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Intrathecal pemetrexed chemotherapy combined with systemic therapy in patients with non-small cell lung cancer and leptomeningeal metastases: a retrospective study

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Background: Leptomeningeal metastases (LM) in non-small cell lung cancer (NSCLC) present a challenging prognosis, with systemic therapies often limited by the blood-brain barrier. However, intrathecal pemetrexed injections can increase intracranial drug concentrations, aiding in disease control.

Objective: To evaluate the efficacy and safety of combining intrathecal pemetrexed with systemic therapy in patients with NSCLC and LM.

Methods: Thirty-one patients with NSCLC and LM who received intrathecal pemetrexed chemotherapy between 2018 and 2022 at First Affiliated Hospital of Gannan Medical College were retrospectively reviewed.

Results: Of the 31 patients enrolled, six had LM at initial diagnosis. The median number of intrathecal pemetrexed injections was 4 (2-26), with an intracranial control rate of 87.1% (27/31). Median iPFS was 9 months (95% CI: 2.77-15.23), and median iOS was 12 months (95% CI: 5.94-18.06 months). Most adverse events (AEs) were grade 1-2, with four (12.9%) grade 3 AEs (including two cases of grade 3 leukopenia; one, grade 3 diarrhea; one, grade 3 interstitial pneumonitis). Univariate and multivariate analyses showed that the combination of bevacizumab ($p<0.05$) and an Eastern Cooperative Oncology Group(ECOG) score of ≤ 1 ($p<0.05$) were favorable prognostic factors for survival.

Conclusion: Intrathecal pemetrexed injections combined with systemic treatment demonstrated significant therapeutic efficacy and manageable safety in NSCLC patients with LM.

KEYWORDS

non-small cell lung cancer, leptomeningeal metastases, pemetrexed, intrathecal chemotherapy, EGFR

1 Introduction

Leptomeningeal metastases (LM) occur when tumor cells spread into the subarachnoid space and soft meninges through the bloodstream, direct seeding, or via cranial nerves and spinal nerves (1). The incidence of LM in patients with advanced non-small cell lung cancer (NSCLC) is 3% to 5%, with lung adenocarcinoma accounting for 84% to 96% (2, 3) of cases. Additionally, patients with epidermal growth factor receptor (EGFR) mutations (EGFRm) are more likely to develop LM (4, 5). Once LM occur, the prognosis is extremely poor, with a median survival of only 3-6.6 months (6, 7). Currently, there is no standardized treatment protocol for LM, and the available therapeutic approaches include radiotherapy, targeted therapy, chemotherapy, and immunotherapy; however, the efficacy of one treatment alone remains unsatisfactory. Targeted agents, particularly third-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), have a high blood-brain barrier (BBB) penetration rate and show significant efficacy in the treatment of patients with EGFRm NSCLC (8, 9). However, acquired resistance may develop over time. Intrathecal chemotherapy bypasses the BBB and enables direct delivery of chemotherapeutic agents to the subarachnoid space, providing a highly targeted and effective treatment approach. Conventional drugs for intrathecal injection include methotrexate and cytarabine, however, their therapeutic efficacy remains unsatisfactory.

Pemetrexed is an antimetabolic anticancer drug that can block the cell cycle in the S phase, effectively inhibiting the growth of tumor cells. It is a first-line chemotherapeutic agent for patients with advanced lung adenocarcinoma (10). Patients with EGFRm NSCLC who developed LM experienced longer survival when treated with pemetrexed than those who did not receive pemetrexed (13.7 months vs 4.0 months) (11). A low dose of pemetrexed has been shown to achieve therapeutically high and sustained cerebrospinal fluid (CSF) concentrations in a rat model of intrathecal injection (12). A phase I clinical trial of intrathecal pemetrexed chemotherapy as a salvage treatment of patients with NSCLC and LM showed a clinical response rate of 31% (4/13) and a disease control rate of 54% (7/13) with a dosage of 10 mg (13). Results of another clinical trial demonstrated that intrathecal pemetrexed chemotherapy had a clinical efficacy of 84.6% (22/26), with two patients achieving complete remission and seven patients achieving partial remission (median OS, 9.0 months) (14). These studies suggest that intrathecal pemetrexed has good efficacy in patients with NSCLC and LM; however, limited reports on intrathecal pemetrexed chemotherapy exist. Therefore, we conducted a retrospective study to evaluate the efficacy and safety of intrathecal pemetrexed chemotherapy combined with systemic therapy in patients with NSCLC and LM.

2 Materials and methods

2.1 Patients

The present study included 31 patients diagnosed with NSCLC and LM who were admitted to the First Affiliated Hospital of Gannan Medical College between January 1, 2018, and December 31, 2022. Inclusion criteria included the following: (i) patients with pathologically confirmed NSCLC; (ii) patients underwent CSF puncture examination and enhanced head magnetic resonance imaging (MRI); (iii) patients were diagnosed with LM according to the European Society for Medical Oncology-European Association of Neuro-Oncology guidelines and received at least two doses of intrathecal pemetrexed chemotherapy. Exclusion criteria included the following: (i) patients who discontinued treatment; (ii) patients with more than two primary tumors; (iii) patients with missing follow-up information. Intracranial progression-free survival (iPFS) was defined as the time from LM diagnosis to tumor progression, while intracranial overall survival (iOS) was defined as the time from LM diagnosis to either death or the last follow-up. This study was approved by the Ethics Committee of the First Affiliated Hospital of Gannan Medical College.

2.2 Data collection

Patients' clinical data were collected from the electronic medical record database, including information such as age, sex, smoking, Eastern Cooperative Oncology Group (ECOG) score, histological type, TNM stage, gene mutation status, brain-enhanced MRI, CSF cytology, treatments before and after LM diagnosis, and adverse drug reactions after pemetrexed injection. Univariate and multivariate analyses were performed in patients using Cox regression models to clarify prognostic correlates.

2.3 Intrathecal chemotherapy

After the onset of LM, all patients were treated with intrathecal pemetrexed injections in combination with systemic therapy. Pemetrexed was administered uniformly through lumbar puncture at a dose of 20-30 mg per dose. The frequency of intrathecal injections was 1-2 times in the first week, 2-4 times in the first month, and 1-2 times every month thereafter. Intrathecal injection therapy could only be discontinued if CSF cytology was negative for more than 3 consecutive tests, if adverse drug reactions became intolerable, if patients refused to continue therapy, or if the disease progressed. Before pemetrexed, dexamethasone (5 mg) was injected intrathecally. All patients should be supplemented with folic acid and vitamin B12.

2.4 Evaluation of treatment response and adverse events

We comprehensively assessed the patient's treatment response using intracranial neurological symptoms, cranial enhancement MRI, CSF cytology, and Karnofsky Physical Status Score (KPS) according to the Response Assessment in Neuro-Oncology (RANO) - LM radiological criteria (15). Imaging assessments were

performed independently by two experienced radiologists and AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

2.5 Follow up

Patients were followed-up via telephone or electronic case system, and those who could not be contacted were considered lost to follow-up.

2.6 Statistical methods

Statistical analyses were performed using SPSS version 24.0. Categorical variables were analyzed using either the Pearson χ^2 test or the Fisher exact test. Survival was calculated using the Kaplan–Meier method with a 95% confidence interval. The Cox proportional hazards regression model was employed to perform univariate and multivariate prognostic analyses on patients' sex, age, smoking status, MRI, Gene mutation, ECOG score, combined metastases, CSF pressure, CSF protein levels, radiotherapy, and combination with bevacizumab therapy, and $P<0.05$ was considered statistically significant.

3 Results

3.1 Baseline characteristics of the patients

All 31 patients had lung adenocarcinoma, including 15 males and 16 females, aged 42-75 years, with a median age of 58.3 years. Among them, 14 were smokers, and 17 were non-smokers. The gene mutation status was EGFR 21 L858R mutation in 14 cases, EGFR 19 Del in seven cases, EGFR20 ins in four cases, EGFR T790M in one case, negative driver gene in three cases, KRAS mutation in one case, and ROS1 fusion in one case. At the time of diagnosis of LM, 23 cases (74.19%) had an ECOG score of 0-1, eight (25.81%) had an ECOG score of ≥2, 18 cases (58.06%) had brain metastases, and 21 cases (67.74%) had extracranial metastases (Table 1).

3.2 Clinical manifestations, imaging, and CSF cytology

The patients presented with various clinical manifestations, including dizziness and headache in 22 patients, nausea and vomiting in 13, fatigue and difficulty walking in 15, blurred vision and diplopia in five, distortion of the commissure and facial numbness in two, hypophasis in one, hearing loss in two, dysphagia in two, convulsions in four, shoulder and neck pain in one, slow reaction in 10, slurred speech in two, urinary and bowel

TABLE 1 Basic characteristics of patients with NSCLC and leptomeningeal metastases (N=31).

Factor	Number of patients (%)
Age	
<60	16 (51.61%)
≥60	15 (48.39%)
Sex	
Male	16 (51.61%)
Female	15 (48.39%)
ECOG score	
0-1	23 (74.19%)
≥2	8 (25.81%)
Smoking	
Yes	14 (45.16%)
No	17 (54.84%)
MRI	
Negative	5 (16.13%)
Positive	26 (83.87%)
Brain metastases	
Yes	18 (58.06%)
No	13 (41.94%)
Extracerebral metastasis	
Yes	21 (67.74%)
No	10 (32.26%)
Gene mutation	
EGFR21 L858R	14 (45.17%)
EGFR19DEL	7 (22.58%)
EGFR T790M	1 (3.22%)
EGFR 20ins	4 (12.90%)
ROS1	1 (3.22%)
KRAS	1 (3.22%)
Negative	3 (9.68%)
High protein in CSF	
Yes	21 (67.74%)
No	10 (32.26%)
CSF pressure	
High	13 (41.94%)
Normal	18 (58.06%)

(Continued)

TABLE 1 Continued

Factor	Number of patients (%)
Combined treatment after LM	
Targeted therapy	24 (77.42%)
Chemotherapy	7 (22.58%)
Radiotherapy	3 (9.68%)
Anti-vascular treatment	20 (64.52%)
Immunotherapy	2 (6.45%)
Surgery	1 (3.22%)
Third-generation EGFR-TKI therapy	
Before LM	3 (9.68%)
After LM	11 (35.48%)
Before and after LM	12 (38.71%)
None	5 (16.13%)
Combine radiotherapy	
Yes	10 (32.26%)
No	21 (67.74%)
IP number	
1-5	20 (64.52%)
6-10	8 (25.81%)
>10	3 (9.68%)
Combine BEV	
Yes	26 (83.87%)
No	5 (16.13%)

IP, intrathecal chemotherapy of pemetrexed; BEV, bevacizumab.

incontinence in one, upper-limb numbness in two, and increased intracranial pressure in 22. Twenty-six patients (83.87%) exhibited positively enhanced brain MRI, with the majority displaying linear or nodular meningeal enhancement, or accompanied by nodular cerebral parenchymal enhancement, ventricular enlargement, cranial (spinal) nerve enhancement or thickening, enhanced nodules in the spinal arachnoid space, and hydrocephalus (Figure 1). Intracranial pressure was increased in 13 patients (41.94%). CSF analysis revealed hypoglycemia in 18 patients (58.06%) and hyperproteinemia in 21 patients(67.74%). Cancer cells were detected in the CSF of all patients.

3.3 Treatment

Prior to diagnosis of LM, 13 patients (41.94%) received first - or second-generation EGFR-TKIs, three (9.68%) received third-generation EGFR-TKIs, and 10 (32.26%) received first- to third-generation EGFR-TKIs. One patient (3.2%) received ALK inhibitor (crizotinib), and 11 patients (35.48%) received systemic chemotherapy with or without immunotherapy. After the onset of LM, 23 patients (74.19%) were treated with third-generation EGFR-TKIs (osimertinib, furmonertinib, or aumolertinib), of whom 18 (58.06%) were treated with high-dose third-generation EGFR-TKIs. One patient underwent a ventriculo-peritoneal (VP) shunt surgery. During the entire treatment period, 10 patients (32.26%) received radiotherapy (seven brain stereotactic body radiotherapy (SBRT) before LM, two brain SBRT after LM, one whole brain radiotherapy (WBRT) after LM), and 26 patients (83.87%) were treated with combination of bevacizumab (six before LM, 13 after LM, seven before and after LM) (Table 2). Patients received an average of 5.8 intrathecal pemetrexed injections, with 28 patients receiving a dose of 30 mg/injection and three patients receiving a dose of 20 mg/injection. Moreover, 27 patients showed improvement in intracranial symptoms after intrathecal pemetrexed chemotherapy and systemic therapy, with an intracranial control rate of 87.1%; of these, eight (25.81%) had CSF that was either negative for cancer cells or contained only a small amount of residual cellular debris.

3.4 Survival and prognosis factors

By the date of the last follow-up, all 31 patients had completed follow-up, with a median follow-up time of 20.4 (1-35) months; 23 patients had died, and eight patients are still alive. The median iPFS was 9 months (95% CI: 2.77-15.23), and the median iOS was 12 months (95% CI: 5.94-18.06 months) (Figures 2A, B). The univariate and multivariate analyses showed that combined bevacizumab treatment and ECOG ≤1 were favorable prognostic factors for survival, while sex, age, smoking status, brain metastases, extracerebral metastases, elevated CSF protein levels, gene mutations, positively enhanced brain MRI, and radiotherapy had no significant influence on OS (Table 3).

3.5 Adverse events

Most common AEs were grade 1-2, including leukopenia in 17 (54.84%) patients, nausea in 10 (32.26%), elevated alanine transaminase/aspartate transaminase levels in seven (22.58%), diarrhea in five (16.13%), weakness in eight (25.80%), rash in seven (22.58%), decreased appetite in six (19. 35%), and elevated gamma-GT in five (16.13%); there were three Grade 3 AEs, including two cases of leukopenia, one case of third-degree diarrhea, and one case of third-degree interstitial pneumonia (Table 4).

4 Discussion

LM is a severe complication of solid tumors, associated with a poor prognosis. The clinical manifestations of LM are complex and vary based on the affected sites (1). Brain parenchymal involvement and meningeal involvement: symptoms include headache, nausea, vomiting, cervical tension, meningeal irritation signs, cognitive impairment, seizures, and limb movement disorders (2). Cerebral neuropathy: symptoms include reduced visual acuity, diplopia, facial

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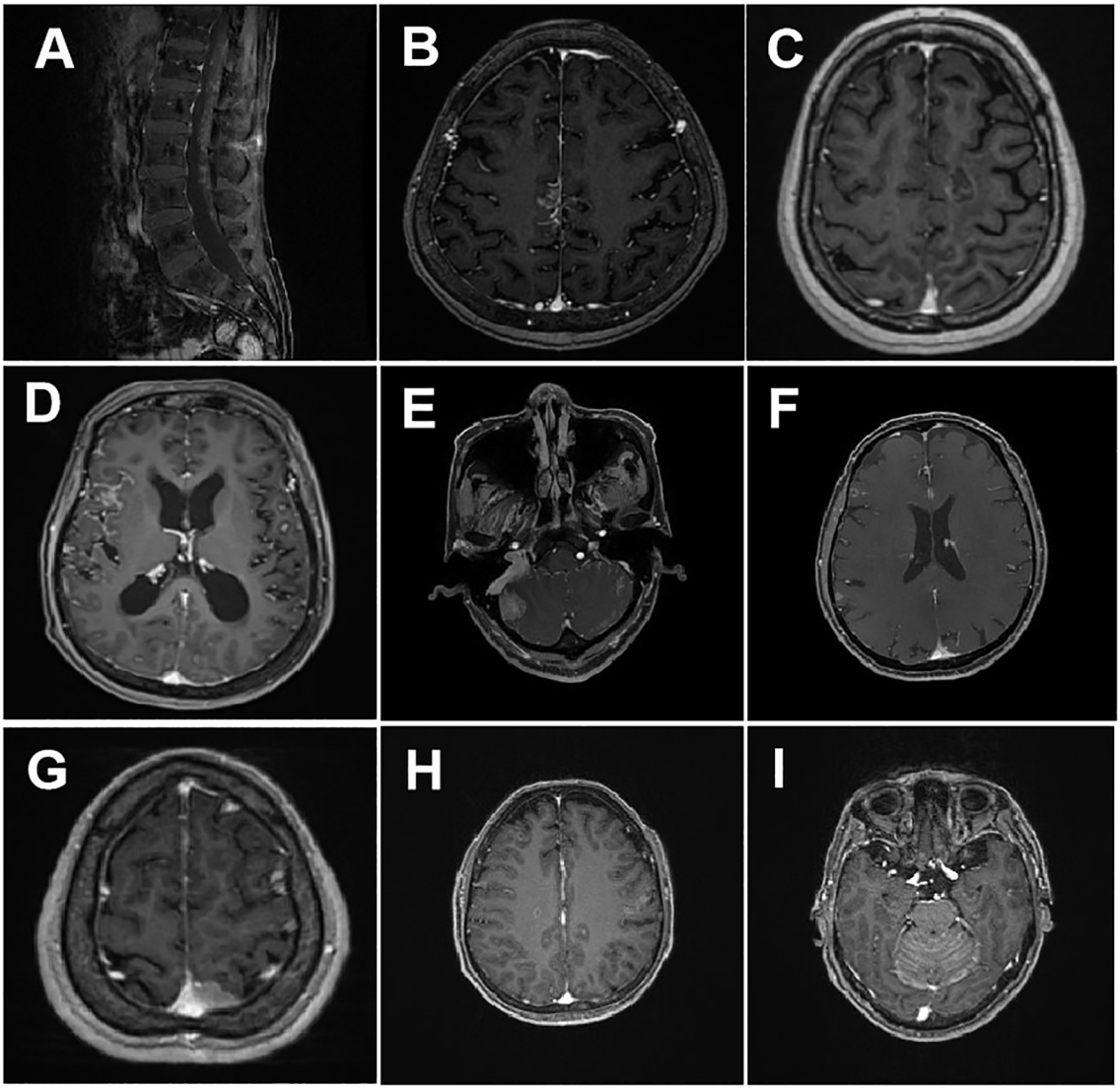

FIGURE 1
Representative brain MRI of patients with leptomeningeal metastases. **(A)** Meningeal metastasis spreading to the spinal cord, with extensive enhancement of the spinal cones and multiple tubercles in the cauda equina; **(B)** Enhanced MRI showing thickening of the meninges in the right upper frontal midline region, with a slightly decreased T1W signal, a slightly increased T2W signal, and a high T2 flair signal; **(C)** Cranial parenchyma enhancement displaying mild ring-shaped enhancement, with a large patchy high-signal edema band on T2FLAIR surrounding the nodule; **(D)** The meninges of the right frontotemporal lobe showing linear enhancement, along with enlargement of the ventricular system; **(E)** The right cerebellar hemisphere showing a patchy low-signal on T1WI, high-signal on T2WI, low signal on DWI, high signal on T2 FLAIR, and marked enhancement on post-contrast imaging; **(F)** The brain parenchyma and cerebral hemispheric meninges showing uneven thickening and marked enhancement; **(G)** The left parietal dura exhibiting nodular thickening with prominent enhancement; **(H)** Multiple abnormally enhanced nodules were observed in both hemispheres; **(I)** The cerebellar hemispheres displaying multiple abnormally enhanced nodules, with diffuse thickening and enhancement of the cerebellar meninges.

numbness, taste and hearing abnormalities, and difficulties with swallowing and articulation (3). Progressive cerebral dysfunction: this may result from increased intracranial pressure and hydrocephalus (4). Urinary and bowel dysfunction: these symptoms arise from spinal membrane invasion (16). In this study, there were 22 cases of cerebral parenchymal and meningeal stimulation, 14 cases of cerebral neuropathy, one case of urinary and bowel incontinence caused by meningeal invasion, and 22 cases of intracranial hypertension. Early diagnosis of LM is difficult because of the lack of specificity of clinical manifestations; consequently, LM is prone to misdiagnosis or missed diagnosis. Cranial MRI is essential for the diagnosis of LM, especially enhanced MRI, which has a specificity of 77% and a sensitivity of 76% in patients with LM harboring solid tumors (17). Typical cranial MRI enhancement may show enhancement of the soft meninges and ventricular meninges; plaques, nodules, or masses in the subarachnoid or intraventricular spaces; enhancement or thickening of the cranial (spinal) nerves; ventricular dilatation; and hydrocephalus (18, 19). Owing to the enhanced contrast of pia meningeal MRI caused by external stimulation, MRI is recommended before performing a lumbar

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TABLE 2 Treatment of patients (N=31).

Patient	Gene mutation	Treatment before LM	Systemic treatment after LM	Number of IP	Response	iPFS (m)	iOS (m)
1	EGFR21 L858R	Gefitinib,Endostar,Osimertinib,BEV +Pemetrexed+Platinum	IP+Anlotinib	4	Improved	5	8
2	EGFR 19Del	Pemetrexed+Platinum,Gefitinib, Osimertinib, BEV,SBRT	IP+Osimertinib	6	Improved	2	2
3	Wild-type (LM was found at initial diagnosis)		IP+Pemetrexed+Platinum	2	Worsened	1	1
4	EGFR21 L858R	Osimertinib	IP+Osimertinib+SBRT	2	Worsened	4	5
5	KRAS+	Pemetrexed+Platinum+BEV, Camrelizumab+Docetaxel +Anlotinib, SBRT	IP+BEV, Anlotinib	6	Improved	6	8
6	EGFR21 L858R	Aumolertinib	IP+Aumolertinib+BEV	3	Improved	7	7
7	EGFR T790M	Gefitinib,Osimertinib,	IP+Osimertinib +BEV	26	Improved	35.2+	35.2 +
8	EGFR21 L858R	Osimertinib	IP+Osimertinib	5	Worsened	2	3
9	EGFR 19Del	Aumolertinib,Pemetrexed+Platinum +BEV,Etoposide+Platinum+Anlotinib	IP+Irinotecan+Sintilimab	3	Worsened	2	2
10	EGFR 20ins	Pemetrexed+Platinum+Sintilimab	IP+Furmonertinib+BEV	10	Improved	14.6+	14.6 +
11	EGFR21 L858R	Aumolertinib+BEV	IP+Aumolertinib +Icotinib+BEV	4	Improved	14	21+
12	EGFR 20ins	Furmonertinib, Pemetrexed+Platinum +SBRT,TAK788	IP+WBRT,Anlotinib	3	Improved	21	25
13	EGFR20ins	Pemetrexed+Platinum+BEV	IP+BEV+Osimertinib +VP shunt	14	Improved	10	12
14	EGFR 19Del	Gefitinib	IP+Osimertinib+BEV	2	Improved	6	8
15	EGFR21 L858R	Icotinib+BEV,SBRT	IP+Aumolertinib	2	Improved	6	8
16	EGFR21 L858R (LM was found at initial diagnosis)		IP+Osimertinib+BEV	6	Improved	18+	18+
17	EGFR21 L858R (LM was found at initial diagnosis)		IP+Osimertinib+BEV	4	Improved	14	16
18	Wild-type	Pemetrexed+Platinum+Camrelizumab, SBRT+Docetaxel,Anlotinib	IP+Pemetrexed+Platinum	4	Improved	8.7	10
19	EGFR21 L858R (LM was found at initial diagnosis)		IP+Furmonertinib+BEV	8	Improved	20.2+	20.2 +
20	EGFR 19Del	Gefitinib, Osimertinib	IP+Osimertinib	5	Improved	8.6	12.2
21	ROSI (LM was found at initial diagnosis)		Crizotinib+BEV, IP +Pemetrexed+Platinum+BEV	3	Improved	25	28
22	EGFR21 L858R	Gefitinib	IP+BEV +OsimertinibPemetrexed +Platinum+Aumolertinib	9	Improved	6.3	11.3
23	EGFR21 L858R	Gefitinib,Furmonertinib,SBRT	IP+Furmonertinib	4	Improved	8.2	8.2
24	EGFR21 L858R	Gefitinib	IP+Osimertinib	6	Improved	5.1	6.1
25	EGFR 19Del	Icotinib,Aumolertinib, SBRT	IP+Aumolertinib+BEV	2	Improved	17	23
26	EGFR 19Del (LM was found at initial diagnosis)		IP+Osimertinib+BEV	3	Improved	9	11
27	EGFR21 L858R	Gefitinib,Osimertinib,SBRT	IP+Osimertinib+BEV	14	Improved	27	29

(Continued)

TABLE 2 Continued

Patient	Gene mutation	Treatment before LM	Systemic treatment after LM	Number of IP	Response	iPFS (m)	iOS (m)
28	EGFR21 L858R	Gefitinib	IP+Osimertinib+BEV	2	Improved	14.2+	14.2 +
29	EGFR 19Del	Gefitinib	IP+Osimertinib+BEV	9	Improved	13	13.6 +
30	Wild-type	Docetaxel+Platinum+BEV	IP+Pemetrexed+Platinum +Sintilimab,SBRT	4	Improved	26	28
31	EGFR 20ins	Osimertinib	IP+Osimertinib+BEV	5	Improved	14.2+	14.2 +

BEV, bevacizumab; + means the patient is still alive.

puncture. CSF cytology is the gold standard for the diagnosis of LM, but its sensitivity is lower than that of MRI, with malignant cells detected in only 50-67% of patients. Nevertheless, the sensitivity can be increased to 80-90% after 2-3 consecutive CSF examinations (20, 21); 90% of patients with LM exhibit abnormal levels of CSF cells and protein expression (22). In this study, cancer cells were detected in the initial lumbar puncture of all 31 patients, and elevated levels of CSF protein were observed in 21 patients (67.74%). Cell-free DNA is an emerging diagnostic technique with higher sensitivity than CSF cytology and MRI (23, 24), providing valuable genetic information. This is very important for early diagnosis, treatment guidance, and the evaluation of therapeutic efficacy and tumor burden.

Treatment of LM aims to improve neurological symptoms and prolong OS, taking into account the patient's histology, molecular typing, clinical presentation, MRI, neurological function, and prognosis. Radiotherapy is the primary treatment for LM, including WBRT and SBRT. WBRT is commonly used in patients with extensive nodal or linear meningeal metastases and is considered a palliative treatment for symptomatic relief. However, WBRT may not provide a significant survival benefit and can lead to cognitive decline (25, 26). SBRT may be considered for focal symptomatic disorders, such as cauda equina syndrome and cranial neuropathy (27). Our study also showed that radiotherapy had no significant influence on OS. VP shunt is an effective treatment for hydrocephalus and intracranial hypertension. A study of 31 patients with leptomeningeal metastasis-related hydrocephalus showed that VP shunt rapidly improved symptoms in 90.3% of patients, with a median OS of 7.7 months after the onset of LM (28). Another study with larger data (70 patients) found that VP shunt resulted in symptomatic improvement in 50% of patients, with complete resolution of symptoms in 34% of patients; however, VP shunt had many adverse effects, including infection in eight patients, shunt malfunction in eight patients, and the need for shunt repair in 17 patients, with a median OS after VP of 4.1 months (29). In this study, one patient underwent a VP shunt owing to refractory intracranial hypertension and experienced rapid improvement of craniocerebral symptoms; however, this patient subsequently developed malignant pleural and abdominal effusions leading to death after 1 month. Systemic chemotherapy combined with antivascular or immunotherapeutic agents is the primary treatment option for NSCLC patients with negative driver gene mutation and LM. However, the presence of the BBB hinders most chemotherapeutic agents from penetrating the pia mater, thereby limiting their therapeutic efficacy; therefore, a combination therapy approach is required. In this study, there were three patients with negative driver gene mutation, of which one received intrathecal pemetrexed injection in conjunction with systemic chemotherapy, immunotherapy, and SBRT. This comprehensive treatment strategy resulted in an impressive iPFS of 26 months.

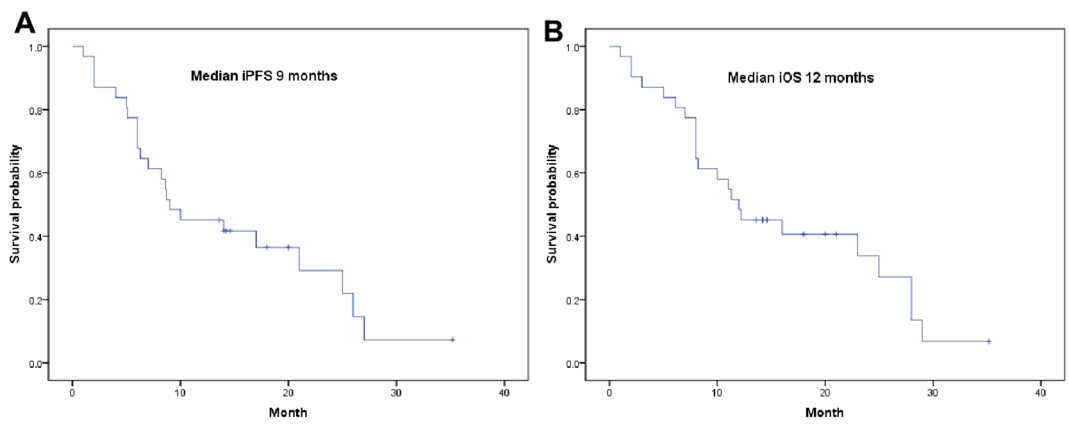

FIGURE 2
Survival curves for patients. **(A)** Kaplan-Meier curve of intracranial iPFS; **(B)** Kaplan-Meier curve of intracranial iOS.

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TABLE 3 Prognostic factor analysis of patients (N=31).

Factor	Media iOS (m)	Univariate *P* value	Multivariate *P* value
Age		0.756	
<60	11.3		
≥60	12.2		
Sex		0.594	
Male	11.3		
Female	12.2		
ECOG score		0.001	0.015
0-1	14.6		
≥2	6.1		
Smoking		0.223	
Yes	8.7		
No	12		
CSF pressure		0.976	
High	11.3		
normal	12.2		
High protein in CSF		0.616	
Yes	11		
No	12		
MRI		0.653	
Negative	11		
Positive	13.6		
Brain metastases		0.660	
Yes	8.2		
No	11.3		
Extracerebral metastasis		0.779	
Yes	12		
No	14.6		
Gene mutation		0.725	
EGFR	12	Ref	
Negative	10	0.651	
KRAS	8	0.370	
ROS1	28	0.608	
IP number		0.215	
1-5	10	Ref	
6-10	11.3	0.538	
>10	29	0.093	
Combine BEV		0.001	0.002
Yes	14.2		
No	6.1		
Combine Radiotherapy		0.452	
Yes	8.2		
No	12.2		
Third-generation EGFR-TKI therapy		0.751	
Yes	12		
No	10		

IP, intrathecal chemotherapy of pemetrexed; BEV, bevacizumab.

Compared with conventional chemotherapeutic agents, third-generation EGFR-TKIs exhibit superior CSF permeability and intracranial response rates. In patients with EGFRm NSCLC and LM, osimertinib shows superior efficacy compared to first- and second-generation EGFR-TKIs, significantly improving PFS and OS (30, 31), regardless of the presence of T790M mutations in the CSF. A retrospective study involving 304 patients with EGFR-mutated NSCLC showed that among the 116 patients receiving osimertinib and the 188 patients receiving first- or second-generation EGFR-TKIs, osimertinib treatment reduced the incidence of LM by 67%,and osimertinib treatment was an independent significant indicator of reduced LM incidence (8). Aumolertinib has high BBB penetration owing to the structural introduction of cyclopropyl; in a mouse model of EGFRm NSCLC brain metastases, aumolertinib exposure in the brain was more than seven times higher than plasma exposure (32). In the phase II APOLLO study, analysis of measurable lesions in brain metastases suggested that the central nervous system (CNS) objective remission rate (ORR) and CNS disease control rates were 60.9% (95% CI: 38.5-80.3) and 91.3% (95% CI: 72.0-98. 9), respectively (33). In the AENEAS CNS full analysis set, the mPFS for patients treated with aumolertinib and gefitinib in the first-line was 29 months and 8.3 months, respectively (34). Furmonertinib is an irreversible third-generation EGFR-TKI whose metabolites enter the brain and persist in brain tissue for a long period (35). A prospective real-world study of furmonertinib in patients with LM from EGFRm NSCLC found a median OS of 8.43 months (95% CI: 5.48-11.39 months) following treatment with furmonertinib, with an LM objective response rate of 50.0% and a disease control rate of 92.1%, respectively (36). In this study, three patients received third-generation EGFR-TKIs prior to LM; 11, after LM; 12, both before and after LM; and five, did not receive third-generation EGFR-TKIs. The median OS for the groups using third-generation EGFR-TKIs before, after, and before and after LM, as well as for those not using any third-generation EGFR-TKIs, was 9, 14, 12, and 10 months, respectively. The relatively short OS with third-generation EGFR-TKIs before LM, which is inconsistent with previous studies, may be related to the small sample size.

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TABLE 4 Adverse events (N= 31).

Adverse event	Any Grade	Grade 1 (n)	Grade 2 (n)	Grade 3 (n)	Grade 4 (n)
leukopenia	17 (54.84%)	11	4	2	0
Nausea	10 (32.26%)	7	3	0	0
Vomiting	6 (19.35%)	4	2	0	0
Elevated ALT/AST	7 (22.58%)	6	1	0	0
Diarrhea	5 (16.13%)	3	1	1	0
Fatigue	8 (25.80%)	6	2	0	0
Rash and acnes	7 (22.58%)	5	2	0	0
Paronychia	2 (6.45%)	2	0	0	0
Stomatitis	3 (9.68%)	2	1	0	0
Decreased appetite	6 (19.35%)	4	2	0	0
Elevated γ-GT	5 (16.13%)	4	1	0	0
Pneumonia	2 (6.45%)	1	0	1	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, Gamma-glutamyl transpeptidase.

EGFR-TKIs also encounter the challenge of drug resistance, with 40% of relapses occurring after treatment with first- and/or second-generation targeted agents (37). This resistance is mainly due to the inability of standard doses of the drug to achieve effective CSF concentrations. Therefore, high-dose EGFR-TKIs have become a viable therapeutic option for patients with NSCLC and LM after failure of standard-dose EGFR-TKI treatment (38, 39). The study found that administering 160 mg of osimertinib to patients with EGFRm NSCLC and LM who had progressed after prior EGFR-TKI therapy resulted in a remission duration of 8.3 months, an ORR of 41%, a median PFS of 8.6 months, and a median OS of 11.0 months, with a manageable safety profile (40). EGFR-TKIs combined with anti-vascular drug therapy shown to improve treatment response. Professor Jiang concluded that osimertinib in combination with bevacizumab in patients with NSCLC and LM also showed sustained clinical and radiological responses at 10 months. (41). However, combination immunotherapy with EGFR-TKIs is ineffective in patients with NSCLC and EGFR-sensitive mutations, increasing the risk of treatment (42). In this study, 23 patients received third-generation EGFR-TKI therapy after LM, of whom 18 received high-dose third-generation EGFR-TKI therapy, and drug resistance was observed in 19. Further second-generation gene sequencing of lung tumors or CSF revealed a RET gene fusion in one patient, MET amplification in one patient, EGFR20 C797s mutation in one patient, TP53 mutation in three patients, EGFR amplification in one patient, and small cell transformation in one patient. One patient retained the original mutation, while the remaining individuals refused further genetic sequencing.

After patients developed LM, intrathecal pemetrexed injections were administered in combination with high-dose third-generation EGFR-TKIs, a RET inhibitor, a MET inhibitor, bevacizumab, first- and third-generation EGFR-TKIs, or intravenous chemotherapy. There is no consensus on the optimal administration frequency and concentration of intrathecal pemetrexed injection, and previous studies have primarily used 10-50 mg per administration (13, 14). Considering the necessity for patients to undergo combination therapies, pemetrexed was administered at a dosage of 20-30 mg/dose in the patients of this study. Intrathecal pemetrexed injection chemotherapy was administered 2-4 times in the first month, and 1-2 times every month thereafter. After intrathecal pemetrexed chemotherapy, 27 patients experienced significant relief from intracranial symptoms, and eight patients had cancer cells disappeared in their CSF. As a result, some patients refused intrathecal injections after symptom relief, whereas others opted for intermittent intrathecal injections because of recurrent cranial symptoms. The mean number of intrathecal injections in patients was 5.8, with a median iPFS of 9 months (95% CI:2.77-15.23) and a median iOS of 11 months (95% CI:5.94-18.06 months),which was better than the previously reported OS of 3-8.8 months (43, 44).

EGFR-TKI use is a significant prognostic indicator of good survival, while poor physical status, elevated CSF protein levels, and elevated CSF leukocyte counts suggest poor outcomes (45). In an analysis of 155 patients with LM, advanced age (>60 years) and elevated CSF albumin levels were identified as treatment-independent predictors of poor survival (46). In our study, univariate and multivariate analyses showed that the combination of bevacizumab was associated with a good survival prognosis, while ECOG ≥ 2 was a significant predictor of poor survival. As the number of intrathecal pemetrexed injections increased, the median iOS was prolonged, but there was no statistical difference. In terms of safety, most of the manifestations were grade 1-2 AEs, including nausea, vomiting, fatigue, rash and acnes, paronychia, elevated ALT/AST, and there were four cases (12.9%) of grade 3 AEs (including two cases of leukopenia, one case of diarrhea, and one case of interstitial pneumonitis), which were mainly related to high doses of the targeted drug. However, as a single-center, retrospective study with a small sample size, it had some shortcomings. In addition, the dose and frequency of pemetrexed administration were inconsistent.

In conclusion, the combination of intrathecal pemetrexed chemotherapy with systemic therapy represents a promising strategy with manageable safety for the treatment of LM in patients with NSCLC.

Author contributions

WZ: Data curation, Methodology, Writing – original draft. LW: Writing – review & editing, Conceptualization, Methodology. ZQ: Writing – review & editing, Data curation. WY: Writing – review & editing, Data curation. LL: Writing – review & editing, Data curation. HS: Writing – review & editing, Supervision. SW: Project administration, Validation, Writing – review & editing, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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