboratory, The First
Hospital of Jilin University,
71 Xinmin Street,
Changchun, 130021, China
songyy@jlu.edu.cn

Zhenyu Pan
Department of Radiation-
Oncology, The First
Hospital of Jilin University,
Changchun, China

Department of Neuro-
Oncological Surgery, The
First Hospital of Jilin
University, Changchun,
China

Stanford University
Medical School, VA Palo
Alto Health Care System,
Palo Alto, CA, USA

Guozi Yang
Department of Radiation-
Oncology, The First
Hospital of Jilin University,
Changchun, China

Stanford University
Medical School, VA Palo
Alto Health Care System,
Palo Alto, CA, USA

Hua He
Jiuwei Cui
Wei Li
Xiaofeng Cong
Zhi Li
Cancer Center, The First
Hospital of Jilin University,
Changchun, China

Tingting Yuan
Department of Radiology,
The First Hospital of Jilin
University, Changchun,
China

Kunzhi Chen
Tongchao Jiang
Pengxiang Gao
Yanan Sun
Department of Radiation-
Oncology, The First
Hospital of Jilin University,
Changchun, China

Yongxiang Wang
Xiaochuan Pang
Department of Clinical
Laboratory, The First
Hospital of Jilin University,
Changchun, China

*These authors
contributed equally to this
work.

against a variety of malignancies and central nervous system (CNS) tumors.² In a phase I study,³ intrathecal pemetrexed (IP) showed controllable toxicities and potential promising efficacy for refractory LMs from non-small-cell lung cancer (NSCLC) patients. The recommended dose of IP for LM was 10 mg on a schedule of 1–2 times per week based on pharmacokinetic studies.³

Involved-field radiation therapy (IFRT) is a part of the specific treatment of LM, which is defined in the National Comprehensive Cancer Network (NCCN) guidelines as radiotherapy to neurologically symptomatic sites or visible CNS disease on neuroimaging findings, including whole brain radiotherapy (WBRT) and partial spine field. Radiotherapy has been proved to improve neurologic function and control of parenchymal brain metastases in LM treatment.⁴ More importantly, radiotherapy is revealed to improve the efficacy and attenuate toxicity of intrathecal chemotherapy as a result of normal CSF reestablishing,^{5,6} aspects that commend the requirement for early LM treatment.⁷ In 1987,⁸ Hitchins *et al.* reported that concurrent therapy of intrathecal chemotherapy (methotrexate or arabinoside) and CNS radiotherapy was associated with significantly improved efficacy and no obvious CNS toxicity compared with single intra-CSF chemotherapy. The concurrent therapeutic modality was also administrated in another LM study.⁹

LM patients with or without adverse prognostic factors are divided into high-risk or low-risk groups in NCCN guidelines. Up to date, few therapeutic approaches are available for LM patients with adverse prognostic factors. We have previously reported for the first time in a prospective study of concomitant intrathecal methotrexate combined with IFRT¹⁰ that the concomitant regimen could improve the prognosis of LM patients with adverse prognostic factors.

We conducted this study to demonstrate the efficacy and safety of IP as first-line intrathecal chemotherapy for patients with LM from solid tumors. Furthermore, the study of effective treatment modality is of great significance. The feasibility and antitumor activity of IP combined with IFRT were also assessed to validate the efficacy and safety of the concomitant regimen.

Patients and methods

Study design

In this phase I/II, open-label, single-arm study, the feasibility, safety, and antitumor activity of IP combined with IFRT were investigated. Patients with LM from solid tumors with no history of intra-CSF therapy were enrolled. The primary endpoint was safety. The secondary endpoints were response rate, neurological progression-free survival (NPPFS), and overall survival (OS).

This clinical trial had two stages. In phase I, six patients were recruited to determine the feasibility and tolerability of concomitant regimen by adverse events (AEs). Dose-limiting toxicity (DLT) was defined as grade 3 neurological toxicities (e.g., chemical meningitis) or any grade 4 toxicities. If two or more participants experienced DLT in phase I, the regimen was considered too toxic and the study was to be halted. Otherwise, the study was moved into phase II and 28 more patients were recruited. All patients were observed to investigate the safety, response rate, NPPFS, and OS.

Patients

LM diagnosis was ascertained according to the NCCN guidelines and the European Association of Neuro-Oncology–European Society for Medical Oncology (EANO-ESMO) guidelines.¹ The eligibility criteria were: (i) patients with a confirmed or probable diagnosis of LM; (ii) participants with histologically or cytologically confirmed disease from solid tumors; (iii) patients without a history of intra-CSF therapy or WBRT; (iv) patients aged between 18 and 75 years. The exclusion criteria were: (i) leukocyte count of $<3.5 \times 10^{12}/l$, or platelet count of $<100 \times 10^9/l$; (ii) hepatic dysfunction (alanine aminotransferase >40 U/l, aspartate aminotransferase >40 U/l) or renal dysfunction (serum creatinine >1.2 mg/dl, blood urea nitrogen >20 mg/dl); (iii) patients with lethal or extensive systemic diseases with few treatment options; (iv) patients with poor compliance.

Treatment regimen

Patients received the same regimen in phase I and phase II. Pemetrexed (Alimta, Eli Lilly and Company) at a dose of 10 mg was administrated by intrathecal injection *via* lumbar puncture. Dexamethasone at a dose of 5 mg was also administrated by intrathecal injection at each IP

to minimize arachnoiditis. Vitamin B12 and folic acid supplementation were given at the beginning of IP administration. Vitamin B12 (1000 µg) was given *via* intramuscular injection as a single dose. Oral administration of folic acid (400 µg, q.d.) was given daily until 21 days after the last IP. All participants were treated with induction IP first. Concomitant IFRT given within 3 days following induction IP was administrated with a daily dose of 2 Gy × 5 days each week for 4 weeks to a total dose of 40 Gy. The planning volume consisted of sites of symptomatic disease and the involved region observed on magnetic resonance imaging (MRI), including the whole brain and basis crania and/or segment of the spinal canal. Concomitant IP was given on a schedule of once per week for 4 times in 4 weeks during IFRT. For participants with severe neurological status (e.g., severe headache, vomiting, confusion, abnormal consciousness, or high seizure frequency) who could not stay still long enough to coordinate IFRT, successive induction IP was given twice per week until improvement of neurological status and radiotherapy cooperation. Concomitant IFRT would be given as soon as radiotherapy cooperation. If neurological status presented continued deterioration after three courses of induction IP or the participant remained unable to coordinate radiotherapy after four courses of IP, the participant was determined as ineffective and taken off the study.

The schema of the treatment regimen is provided in Figure 1.

In patients who developed grade 3 neurological toxicities or hematologic toxicities, treatment was delayed until the AEs were controlled. Patients with treatment cessation for more than 10 days or patients determined as LM progression by neurological examination were withdrawn from the study. Symptomatic therapy and supportive care were permitted.

The study procedures were compliant with the Declaration of Helsinki. The study protocols were approved by the Ethics Committee of the First Hospital of Jilin University (approval number: 18k017-001). Prior to treatment, written informed consent about enrolling in this clinical trial was obtained from each patient or their guardians. This study (IPLM) was registered at <https://register.clinicaltrials.gov> [ClinicalTrials.gov identifier:NCT03507244].

Evaluation, outcomes, and follow-ups

The following parameters were determined before treatment: general health conditions, Karnofsky Performance Status Scale (KPS) score, neurological status, Glasgow coma scale (GCS), CSF cytology, CSF biochemistry, full blood count, and multichannel biochemical profile. A standardized

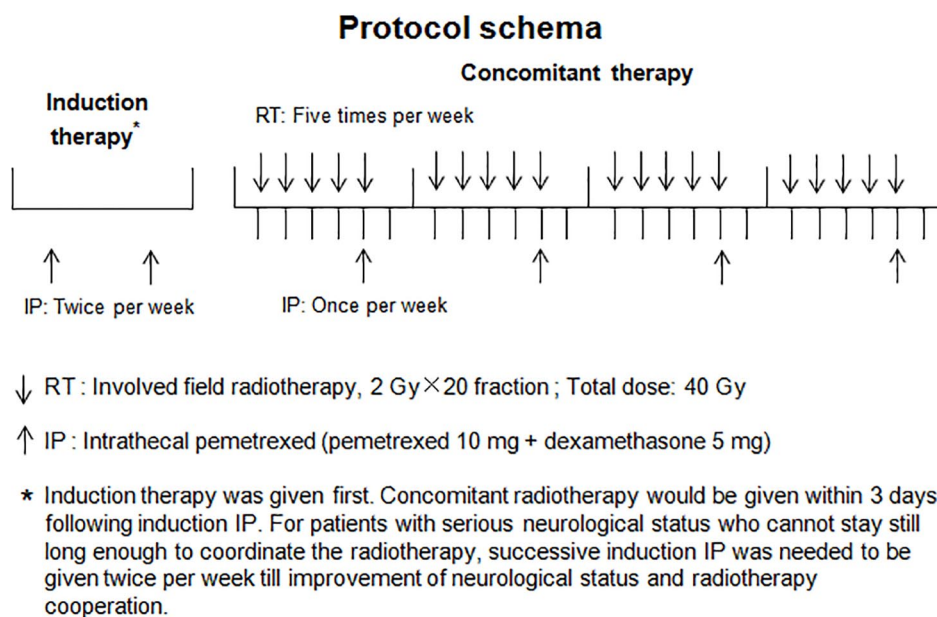


Figure 1. Study schema.

neurological examination, LM-related neurological symptoms, and KPS records were performed before and after treatment. Imaging examination was used to evaluate systemic disease status. A neurological examination was performed weekly. The changes in neurological signs and symptoms, as well as KPS, were recorded weekly. CSF cytology examination was determined by three blinded cytopathologists using Thinprep plus Papanicolaou stain method every 2 weeks until 1 month after the end of concurrent treatment. CSF cytology should be monitored for at least 1 month in patients with conversion of a previously positive CSF cytology to negative. Cerebrospinal MRI was performed before and after concurrent therapy completion and repeated 4 weeks later using a scanner of 3.0 T field strength. LM-related imaging findings were recorded. AEs were evaluated by physical examination, CSF examination, full blood count, and multichannel biochemical profile monitoring at least weekly during treatment according to the Common Terminology Criteria for AEs (CTCAE, version 4.03). Events of grade 4–5 were defined as severe AEs.

Response assessment was determined by three blinded neuro-oncologists according to the RANO proposal criteria.¹¹ Neuroimaging assessment was performed according to the proposal for a revised Leptomeningeal Metastasis Working Group grid⁷ by three neuroradiologists and two neuro-oncologists. Patients with an improved neurological assessment, cytological assessment, or neuroimaging assessment but without neurological or neuroimaging progression were assessed as response.

Follow-up physical examinations, standardized neurological examinations, and CSF cytology were carried out every 2–3 months or at any instance of suspected clinical progression until death. Neuroimaging examinations were used to assess CNS progression and AEs (e.g., leukodystrophy) and carried out every 2 months or at any instance of suspected progression and CNS toxicity. NPFS was defined as the time from the start of treatment until LM progression or death. LM progression was defined as follows: progressively deteriorative neurological symptoms/signs typically associated with LM for more than 1 week; worsening LM-related neuroimaging findings. All patients were followed-up until death or for at least 8 months. Survival time was measured from the enrollment of this study until death or the last follow-up.

Statistical analysis

The outcome measures were assessed on all participants using intention-to-treat analyses. SPSS 17.0 software was used for data analyses. Survival analyses were performed using the Kaplan–Meier method. Log-rank test was used to compare the survival time of patients. Univariate and multivariate Cox regression analyses were carried out to determine the risk factors of OS. Fisher's exact tests were used to evaluate the difference of response rate between patients with various features. $p < 0.05$ demonstrated a significant difference.

Results

Patient characteristics

Between April 2018 and December 2018, 34 participants were enrolled, including 6 cases in phase I and 28 cases in phase II. LM diagnosis was confirmed in 32 cases and probable in 2 cases according to the EANO-ESMO guidelines.¹ All patients showed LM-related neurological symptoms. Twenty-eight patients presented with LM-related neurological dysfunctions. Thirty-two participants presented with positive CSF cytology. Thirty participants showed LM-related neuroimaging findings and 4 with normal neuroimaging. Thirty-one patients presented at least one adverse prognostic factor. These factors consisted of KPS score less than 60 ($n = 24$), severe and multiple neurological deficits ($n = 26$), encephalopathies ($n = 13$), and bulky brain metastases ($n = 6$). Active systemic disease was observed in 14 patients. Fifteen patients had stable systemic disease outside the CNS. Systemic diseases were not observed in five patients. Twenty-nine patients had received systemic therapy before enrollment. In a total of 21 NSCLC patients, 15 patients had *EGFR* mutations detected and 6 were *EGFR* wild type. Prior to enrollment, 13 patients had received *EGFR*-tyrosine kinase inhibitor (TKI) agents including 12 cases with first-generation *EGFR*-TKI, 1 with second-generation *EGFR*-TKI, and 5 with first-generation and third-generation *EGFR*-TKI. Patients' characteristics are summarized in Table 1.

Treatment

Among the six patients enrolled in the phase I study, five participants completed the concomitant treatment. No DLT was observed. Then,

Table 1. General information of the patients prior to treatment.

Characteristic	n = 34 (%)
Gender	
Male	15 (44%)
Female	19 (56%)
Median age	56 (43–73) years
Onset as LM ^a	5 (15%)
Pathological types of primary disease	
NSCLC ^b	21 (62%)
SCLC	5 (15%)
Breast cancer	4 (12%)
Others ^c	4 (12%)
Neuroimaging features	
Positive	30 (88%)
Negative	4 (12%)
CSF biochemistry	
Abnormal	28 (82%)
Negative	6 (18%)
CSF cytology	
Positive	32 (94%)
Negative	2 (6%)
GCS	
15	12 (35%)
13–14	10 (29%)
9–12	10 (29%)
3–8	2 (6%)
KPS	10–90
80–90	2 (6%)
60–70	8 (24%)
40–50	8 (24%)
10–30	16 (47%)
Median KPS	40 score
Adverse prognostic factors	31 (91%)
KPS < 60	24 (71%)

*(Continued)***Table 1.** (Continued)

Characteristic	n = 34 (%)
Serious, multiple or major neurologic deficits	26 (76%)
Coexistent brain metastasis (short diameter >1 cm)	6 (18%)
Encephalopathy	13 (38%)
NSCLC participants	21 (62%)
EGFR mutation	15 (71%)
EGFR wild type	6 (29%)
TKI therapy prior to enrollment	13 (38%)
First-generation EGFR-TKIs	12 (35%)
Second-generation EGFR-TKIs	1 (3%)
Third-generation EGFR-TKIs	5 (15%)
CSF, cerebrospinal fluid; EGFR, epidermal growth factor receptor; GCS, Glasgow coma scale; KPS, Karnofsky Performance Status Scale score; LM, leptomeningeal metastases; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; TKI, tyrosine kinase inhibitor.	
^a LM was the initial manifestation of malignancy.	
^b Includes lung adenocarcinoma (<i>n</i> = 20) and pulmonary neuroendocrine carcinoma (<i>n</i> = 1).	
^c Includes gastric adenocarcinoma (<i>n</i> = 2), glioblastoma (<i>n</i> = 1), and endometrial cancer (<i>n</i> = 1).	

another 28 patients were enrolled. The study profile was provided in Figure 2.

All patients received induction IP. Owing to serious neurological status, 12 participants received successive induction IP prior to concomitant therapy. Ten participants presented with improved neurological symptoms/signs and radiotherapy tolerance after induction IP. Two cases presented with progressive and uncontrolled LM disease after induction IP and died 3–5 days later after the third and fourth IP. Thirty-two patients (94%) received concurrent therapy. Thirty-one patients received WBRT. Three patients received lumbosacral spinal irradiation, including two that received both WBRT and partial spinal field irradiation. Twenty-five (74%) patients completed the concurrent therapy, including 1 with

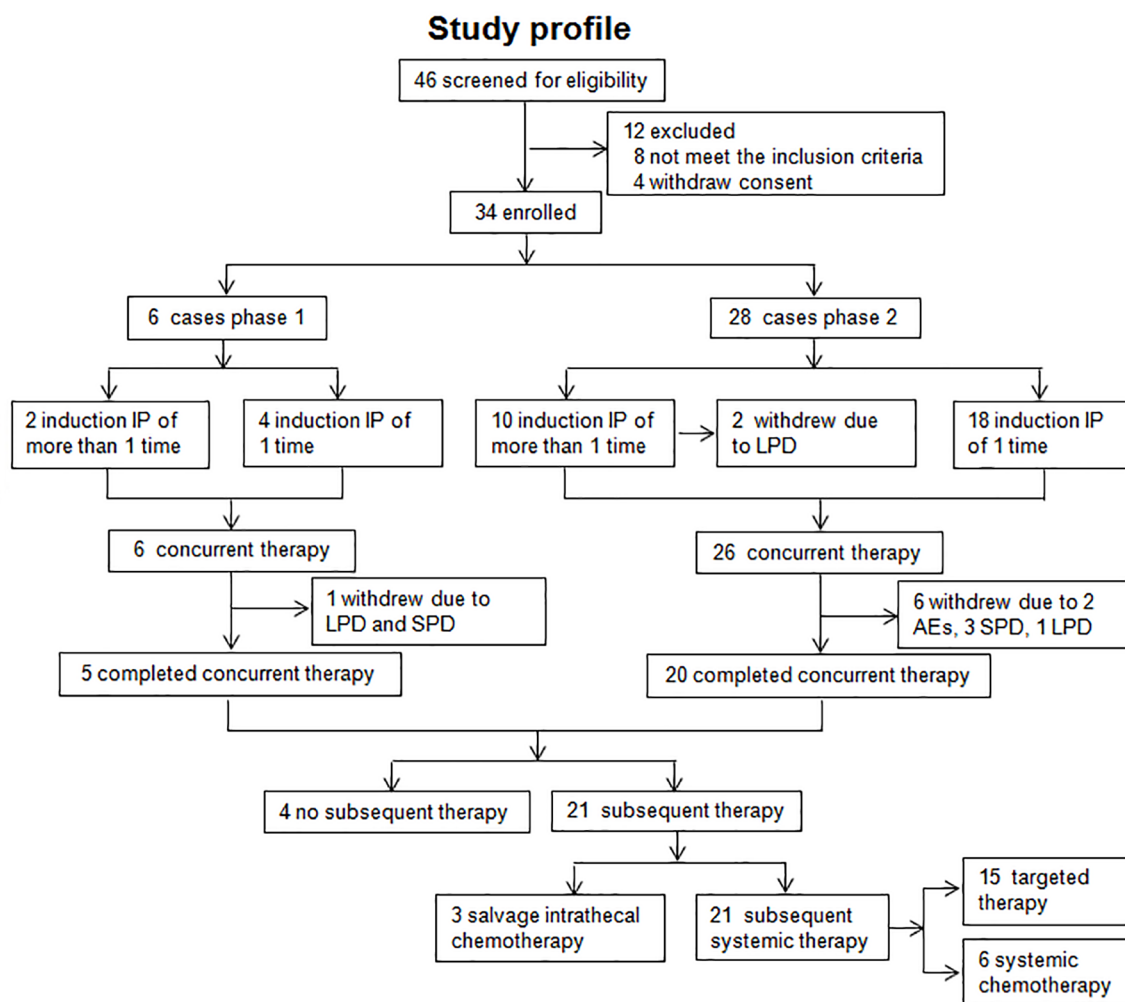


Figure 2. Study profile.

AEs, adverse events; IP, intrathecal pemetrexed; LPD, leptomeningeal metastases progressive disease; SPD, systemic progressive disease.

temporary cessation (5 days) due to grade 3 myelosuppression. Seven patients failed to complete the concomitant therapy due to systemic disease progression ($n=3$), LM and systemic disease progression ($n=1$), deteriorating brain edema ($n=1$), and AEs ($n=2$). A total of 165 courses of IP were given.

Eleven NSCLC patients with *EGFR* driver oncogene continued previous molecular target therapy during this study, including six patients with active systemic diseases. One patient with glioblastoma received temozolomide chemotherapy in the study. Eight patients with active systemic diseases, including small-cell lung cancer (SCLC, $n=1$), breast cancer ($n=2$), gastric adenocarcinoma ($n=1$), and NSCLC ($n=4$), did not receive systemic chemotherapy owing to low KPS score

(less than 50) or severe neurological status. Thirty patients (88%) received symptomatic treatment or supporting treatment. Treatment outcomes are summarized in Table 2.

Safety and toxicity

All participants were evaluated for AEs. Mild or moderate skin reactions and hair loss were common radiotherapy-related AEs. Radiotherapy-related mild and moderate otitis media was observed in three patients. The major AEs were myelosuppression ($n=13$), radiculitis ($n=4$), and elevation of hepatic aminotransferases (EHA, $n=10$). The total rate of AEs was 53% (18/34). Six patients (18%) had grade 3 AEs, including myelosuppression ($n=2$), EHA ($n=3$), and radiculitis ($n=1$). Only one patient (3%)

Table 2. Treatment outcomes.

Characteristics	n = 34
Total IP courses	165 times
Induction IP	34 (100%)
One course of induction IP	22 (65%)
Two courses of induction IP	6 (18%)
Three courses of induction IP	4 (12%)
Four courses of induction IP	2 (6%)
Concomitant therapy	32 (94%)
Completion of concomitant therapy	25 (74%)
Uncompleted concomitant therapy	9 (26%)
Owing to LPD	3 (9%)
Owing to SPD	3 (9%)
Owing to LPD and SPD	1 (3%)
Owing to AEs	2 (6%)
Continued TKI therapy during this study	11 (32%)
Systemic chemotherapy during this study	1 (3%)
Subsequent targeted therapy after this study ^a	15 (44%)
Subsequent systemic chemotherapy after this study	6 (18%)
Salvage intrathecal chemotherapy	3 (9%)

AE, adverse event; IP, intrathecal pemetrexed; LPD, leptomeningeal metastases progressive disease; SPD, systemic progressive disease; TKI, tyrosine kinase inhibitor.
^aIncludes EGFR-TKI therapy (n = 14) and bevacizumab (n = 1).

Table 3. Adverse events and toxicities.

Variables	n = 34 (%)
Major adverse events	18 (53%)
I–II degree	11 (32%)
III degree	6 (18%)
IV degree	1 (3%)
Hematologic toxicities	13 (38%)
I–II degree	10 (29%)
III degree	2 (6%)
IV degree	1 (3%)
Leukopenia	8 (24%)
I–II degree	6 (18%)
III degree	1 (3%)
IV degree	1 (3%)
Thrombocytopenia	11 (32%)
I–II degree	8 (24%)
III degree	2 (6%)
IV degree	1 (3%)
Elevation of hepatic aminotransferases	10 (29%)
I degree	4 (12%)
II degree	3 (9%)
III degree	3 (9%)
Radiculitis	4 (12%)
I degree	2 (6%)
II degree	1 (3%)
III degree	1 (3%)
Leukoencephalopathy (n = 17)	8 (47%)
I–II degree	7 (41%)
III degree	1 (6%)

experienced severe AEs shown as myelosuppression (Table 3).

The incidence of myelosuppression was 38% (13/34) and of severe myelosuppression was 3% (1/34). The incidence of thrombocytopenia (32%, 11/34) was higher than that of leukopenia (24%, 8/34). Ten patients did not receive folic acid daily supplementation at the beginning of treatment owing to severe illness. Seven of them

developed grade 1–3 myelosuppression within 1–2 weeks. In the remaining 24 patients who had received folic acid daily supplementation at the beginning of treatment, six patients developed grade 1–4 myelosuppression. The hematological toxicities were recovered in 10 patients after increasing folic acid dose to 800 µg per day and symptomatic treatment, including recombinant human granulocyte colony-stimulating factor (rhG-CSF), recombinant human interleukin 11

(rhIL-11), and recombinant human thrombopoietin (rhTPO). Two patients did not complete concurrent therapy owing to persistent myelosuppression and treatment delay for more than 10 days. These two patients were the only vegetarians in the study.

The incidence of EHA was 29% (10/34) and the incidence of grade 3 EHA was 9% (3/34). EHA occurred after two or three courses of IP in nine patients. It is worth noting that delayed grade 2 EHA occurred in a breast cancer patient 1 week after the completion of concurrent therapy, suggesting that liver function should be tested till at least 2 weeks after the treatment. Agents including glutathione, monoammonium glycyrrhizinate, and bicyclol were given in four patients with grade 2–3 EHA who showed a gradual decrease of hepatic aminotransferases in 1–3 weeks and reached normal ranges within 1–2 months.

The incidence of radiculitis was 12% (4/34). Only one patient showed grade 3 radiculitis. Radiculitis commonly occurred after 3–4 courses of IP manifested as symptoms of nerve root irritation, including severe numbness and pain of lower extremities and bilateral hips. The symptoms dissipated spontaneously 1–2 weeks after concurrent therapy.

Leukoencephalopathy refers to a type of delayed and chronic neurotoxicity assessed by neuroimaging. Two patients had preexisting leukoencephalopathy prior to treatment that did not worsen after concurrent therapy. A total of 17 patients received cranial MRI within 1–15 months after concomitant therapy, 8 of whom presented with leukoencephalopathy (Table 3). No significant neurological symptoms or signs were observed except for mild or moderate short-term memory loss, depression or dullness of mind in five patients.

Response evaluation

Response evaluation and outcomes are listed in Table 4. In the neurological assessment, 18 patients presented with an improvement of neurological dysfunction after treatment. Four cases of neurological dysfunction worsened. Twelve cases were stable, including six cases without neurological deficits prior to treatment. Twenty-eight patients showed remission of symptoms associated with LM. The median KPS score was 70 after treatment.

CSF cytological examinations were not reviewed after treatment in nine patients who did not complete the treatment schema, including two patients with a conversion of CSF cytology from positive to negative and seven that remained positive. These patients could not be evaluated as cytological response due to failing to meet the requirement of maintaining negative cytology for 4 weeks. In the CSF cytologic evaluation, eight patients were assessed as cytological response. CSF cytology was stable in 17 patients, 2 of which remained negative and 15 remained positive.

Nine patients who did not complete the treatment schema were not followed up by MRI after treatment. In neuroimaging assessment, 25 participants with repeated MRI after treatment were evaluated. Nine patients were assessed as improved and 16 patients were stable or equivocal, including 4 of whom that remained negative and 12 with positive neuroimaging findings.

Twenty-three patients were assessed as response, including three cases with improved neuroimaging assessment, improved neurological examination, and cytological response, three with improved neurological examination, improved neuroimaging assessment, and stable CSF cytology, one with improved neurological examination, cytological response, and stable neuroimaging assessment, nine with improved neurological examination, stable neuroimaging assessment, and stable CSF cytology, three with improved neuroimaging assessment, stable neurological examination, and stable CSF cytology, four with cytological response, stable neuroimaging assessment, and stable neurological examination. Two patients were assessed as stable disease based on stable neurological exam, neuroimaging assessment, and CSF cytology. Four patients were assessed as having progressive disease based on worsening neurological examination. The remaining five participants without MRI or CSF review after treatment were not evaluable.

On intention-to-treat analysis, the response rate was 68% (23/34). The total disease control rate (DCR) was 74% (25/34). The response rates based on pathological types were evaluated, and the response rates were 67% (14/21) for NSCLC, 80% (4/5) for SCLC, 75% (3/4) for breast cancer, and 50% (2/4) for other tumors. Stable patients included two lung adenocarcinoma patients. Progressive disease patients included one with breast cancer, one with gastric

Table 4. Clinical response evaluation and outcomes.

Characteristics	<i>n</i> = 34
Neurological exam assessment	
Improved	18 (53%)
Worse	4 (12%)
Stable	12 (35%)
Neurological symptoms assessment	
Improved	28 (82%)
Worse	4 (12%)
Stable	2 (6%)
CSF cytological assessment	
N/A	9 (26%)
CSF cytological response	8 (24%)
Stable positive	15 (44%)
Stable negative	2 (6%)
Neuroimaging assessment	
N/A	9 (26%)
Definite improvement	9 (26%)
Stable/equivocal	16 (47%)
Clinical response evaluation	
Response ^a	23 (68%)
Progressive or refractory disease ^b	4 (12%)
Stable disease	2 (6%)
N/A	5 (15%)
Median NPFS	3.5 (range 0.3–15.2) months
Median OS	5.5 (range 0.3–16.6) months
CSF, cerebrospinal fluid; N/A, not applicable assessment; NPFS, neurological progression-free survival; OS, overall survival. ^a The three elements (neurological examination, CSF cytology examination, and neuroimaging examination) are used together according to the Response Assessment in Neuro-Oncology (RANO) proposal. ^b Patients presented progressively deteriorative neurological symptoms/signs typically associated with LM or worsening LM-related neuroimaging findings.	

adenocarcinoma, and two with NSCLC. In 12 patients receiving successive induction IP, the response rate was 58% (7/12) and the progressive disease rate was 25% (3/12). The remaining two patients were not applicable assessments. In 22 patients receiving one course of induction IP, the response rate was 68% (15/22) and the progressive disease rate was 5% (1/22). The response rate was not influenced by courses of induction IP ($p = 0.459$).

A Fisher's exact test was applied to the baseline patient characteristics listed in Table 1. Response rate was not influenced by age ($p = 1.000$), gender ($p = 1.000$), severe and multiple neurological deficits ($p = 0.638$), KPS score < 40 ($p = 0.717$), KPS score < 60 ($p = 0.437$), encephalopathy ($p = 0.262$), primary lung cancer ($p = 1.000$), NSCLC with *EGFR*-mutation ($p = 1.000$), previous TKI therapy ($p = 0.709$), and continued TKI therapy during this study ($p = 1.000$). The following factors have potential trends for significant differences, including previous systemic pemetrexed chemotherapy prior to enrollment ($p = 0.178$) and the onset of LM ($p = 0.150$). DCR was not influenced by age ($p = 1.000$), gender ($p = 0.462$), severe and multiple neurological deficits ($p = 1.000$), KPS score < 40 ($p = 0.250$), KPS score < 60 ($p = 0.225$), multiple induction IP ($p = 0.224$), onset of LM ($p = 0.293$), primary lung cancer ($p = 0.704$), *EGFR*-mutation ($p = 0.697$), previous *EGFR*-TKI therapy ($p = 1.000$), and continued TKI therapy during this study ($p = 0.682$). The following factors have potential trends for significant differences, including encephalopathy ($p = 0.057$) and previous systemic pemetrexed chemotherapy ($p = 0.061$). No statistical difference was observed in the response of the patients with various primary tumors (Table 5).

Follow-up, subsequent treatments, and outcomes

Twenty-one patients received subsequent systemic therapy. Among these cases, six received systemic chemotherapy using etoposide and cisplatin ($n = 2$), capecitabine ($n = 1$), pemetrexed and cisplatin ($n = 2$), and docetaxel ($n = 1$). Fifteen patients received molecular targeted therapy using TKIs [erlotinib ($n = 2$), icotinib ($n = 2$), gefitinib ($n = 4$), afatinib ($n = 1$), and osimertinib ($n = 7$)] or bevacizumab ($n = 1$). One breast cancer patient received hormonal therapy. In 25 patients who were evaluated as responding or stable, 11 patients

Table 5. Clinical response, NPFS, and OS of patients with various pathological features.

	NSCLC (n=21)	SCLC (n=5)	Breast cancer (n=4)	Others (n=4)
Response	14 (67%)	4 (80%)	3 (75%)	2 (50%)
Stable disease	2 (10%)	0	0	0
Progressive disease	2 (10%)	0	1 (25%)	1 (25%)
N/A assessment	3 (14%)	1 (20%)	0	1 (25%)
Median NPFS (months)	6.5	3.5	2.5	1.5
Median OS (months)	7.3	3.5	3.3	1.5

N/A, not applicable assessment; NPFS, neurological progression-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival; SCLC, small-cell lung cancer.
 No statistical difference was observed in the response assessment of the patients with various primaries ($p=0.878$, 1.000, 0.317).
 No statistical difference was observed in NPFS of the patients with various primaries ($p=0.859$).
 No statistical difference was observed in OS of the patients with various primaries ($p=0.826$).

were determined as relapsing in the follow-up. Five patients only received supportive care and died within 4 weeks. Six patients received salvage treatment, including salvage intrathecal chemotherapy ($n=3$) and the third-generation TKI agent ($n=3$). Three patients, including two cases of breast cancer and one NSCLC patient with *EGFR* wild type, were treated with intrathecal methotrexate after LM relapse, which was invalid and LM was progressed. After switching to IP, the condition was relieved. Three NSCLC patients with *EGFR* mutation who had received the first-generation targeted agents previously were treated with osimertinib at 160 mg per day after LM relapse, but it was ineffective in two of the patients and they died within 4 weeks. The treatment was effective in the other patient who survived for 10 months after relapse.

All patients were followed up 0.3–16.6 months until 30 August 2019. Median NPFS was 3.5 (range 0.3–15.2) months (95% confidence interval [CI], 0–8.1 months). Six-month NPFS rate was 47%. Median OS was 5.5 (range 0.3–16.6) months (95% CI, 0.2–10.8 months). One-year survival rate was 21.6%. Twenty-five patients died. Twenty-two (92%) died from

cancer progression, among whom 12 (48%) died exclusively from LM, 8 (32%) exclusively from systemic disease. The remaining two patients (8%) died from non-cancer disease. The median OS for NSCLC, SCLC, breast cancer, and other tumors patients was 7.3, 3.5, 3.3, and 1.5 months, respectively (Table 5). No statistical difference was observed in the OS ($p=0.826$). The median OS for NSCLC patients with *EGFR* mutation and others were 8.5 months and 3.3 months ($p=0.052$), respectively.

On univariate analyses by Cox regression analysis, OS was not influenced by age ($p=0.999$), gender ($p=0.620$), severe and multiple neurological deficits ($p=0.182$), KPS score < 40 ($p=0.685$), KPS score < 60 ($p=0.917$), encephalopathy ($p=0.897$), onset of LM ($p=0.437$), previous systemic pemetrexed chemotherapy ($p=0.378$), primary lung cancer ($p=0.443$), NSCLC with *EGFR*-mutation ($p=0.059$), previous TKI therapy ($p=0.897$), and continued TKI therapy during this study ($p=0.917$). Twelve patients with severe conditions receiving successive induction IP showed inferior OS than those received one course of induction IP (3.3 versus 5.6 months, $p=0.351$). The CSF cytological response and improved neuroimaging assessment showed no protective effects against the OS ($p=0.195$ and $p=0.271$, respectively). Several variables were found to be associated with significantly improved OS: clinical response ($p=0.000$), improved neurological dysfunction ($p=0.005$), accomplished concomitant therapy ($p=0.000$), subsequent TKI therapy after this study ($p=0.026$), and subsequent systemic therapy ($p=0.000$). Multivariate analyses revealed that NSCLC patients with *EGFR*-mutation ($p=0.093$) was a potential protective prognostic factor. In addition, primary lung cancer ($p=0.654$), successive induction IP ($p=0.371$), or previous systemic pemetrexed chemotherapy ($p=0.336$) caused no significant effects on prognosis.

On univariate analyses, NPFS was not influenced by age ($p=0.762$), gender ($p=0.416$), severe and multiple neurological deficits ($p=0.226$), KPS score < 40 ($p=0.894$), KPS score < 60 ($p=0.981$), encephalopathy ($p=0.431$), onset of LM ($p=0.338$), previous systemic pemetrexed chemotherapy ($p=0.431$), primary lung cancer ($p=0.460$), *EGFR*-mutation ($p=0.071$), previous TKI therapy ($p=0.469$), and continued TKI therapy ($p=0.503$). Patients that received successive induction IP showed inferior NPFS than

those received one course of induction IP (2.5 *versus* 5.6 months, $p=0.287$). The CSF cytological response and improved neuroimaging assessment showed no protective effects against the NPFS ($p=0.195$ and $p=0.256$, respectively). Significant NPFS benefits were observed in patients with clinical response ($p=0.000$), improved neurological dysfunction ($p=0.005$), accomplished concomitant therapy ($p=0.000$), subsequent TKI therapy ($p=0.032$), and subsequent systemic therapy ($p=0.000$).

Separate analyses on OS were performed in 21 patients with NSCLC. On univariate analyses by Cox regression analyses, OS was not influenced by age ($p=0.421$), gender ($p=0.916$), severe and multiple neurological deficits ($p=0.175$), KPS score < 40 ($p=0.328$), KPS score < 60 ($p=0.494$), onset of LM ($p=0.558$), encephalopathy ($p=0.668$), previous systemic pemetrexed chemotherapy ($p=0.199$), successive induction IP ($p=0.539$), previous TKI therapy ($p=0.542$), and continued TKI treatment during this study ($p=0.547$). Three variables were found to be associated with significantly improved OS, including accomplished concomitant therapy ($p=0.001$), NSCLC with *EGFR*-mutation ($p=0.035$), and subsequent TKI therapy ($p=0.008$).

Discussion

This is the first clinical trial on IP as the first-line intrathecal chemotherapy for LM from solid tumors. In this study, IP at a dose of 10 mg combined with IFRT showed the feasibility and controllable AEs. Meanwhile, it presented satisfactory efficiency in patients with adverse prognostic factors. It has been proved that pemetrexed as a novel intrathecal drug exhibited promising anti-tumor effects in CSF with a recommended dose of IP of 10 mg on the schedule of 1–2 times per week. Moreover, the concomitant therapeutic modality is an optimal treatment option for LM from solid tumors.

It was previously thought that, for patients with adverse prognosis factors, the clinical status may be improved by intrathecal chemotherapy; however, patients commonly relapse within a short time.^{12,13} LM-specific treatment did not provide survival benefits.^{14–18} In our previous study, concomitant radiotherapy contributed to long-term neurologic remission and extension of OS that revealed several advantages of concurrent therapy.¹⁰ In addition, pemetrexed is a multi-

targeted antifolate agent. By targeting different enzymes, pemetrexed affects the synthesis of substrates necessary for cell growth and division and causes cell cycle arrest by an accumulation of cells in the G1 phase.¹⁹ Cancer cells at G1 phase are sensitive to irradiation. Hence, the concurrent regimen of radiotherapy and pemetrexed contributes to synergistic antitumor effects in theory.

In this study, the concomitant regimen of IP combined IFRT was effective for LM from various primary solid tumors. Compared with the previous study on intra-methotrexate and concurrent IFRT, the 1-year survival rate was similar, but the median OS of this study was shorter than that of the previous study (5.5 months *versus* 6.5 months).¹⁰ It may be related to the following factors. First, the proportion of critically ill patients is higher in this study, especially 47% of patients with 10–30 KPS score. Second, maintenance intrathecal chemotherapy was not designed in this study. Patients in this study received fewer courses of intrathecal chemotherapy than in the previous study. This may have an adverse effect on OS and NPFS. However, it is worth noting that the application of intra-methotrexate as salvage intrathecal chemotherapy was ineffective in two patients with LM relapse, and the following salvage IP was effective. This indicates that pemetrexed presented a potentially stronger antitumor effect than methotrexate in CSF.

Several variables were found to be associated with significantly improved OS and NPFS, including clinical response, improved neurological dysfunction, accomplished concomitant therapy, subsequent TKI therapy, and subsequent systemic therapy. It should be noted that most patients treated with subsequent systemic therapy were clinical response (81%, 17/21, $p=0.060$) or disease control (90%, 19/21, $p=0.013$). Therefore, it is not clear whether the subsequent systemic treatment has a specific survival benefit to LM. However, patients treated with subsequent TKI therapy had no significant difference in response ($p=1.000$) or disease control ($p=0.250$). In addition, in multivariate analyses, the pathological type of NSCLC showed no protective effects against OS, but NSCLC with *EGFR*-mutation was a potential protective prognostic factor ($p=0.093$). It indicated that the subsequent application of TKI therapy had a potential survival benefit in NSCLC patients with *EGFR*-mutation. In this study, NSCLC patients exceeded 60%. 72% (16/22) of NSCLC patients

had EGFR-mutation. Among them, 13 patients (81%, 13/16) had previously applied TKI therapy. For these patients, intrathecal chemotherapy and radiotherapy are the main treatment options for LM. In conclusion, for LM patients from NSCLC with EGFR-mutation, the treatment modality of concurrent therapy followed by TKI therapy presented a good survival benefit.

A problem worthy of attention is whether IP was still effective for patients who had received systemic pemetrexed chemotherapy previously. In this study, seven NSCLC patients had previously received systemic pemetrexed chemotherapy prior to enrollment. The OS of these patients was inferior to others (2.0 months *versus* 5.6 months, $p=0.373$). Among the seven patients, three responded, one progressed, and three patients were not applicable to assessment owing to uncompleted concurrent therapy. In addition, previous systemic pemetrexed chemotherapy showed a tendency of significantly inferior DCR ($p=0.061$), indicating that previous systemic pemetrexed chemotherapy was a potential adverse factor for IP therapy, which deserves further study.

The main AEs in this study were consistent with the previous phase I IP study. Hematologic toxicity was still one of the main factors that interfere with the treatment. Hematologic toxicities occurred in 70% (7/10) of patients who did not receive folic acid supplementation on time, as compared with 25% (6/24) in the remaining patients. It further proved that folic acid supplementation was indispensable. For patients who cannot take folic acid orally, alternative routes are needed. Only two patients were vegetarians in this study. Both did not complete concurrent therapy owing to persistence grade 3–4 hematologic toxicities. This suggested that vegetarian patients should use IP with caution. If IP is required, high-dose folic acid supplements should be taken before treatment.

In this study, the incidence of grade 3 EHA was consistent with the previous phase I IP study (8% *versus* 9%),³ and similar to systemic pemetrexed chemotherapy.²⁰ The total incidence of EHA was higher compared with previous studies.^{3,20} However, most of the patients with grade 1–2 EHA did not receive any treatment and returned to normal or stable condition within 2–3 weeks. We speculated that EHA is partially attributed to the frequency of pemetrexed regimens in our

previous study.³ In this study, we further proved that the frequency of IP is associated with EHA. There were three patients with grade 3 EHA in this study, two of whom (67%) received three and four courses of induction IP (twice per week). From another perspective, a total of six patients in this study received 3–4 courses of induction IP, of which 33% (2/6) had grade 3 EHA. Meanwhile, of the remaining 28 patients who did not receive more than 2 courses of induction IP, only 1 (4%) had grade 3 EHA, indicating that IP administration twice per week for more than three successive courses may increase the incidence of high-grade EHA. It may hamper hepatic metabolism that the interval of IP regimen was extremely shorter than systemic administration.

The incidence of radiculitis was obviously lower than that of previous phase I IP study. This may be associated with the fact that most of the participants in that study had received multiple courses of intrathecal chemotherapy previously.

Compared with the previous study on concurrent therapy of intra-methotrexate and IFRT,¹⁰ the severe AEs rate was only 3% in this study, which was much lower. The incidences of hematological toxicities and EHA were higher in this study. However, these AEs are often controllable and do not significantly affect the quality of life of patients. In addition, the incidences of mucositis and radiculitis were lower compared with that study. The safety of pemetrexed, especially the CNS toxicities, is not inferior compared with other intra-CSF agents, including topotecan and etoposide.^{21,22} No acute or subacute CNS toxicity was observed. Moreover, in the case of combined concurrent radiotherapy, pemetrexed showed a better response rate, 6-month NPFS, and median OS.

There were limitations in this study. First, we did not objectively verify the reestablished normal CSF flow before and after the concurrent therapy using CSF flow scan, which was not routinely carried out by any medical institution in mainland China to the best of our knowledge. Second, the intrathecal approach is not used as a common therapeutic method for LM treatment, especially in developed countries. Intraventricular administration is acknowledged as an administration route with several advantages.²³ However, because of the risk and complications in reservoir implantation surgery and high medical and nursing expenses, intraventricular administration was not carried out routinely for LM treatment by

any medical institutions in mainland China to the best of our knowledge. Intrathecal injection is still the most common route of administration for LM. Indeed, intraventricular administration may provide a better drug CSF distribution and potential therapeutic advantages than lumbar puncture administration. Further study is warranted. Last, LM is an end-stage cancer complication. Several complex factors, such as primary tumor type, previous treatment, systemic tumor status, follow-up treatment, etc., may have a potential effect on the OS and NPFS.

Despite the unavoidable limitations, pemetrexed showed a promising antitumor effect and low rate of AEs in intrathecal administration. This study revealed that pemetrexed at a 10 mg dose on a schedule of 1–2 times per week was applicable to intrathecal administration for patients with LM from solid tumors. Pemetrexed is a novel intrathecal chemotherapy agent with safety and efficacy. In addition, the concomitant regimen is an effective therapeutic option, especially for LM patients with adverse prognosis factors.

Author contributions

PZY contributed to the conception and design of the study. PZY, YGZ, CJW, LW, YTT, CKZ, JTC, GPX, SYN, CXF, LZ, WYX, PXC, SYY, and ZG contributed to the acquisition of the data. PZY and HH contributed to the analysis of the data. PZY and YGZ contributed to drafting the text and preparing the figures.


Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grants from the Jilin Provincial Education Department “13th Five-Year” Science and Technology Project (grant number JJKH20170850KJ to Z.P. and grant number JJKH20201082KJ to G.Y.), and the S&T Development Planning Program of Jilin Province (grant number 20190201004JC to Z.P. and grant numbers 20180520133JH and 20200201365JC to G.Y.).

ORCID iD

Gang Zhao  <https://orcid.org/0000-0003-0403-5561>

References

1. Le Rhun E, Weller M, Brandsma D, *et al.* EANO-ESMO clinical practice guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours. *Ann Oncol* 2017; 28: iv84–iv99.
2. Chattopadhyay S, Moran RG and Goldman ID. Pemetrexed: biochemical and cellular pharmacology, mechanisms, and clinical applications. *Mol Cancer Ther* 2007; 6: 404–417.
3. Pan Z, Yang G, Cui J, *et al.* A pilot phase 1 study of intrathecal pemetrexed for refractory leptomeningeal metastases from non-small-cell lung cancer. *Front Oncol* 2019; 9: 838.
4. Gani C, Muller AC, Eckert F, *et al.* Outcome after whole brain radiotherapy alone in intracranial leptomeningeal carcinomatosis from solid tumors. *Strahlenther Onkol* 2012; 188: 148–153.
5. Chamberlain MC, Kormanik P, Jaeckle KA, *et al.* ¹¹¹Indium-diethylenetriamine pentaacetic acid CSF flow studies predict distribution of intrathecally administered chemotherapy and outcome in patients with leptomeningeal metastases. *Neurology* 1999; 52: 216–217.
6. Chamberlain MC and Kormanik PA. Prognostic significance of ¹¹¹indium-DTPA CSF flow studies in leptomeningeal metastases. *Neurology* 1996; 46: 1674–1677.
7. Le Rhun E, Devos P, Boulanger T, *et al.* The RANO Leptomeningeal Metastasis Group proposal to assess response to treatment: lack of feasibility and clinical utility and a revised proposal. *Neuro Oncol* 2019; 21: 648–658.
8. 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: 1655–1662.
9. Glantz MJ, Jaeckle KA, Chamberlain MC, *et al.* A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. *Clin Cancer Res* 1999; 5: 3394–3402.
10. Pan Z, Yang G, He H, *et al.* Concurrent radiotherapy and intrathecal methotrexate for treating leptomeningeal metastasis from solid tumors with adverse prognostic factors: a prospective and single-arm study. *Int J Cancer* 2016; 139: 1864–1872.
11. Chamberlain M, Junck L, Brandsma D, *et al.* Leptomeningeal metastases: a RANO proposal for response criteria. *Neuro Oncol* 2017; 19: 484–492.

12. Courchesne E, Chisum HJ, Townsend J, *et al.* Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. *Radiology* 2000; 216: 672–682.
13. Zhang JP, Lee EQ, Nayak L, *et al.* Retrospective study of pemetrexed as salvage therapy for central nervous system lymphoma. *J Neurooncol* 2013; 115: 71–77.
14. Chamberlain MC, Tsao-Wei D and Groshen S. Neoplastic meningitis-related encephalopathy: prognostic significance. *Neurology* 2004; 63: 2159–2161.
15. Chamberlain MC, Glantz M, Groves MD, *et al.* Diagnostic tools for neoplastic meningitis: detecting disease, identifying patient risk, and determining benefit of treatment. *Semin Oncol* 2009; 36: S35–S45.
16. Brem SS, Bierman PJ, Black P, *et al.* Central nervous system cancers: clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2005; 3: 644–690.
17. Chamberlain MC and Kormanik PA. Prognostic significance of coexistent bulky metastatic central nervous system disease in patients with leptomeningeal metastases. *Arch Neurol* 1997; 54: 1364–1368.
18. Chamberlain MC. Leptomeningeal metastases: a review of evaluation and treatment. *J Neurooncol* 1998; 37: 271–284.
19. Ramirez JM, Ocio EM, San Miguel JF, *et al.* Pemetrexed acts as an antimyeloma agent by provoking cell cycle blockade and apoptosis. *Leukemia* 2007; 21: 797–804.
20. Adjei AA. Pharmacology and mechanism of action of pemetrexed. *Clin Lung Cancer* 2004; 5(Suppl. 2): S51–S55.
21. Chamberlain MC, Tsao-Wei DD and Groshen S. Phase II trial of intracerebrospinal fluid etoposide in the treatment of neoplastic meningitis. *Cancer* 2006; 106: 2021–2027.
22. Groves MD, Glantz MJ, Chamberlain MC, *et al.* A multicenter phase II trial of intrathecal topotecan in patients with meningeal malignancies. *Neuro Oncol* 2008; 10: 208–215.
23. Fleischhack G, Jaehde U and Bode U. Pharmacokinetics following intraventricular administration of chemotherapy in patients with neoplastic meningitis. *Clin Pharmacokinet* 2005; 44: 1–31.