Original Study

Safety, Pharmacokinetic and Clinical Activity of Intrathecal Chemotherapy With Pemetrexed via the Ommaya Reservoir for Leptomeningeal Metastases From Lung Adenocarcinoma: A Prospective Phase I Study

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Abstract

Intrathecal pemetrexed is a potential therapeutic strategy for Leptomeningeal metastasis (LM) from lung adenocarcinoma (LUAD), but still faces many obstacles caused by repeated lumbar puncture. In this study, we administered intrathecal pemetrexed via Ommaya reservoir in refractory LUAD-LM patients. This provides the real-world evidence of the safety, pharmacokinetic and clinical activity of intrathecal pemetrexed via Ommaya reservoir in resistant LUAD-LM for the first time.

Introduction: Leptomeningeal metastasis (LM) is a highly fatal and debilitating complication of lung adenocarcinoma (LUAD) with limited therapeutic options. This study aimed to evaluate the efficacy and toxicities of intrathecal chemotherapy (IC) with pemetrexed via Ommaya reservoir in LUAD with refractory LM. **Methods:** In this prospective, single-arm, phase I trial (ChiCTR2000028936), LUAD-LM patients who had progressed after at least two prior treatments were recruited. Pemetrexed from 30 mg to 50 mg was administered on Days 1 and 8 every 3 weeks via Ommaya reservoir. Serial samples of cerebrospinal fluid (CSF) and plasma were obtained for pharmacokinetic studies. The primary endpoint was progression-free survival (PFS), and the secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and therapeutic toxicities. **Results:** Twenty-three patients were enrolled and analyzed, revealing an ORR of 43.5% (95% CI, 23.2%-63.8%) and DCR of 82.6% (95% CI, 61.2%-95.0%). The median PFS and OS were 6.3 and 9.5 months, respectively. Dose-limiting toxicity was only observed in 2 patients (2/23, 8.7%), and 30 mg pemetrexed was considered as the recommended dose for IC. Pharmacokinetic analysis showed that using Ommaya reservoirs, higher pemetrexed concentrations and prolonged half-lives were achieved in

Abbreviations: LM, Leptomeningeal metastasis; LUAD, Lung adenocarcinoma; TKIs, Tyrosine kinase inhibitors; BBB, Blood brain barrier; CSF, Cerebrospinal fluid; IC, Intrathecal chemotherapy; LP, Lumbar puncture; MTD, Maximally tolerated dose; PS, Performance status; ANC, Absolute neutrophil count; WBRT, Whole-brain radiotherapy; DLT, Dose-limiting toxicity; ATDs, Accelerated titration designs; CBC, Complete blood count; MRI, Magnetic resonance imaging; CT, Computed tomography; NGS, Next-generation sequencing; PET, Positron emission tomography; RANO, Neuro-oncology working group; AEs, Adverse events; CTCAE, Common Terminology Criteria for Adverse Events; PFS, Progression-free survival; OS, Overall survival; ORR, Objective response rate; DCR, Disease control rate; HPLC, High-performance liquid chromatography; EGFR, Epidermal growth factor receptor; ALK, Anaplastic lymphoma kinase; BM, Brain metastasis; NE, Non-evaluable; SD, Stable disease; PD, Disease progression; AUC, The areas under the concentration versus time curve; ROS1, ROS proto-oncogene 1; ERBB2, Erb-B2 receptor tyrosine kinase 2; IP, Intrathecal pemetrexed; EHA, Elevation of hepatic aminotransferases.

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the CSF compared with lumbar puncture (LP). **Conclusions:** Intrathecal pemetrexed at a dose of 30 mg via Ommaya reservoirs on Days 1 and 8 every 21 days achieved promising disease control and satisfactory survival with moderate toxicities in resistant LUAD-LM, providing a feasible and effective option, especially for the patients who cannot tolerate LP.

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Introduction

Leptomeningeal metastasis (LM) is a catastrophic complication of advanced lung adenocarcinoma (LUAD) with a morbidity of 3% to 5%, and its incidence has been increasing in recent years due to the extensive appliance of molecular targeted therapy.[1,2] Related clinical symptoms, such as severe headaches, refractory nausea, and vomiting make patients anguished. Tyrosine kinase inhibitors (TKIs) are the first selection for LUAD patients with targetable mutations, but are often accompanied by intractable drug resistance.[2] Despite the continuous development of TKIs and other conventional treatments, the prognosis of LUAD-LM patients remains poor with a medium survival time of only three months.[1,3] Therefore, it is urgent to develop a new effective treatment option for LM to relieve symptoms and improve survival quality further.

The key points for treating LM are penetrating the blood brain barrier (BBB) and reaching effective concentrations in the cerebrospinal fluid (CSF). Intrathecal chemotherapy (IC) could cross the BBB to directly deliver antitumour drugs into subarachnoid space, and thus effectively clear away tumour cells attached to leptomeninges and floating in CSF.[4,5] However, IC still faces many obstacles, such as obvious complications of repeated lumbar puncture (LP) and chemotherapeutic drugs.[6]

Several studies show that Ommaya reservoir is a more convenient and safer route for leptomeningeal disease to implement IC than LP.[5,7] Pemetrexed is a multitargeting antifolate agent, and previous studies have confirmed the effectiveness of intrathecal pemetrexed against LUAD-LM.[6,8,9] Based on these results, we innovatively administered IC with pemetrexed via an Ommaya reservoir in LM patients for the first time, and gained the significant alleviation of the neurological symptoms, and a prolonged survival without notable side effects, providing a new local treatment against LM from LUAD.[10] We designed this phase I study, aimed to further explore the efficacy, safety, optimal dose and maximally tolerated dose (MTD) of intrathecal pemetrexed via the Ommaya reservoir in LUAD patients with refractory LM.

Methods

Study Design and Participants

Given the limited overall survival of LM patients, this study was a prospective, single-institution, single-arm, phase I study with a historical control. Eligibility criteria included: (1) patients aged 18 to 75 years; (2) patients diagnosed with recurrent or progressive LM from LUAD by pathology and positive CSF cytology; (3) patients who had failed at least two prior treatments; (4) performance status (PS) score less than or equal to 3 points; (5) white blood cell count $\geq 3.5 \times 10^9$/L, absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ g/dL and platelet count $\geq 100 \times 10^9$/L; and (6) patients with no obvious bleeding symptoms, haemorrhagic tendency, severe hepatic, cardiac, and renal dysfunction.

The exclusion criteria were as follows: (1) patients with squamous or small-cell lung cancer; (2) patients who were allergic to pemetrexed or had contraindications to pemetrexed; and (3) patients who received systemic treatment, including systemic chemotherapy, intrathecal chemotherapy, and whole-brain radiotherapy (WBRT) within 2 weeks. If patients were treated with TKIs for more than 2 weeks, they could keep the drug but could not switch to other TKIs in the course of the clinical trial; (4) patients with uncontrollable epilepsy; (5) patients with a history of other tumors at the same time; and (6) other reasons that were not suitable for this study.

This study was registered in chictr.org.cn (ChiCTR2000028936), and was approved by the Nanjing Drum Tower Hospital Medical Ethics Committee. Written informed consent was obtained from all the patients. All procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki.

Treatment Regimen

All patients received intraventricular Ommaya reservoir (Medtronic Inc., Goleta, USA) implant surgery at the Department of Neurosurgery, Nanjing Drum Tower Hospital (Nanjing, China). The specific procedure of IC was as follows: (1) the partial scalp was adequately disinfected, and a 24G scalp vein needle (Kindly Medical Instruments Co., Ltd., Shanghai, China) was inserted into the Ommaya reservoir; (2) 2 to 5 mL of CSF (1 mL/min) was extracted based on pressure; (3) 5 mg of dexamethasone (0.5 mL/min) and pemetrexed (Hausen, Co., Ltd., Jiangsu, China) dissolved in 30 mg/mL (0.5 mL/min) were sequentially injected. The folic acid (400 μg daily until 21 days after the last IC) and intramuscular vitamin B12 (1000 μg before each cycle of IC) were given to reduce the adverse effects. Preventative sodium valproate (800 mg) was intravenously administered after IC in patients with a history of epilepsy.

Regarding the optimal dose and schedules of IC, no consensus has yet been reached. Most intrathecally administered drugs have no rapid active transport from the CSF space to the blood, and their elimination by metabolic inactivation in the CSF is basically negligible. Thus, the dosage for IC should be adjusted based on CSF volume and drug concentrations instead of body surface area.[11] As previously described, the total CSF volume (ventricular and subarachnoid) in middle adulthood (40-55 years) was approxi-

mately 250 mL and basically stable among adults.[12] In addition, the median 50% inhibitory concentration (IC50) of pemetrexed was approximately 114 μg/mL,[6] and the peak plasma concentration of intravenous pemetrexed at the recommended dose of 500 mg/m^2 ranged from 100 to 200 μg/mL.[13] Therefore, the initial dose of intrathecal pemetrexed was set at 30 mg, escalated to 40 mg, and then 50 mg. Dose-limiting toxicity (DLT) included grade 3 neurological toxicities and other types of grade 4 toxicities. MTD was defined as the highest dose level of pemetrexed at which no more than 33% of patients experienced DLTs.[14]

The modified accelerated titration designs (ATDs) have been applied in dose escalation to ensure that more patients try higher and perhaps more efficient doses.[14] Only one patient was included per dose level until 1 patient experienced a DLT or 2 patients experienced grade 2 toxic effects during any course of treatments. At that time, 2 additional patients were accrued at the dose, and 3 to 6 patients were treated in each subsequent cohort. For intra-patient dose modification, there was no within-patient dose escalation. If the toxicity was dose limiting in the previous course, the dose would be reduced by one or two levels according to the specific clinical situation.

In the rat LP model, pemetrexed was intrathecally administered on a schedule of twice a week for 2 weeks through an indwelling subarachnoid catheter.[8] In previous studies, the predominant pattern of intrathecal pemetrexed was twice a week, but varied widely in maintenance therapy.[6,15,16] Due to the so-called "reservoir" effect of the brain and CSF, pemetrexed after intraventricular administration showed a prolonged half-life in comparison with intravenous infusion.[11] Taking these into consideration, pemetrexed was implemented on Days 1 and 8 every 3 weeks via the Ommaya reservoir to sustain active levels of drugs and meanwhile produce satisfactory tolerability.

Evaluation and Follow-up

Before treatment, all included patients received neurological examination, complete blood count (CBC), serum chemistries, coagulation indices, tumour markers of blood, cytology, and tumor markers of CSF, electrocardiogram, brain and spinal magnetic resonance imaging (MRI), chest and abdomen computed tomography (CT) scan, and bone scan. The above blood and CSF tests were acquired every cycle of treatment. Imaging examinations were performed every 2 months or in the case of suspected clinical progression until death. Standard next-generation sequencing (NGS) of CSF and blood, positron emission tomography (PET)/CT scan and biopsy were recommended if clinically needed during the treatment and follow-up. In addition, LM-related neurological symptoms, PS score, neuro-oncology working group (RANO) score and headache score were assessed and recorded in detail before each IC. Adverse events (AEs) were graded and recorded according to the Common Terminology Criteria for Adverse Events version (CTCAE, version 5.0).

The therapeutic efficacy was graded according to the RANO LM working group, which was a consensus proposal for evaluating patients treated for LM and had 3 main elements: standardized neurological examination, CSF cytology, and imaging evaluation. The response to treatment was determined by combining these assessments.[17] In patients without radiographic assessment, the isolated worse neurological examination, positive CSF cytology or worse symptoms would be defined as LM disease progression.[17]

The primary endpoint of this study was progression-free survival (PFS), which was defined as the time from the start of IC to the first identification of disease progression or death. The secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR) and therapeutic toxicities. OS was calculated from the initiation of IC to death or the last follow-up which ended on December 31, 2021.

Plasma and CSF Sample Collection

Clinical samples were serially collected before and after IC. CSF samples (>2 mL) from the LM group were obtained via an Ommaya reservoir. Concurrent peripheral blood (>2 mL) samples were collected with EDTA tubes and separated immediately after centrifugation at 5000 rpm for a minimum of 15 minutes. All samples were frozen in a timely manner under liquid nitrogen and kept at -80°C.

Concentration Detection of Pemetrexed in the CSF and Plasma

A Shimazu LC-10Ai series of high-performance liquid chromatography (HPLC) instruments (equipped with SPD-20A UV detectors, SIL-10Ai Autosampler, CTO-20AC column thermostats and CBM-20A system controllers) were used to detect the concentration of pemetrexed. A Kromasil KR100-5C18 column (250 mm × 4.6 mm, 5 μm) was used for detection at 30°C, and the flow rate was 1 mL/min. The mobile phase was sodium phosphate buffer (50 mmol/L, pH 3.35): acetylene = 84:16 (V/V). Detection wavelength was 250 nm. Perchloric acid, with a purity of >99%, was a product of Sigma–Aldrich (Sigma–Aldrich, USA). All other chemicals were of high-performance liquid chromatography grade.

Frozen human plasma and CSF samples were thawed in a water bath at room temperature. Then, 0.5 mL 14% perchloric acid was added to an equivalent plasma or CSF sample. Then, the mixture was vortex-mixed for 2 minutes and frozen centrifuged (4°C) for 5 minutes at 20,800 × g. The supernatant was injected into liquid chromatography analysis through a 0.45 μm microporous membrane.

Statistical Analysis

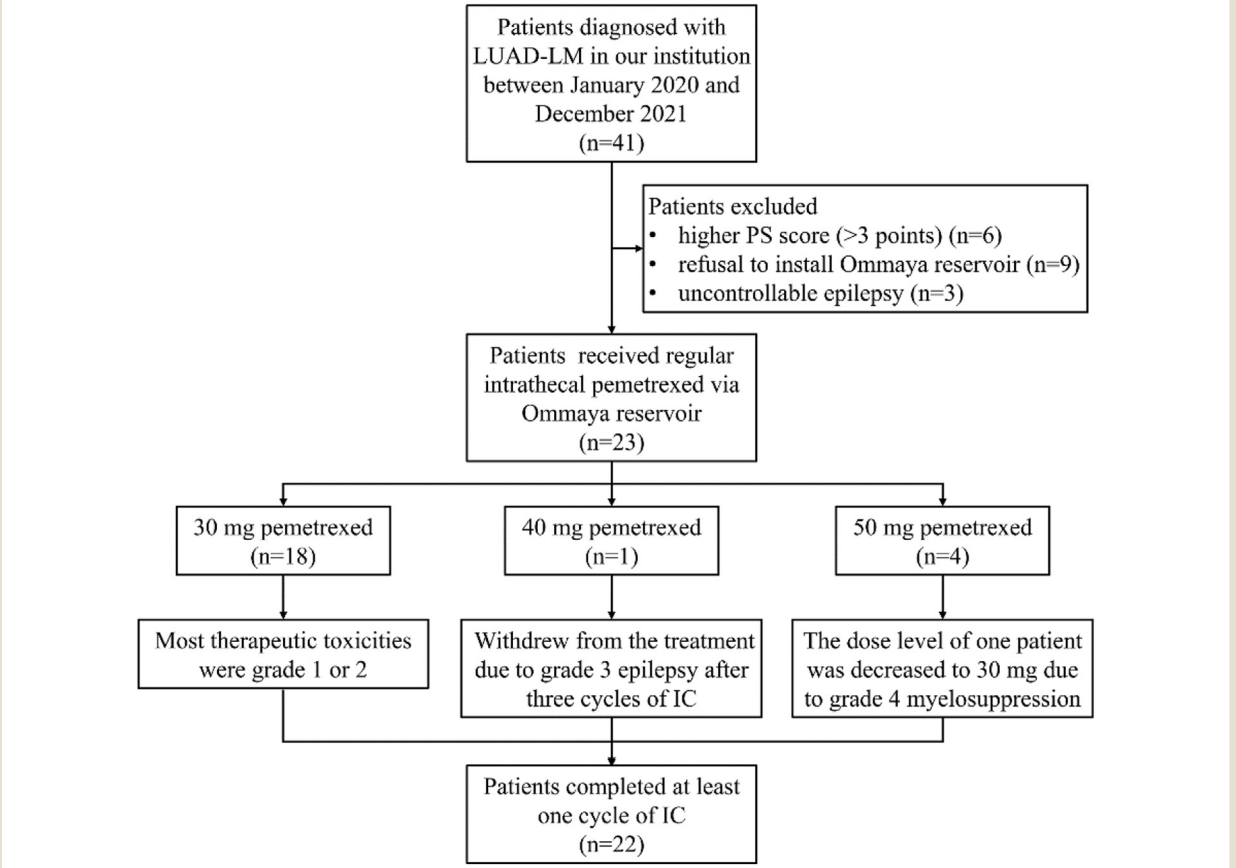
The Kaplan–Meier method was applied to plot the survival curves. ORR and DCR were calculated at a 95% confidence level. Differences in OS and PFS among multiple subgroups were analysed using a nonparametric test (Kruskal–Wallis). Comparisons between the two groups were performed with Student-Newman–Keuls q test (SNK-Q test). All statistical analyses were performed using SPSS 24.0 software (IBM, Chicago, IL, USA). A P value <.05 was considered statistically significant.

Results

Patient Characteristics

A total of 41 LUAD patients with LM were screened between January 2020 and December 2021, and 23 patients who were

Figure 1 CONSORT diagram



all hospitalized were enrolled in the study. Eighteen patients were excluded because of a higher PS score (>3 points) (n = 6), refusal to install the Ommaya reservoir (n = 9) or uncontrollable epilepsy (n = 3) (Figure 1). There were 13 females and 10 males in this cohort with a median age of 54 years, ranging from 36 to 68 years. The median times from the diagnosis of LUAD and LM to enrolment were 32 months (range, 11-91 months) and 5 months (range, 1-28 months), respectively. There were 18 (78.3%) patients diagnosed with epidermal growth factor receptor (*EGFR*) mutations and 5 (21.7%) with anaplastic lymphoma kinase (*ALK*) rearrangements. A total of 18 patients (78.3%) had LM lesions detected by brain and spinal MRI, whereas the remaining 5 (21.7%) patients had negative neuroimaging results. Brain metastasis (BM) was detected among 12 patients, 8 (66.7%) of whom received radiation treatment. All patients had varying degrees of deteriorative neurological symptoms with the failed treatment of multiline therapies, including TKIs, systemic chemotherapy, radiotherapy, and antiangiogenic therapy. The baseline characteristics of the patients are summarized in Table 1.

Treatment and Clinical Response

Detailed treatment information and clinical response are provided in Table 2. A total of 18 (78.3%) patients received 30 mg of intrathecal pemetrexed, 1 (4.3%) received 40 mg and 4 (17.4%) received 50 mg. The dose level of patient 6 was decreased from 50 mg to 30 mg due to grade 4 myelosuppression after two cycles of treatment. Twenty-two participants (95.7%) completed at least one cycle of IC, with a median of 4 (1-8) cycles. One patient (P22) received only one IC (0.5 cycle) and quit from treatment due to personal reasons. Decreases in PS score ($P = .000$), RANO score ($P = .000$) and pain score ($P = .000$) were observed in most patients after treatment. A total of 82.6% (19/23) of the patients gained improvement in neurological examination, 8.7% (2/23) of the patients were stable, and the remaining 8.7% (2/23) of the patients were rated as having worse neurological function. In the symptom assessment, 19 (19/23, 82.6%) patients showed improvement, 1 (1/23, 4.3%) had table symptoms and 3 (3/23, 13.1%) had worse symptoms. Except for one non-evaluable (NE) patient, CSF cytology of 90.9% (20/22) of patients turned negative after IC. Patient 22 was very weak with abnormal consciousness and could not undergo MRI scanning. Among the 22 patients who completed radiologic evaluation after IC, 5 (22.7%) patients improved, 16 (72.7%) patients were stable and only 1 (4.6%) patient was graded as worse.

All the patients were included in the overall response assessment. Among them, 10 patients had a response, 9 patients had stable

Table 1 The Summary of Patient Characteristics

No.	Sex	Age at LM	Tumor History (months)	Time from LM Diagnosis to Enrol-ment(months)	Baseline Mutation	Brain and Spinal MRI	Accompanying BM	WBRT	Systemic Chemotherapy	Antiangiogenic Therapy	TKIs Before LM	TKI During this Study
P1	F	57	91	28	*EGFR L858R*	Present	Y	N	Pemetrexed+Carboplatin	Bevacizumab Anlotinib	Erlotinib, Afatinib	Osimertinib
P2	M	43	62	2	*EGFR Del-19*	Present	Y	N	Pemetrexed+Cisplatin, Docetaxel	Bevacizumab	Erlotinib, Afatinib	Osimertinib
P3	F	54	23	3	*EGFR L858R*	Absent	N	N	Pemetrexed+Carboplatin	None	Erlotinib	Osimertinib
P4	F	36	50	12	*EGFR L858R*	Absent	N	N	Pemetrexed+Carboplatin	Bevacizumab	Erlotinib, AZD3759, Dacomitinib, Capmatinib	None
P5	F	53	63	3	*EGFR L858R*	Absent	N	N	Pemetrexed+Carboplatin	None	Erlotinib, Afatinib	Osimertinib
P6	M	54	16	5	*EGFR Del-19*	Present	Y	Y	None	None	Gefitinib, Osimertinib	Osimertinib
P7	M	56	36	2	*EGFR L858R*	Present	N	N	Pemetrexed+Cisplatin	None	Gefitinib, Erlotinib	Osimertinib
P8	M	54	44	5	*EGFR Del-19*	Present	Y	Y	Pemetrexed+Carboplatin	Bevacizumab	Icotinib, Erlotinib	Osimertinib
P9	M	48	14	2	*EGFR L858R*	Present	Y	Y	Pemetrexed+Cisplatin, Docetaxel+ Carboplatin	Bevacizumab	Gefitinib, Erlotinib	Osimertinib
P10	F	39	45	10	*EGFR L858R*	Present	N	N	Pemetrexed+Carboplatin	None	Icotinib, Erlotinib	Osimertinib
P11	F	58	52	10	*EGFR Del-19*	Present	N	N	None	Bevacizumab	Gefitinib	Osimertinib
P12	F	43	56	6	*EGFR Del-19*	Present	Y	Y	Pemetrexed+Cisplatin	Bevacizumab	Erlotinib	Osimertinib
P13	M	52	60	2	*EGFR Del-19*	Present	Y	Y	Docetaxel+ Carboplatin	Bevacizumab	Afatinib, Erlotinib	Osimertinib
P14	F	56	16	12	*EGFR Del-19*	Present	N	N	Pemetrexed	None	Erlotinib	Osimertinib
P15	M	59	32	4	*EGFR Del-19*	Present	N	N	Pemetrexed+Carboplatin	Bevacizumab Anlotinib	Osimertinib, Gefitinib	None
P16	F	68	27	5	*EGFR Del-19*	Absent	N	N	Pemetrexed	Anlotinib	Icotinib, Erlotinib	Almonertinib
P17	M	62	28	2	*EGFR L858R*	Absent	N	N	Pemetrexed+Nedaplatin	Anlotinib	Gefitinib, Osimertinib	Osimertinib
P18	M	59	31	3	*EGFR L858R*	Present	N	N	Pemetrexed+Carboplatin	Bevacizumab	Osimertinib	Gefitinib
P19	M	46	17	8	*ALK*	Present	Y	Y	Pemetrexed+Carboplatin, Abraxane+ Nedaplatin	None	Crizotinib, Brigatinib	Lorlatinib
P20	F	44	11	5	*ALK*	Present	Y	N	Pemetrexed+Carboplatin	Bevacizumab	Crizotinib, Alectinib	Lorlatinib
P21	F	62	13	5	*ALK*	Present	Y	Y	None	None	Crizotinib, Brigatinib	Lorlatinib
P22	F	48	61	18	*ALK*	Present	Y	Y	Pemetrexed+Carboplatin	Bevacizumab	Ceritinib, Crizotinib, Alectinib	Lorlatinib
P23	F	36	24	1	*ALK*	Present	Y	N	None	None	Crizotinib, Alectinib	Lorlatinib

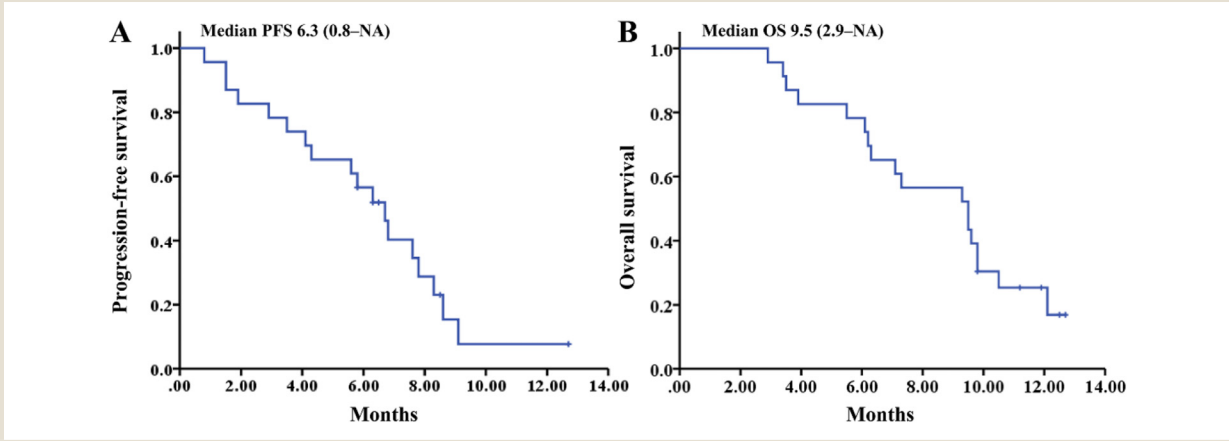
LM, leptomeningeal metastases; MRI, magnetic resonance imaging; BM, brain metastases; WBRT, whole brain radiation therapy; TKIs, tyrosine kinase inhibitors; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; F, female; M, male; N, no; Y, yes.

Table 2 Summary of Treatments and Clinical Response

No.	Dosage (mg)	Number of IC Cycles	PS		RANO Score		Headache Score		Neurological Exam	Symptom Assessment	CSF Cytology After IC	Radiologic Evaluation	Overall Response Assessment	Death	PFS (months)	OS (months)
			Before Treatments	After Treatments	Before Treatments	After Treatments	Before Treatments	After Treatments								
P1	30	4	3	1	8	2	9	1	Improved	Improved	Ne	Improved	Response	Y	6.7	12.1
P2	40	3	3	2	13	9	2	0	Improved	Improved	Ne	Stable	SD	Y	3.5	3.9
P3	50	7	3	1	12	4	6	0	Improved	Improved	Ne	Stable	Response	N	12.7	12.7
P4	50	5	3	2	14	9	4	3	Improved	Improved	Ne	Stable	Response	Y	8.3	9.5
P5	50	5	3	2	9	4	9	2	Improved	Improved	Ne	Stable	Response	N	6.5	11.9
P6	50/30	4	3	2	10	8	3	0	Improved	Improved	Ne	Stable	SD	N	6.3	9.8
P7	30	2	3	1	6	2	8	5	Improved	Improved	Ne	Stable	SD	Y	7.8	9.5
P8	30	2	3	1	6	0	9	0	Improved	Improved	Ne	Stable	SD	Y	2.9	5.5
P9	30	1.5	3	3	3	3	5	4	Stable	Stable	Po	Worse	PD	Y	1.5	6.1
P10	30	5	3	2	2	0	8	1	Improved	Improved	Ne	Improved	Response	Y	9.1	9.8
P11	30	7	3	1	3	2	9	2	Improved	Improved	Ne	Improved	Response	Y	7.6	9.8
P12	30	3	3	1	5	3	8	2	Improved	Improved	Ne	Stable	SD	Y	5.6	7.3
P13	30	4	3	1	6	4	7	1	Improved	Improved	Ne	Stable	SD	Y	5.8	10.5
P14	30	3	3	2	10	9	4	2	Improved	Improved	Ne	Stable	SD	Y	4.3	6.2
P15	30	1	3	4	2	3	10	8	Worse	Worse	Po	Stable	PD	Y	1.5	3.4
P16	30	4	3	1	7	3	4	2	Improved	Improved	Ne	Stable	Response	N	5.8	11.2
P17	30	4	3	3	12	5	4	0	Improved	Improved	Ne	Stable	Response	Y	6.8	7.1
P18	30	1	3	3	12	11	0	3	Stable	Worse	Ne	Stable	PD	Y	1.9	3.5
P19	30	8	3	2	19	1	7	1	Improved	Improved	Ne	Improved	Response	Y	8.6	9.6
P20	30	3	3	1	10	1	8	0	Improved	Improved	Ne	Stable	SD	Y	4.1	6.3
P21	30	2	3	2	14	10	3	0	Improved	Improved	Ne	Improved	Response	Y	6.3	9.3
P22	30	0.5	3	4	16	18	7	7	Worse	Worse	NE	NE	PD	Y	0.8	2.9
P23	30	4	3	1	12	2	6	0	Improved	Improved	Ne	Stable	SD	N	8.5	12.5

IC, intrathecal chemotherapy; PS, performance status; RANO, neuro-oncology working group; CSF, cerebrospinal fluid; PFS, progression-free survival; OS, overall survival; Ne, negative; Po, positive; Y, yes; N, no; SD, stable disease; PD, progressive disease; NE, non-evaluable.

Figure 2 Kaplan-Meier estimation of the PFS (A) and OS (B) of LUAD-LM patients treated with intrathecal pemetrexed via the Ommaya reservoirs



disease (SD) and 4 patients had disease progression (PD), revealing an ORR of 43.5% (95% CI, 23.2%-63.8%) and DCR of 82.6% (95% CI, 61.2%-95.0%).

Follow-up and Survival

Of the enrolled patients, 18 patients died after the treatment of this study, and 5 patients were alive until the last follow-up. The PFS and OS of the cohort from the start of IC were analyzed based on Kaplan-Meier estimation (Figure 2). The median PFS and OS were 6.3 months (range, 0.8 months-upper limit not applicable), and 9.5 months (range, 2.9 months-upper limit not applicable), respectively.

Antiangiogenic therapy history was associated with PFS ($P = .032$). Sex, age, tumor history, time from LM diagnosis to enrolment, baseline mutation, brain and spinal MRI, accompanying BM, WBRT, systemic chemotherapy and TKIs during this study failed to predict PFS and OS (Supplementary Table S1).

Evaluation of Toxicities

Table 3 summarizes the adverse events observed in the cohort. Myelosuppression (Leucopenia), elevation of transaminase and anaemia were the 3 main adverse events, with incidences of 34.8% (8/23), 26.1% (6/23) and 17.4% (4/23), respectively. Epilepsy was observed in 2 (8.7%) patients, and only 1 (4.3%) patient had localized scalp infection associated with reservoir implantation. Most therapeutic toxicities were grade 1 or 2. DLT was observed in 2 patients (2/23, 8.7%) with 1 myelosuppression (grade 4) and 1 epilepsy (grade 3). These 2 cases had received at least 2 prior anti-tumor treatments, which might cause potential cumulative or overlapping toxicities. All side effects were relieved spontaneously or after symptomatic treatments. No fatal adverse events were observed, and no related toxicity was observed in the follow-up.

Recommended Dosage and MTD

During the accelerated phase, 1 patient (P2) received 40 mg of intrathecal pemetrexed, and no toxicities were observed during cycle 1. Next, we moved to the dose of 50 mg, but 2 moderate toxicities were observed in P3 and P4. Then, two more cases were enrolled, and DLT was noted on P6, whose therapeutic dose was reduced in subsequent treatments. The initial dose of 50 mg did not show superiority in PFS ($P = .050$) and OS ($P = .064$) compared with 30 mg, and was conducive to the high incidence of AE. Thus, for purposes of exposing as few patients as possible to potentially intolerable doses, no more cases were enrolled at this level, and MTD was preliminarily identified as 50 mg.

In addition, P2 experienced a DLT (grade 3 epilepsy) after three cycles of IC at the 40 mg level and withdrew from the treatment. It is not clear whether the epilepsy was due to the progression of LM or IC. Due to patients' physical or mental reasons, we failed to recruit other patients into this dose level; thus, more cases are needed to verify the safety of 40 mg. Among 18 patients exposed at 30 mg level, only one patient presented grade 3 adverse events. Based on the above, 30 mg pemetrexed was considered the recommended dose for IC.

Pemetrexed Concentration in Plasma and CSF Samples

The pemetrexed level in the lumbar space can reflect its distribution throughout the neuraxis, which is crucial for leptomeningeal cancer. However, for ethical reasons, we were unable to perform LP to determine the lumbar pemetrexed concentration in these patients who already had Ommaya capsule, in order to avoid the complications of repeated LP. Intrathecal drug delivery via Ommaya is more uniform in the CSF compared to LP because it is more consistent with the circulatory kinetics of the CSF. Moreover, it is safer and more convenient to obtain the CSF via Ommaya.[5,7] Therefore, we've examined the ventricle's dynamic drug level, in an effort to somewhat reflect the drug's intracranial concentration and explore the pharmacokinetic parameters.

Data on the mean concentrations in CSF and plasma at each time point are shown in Figure 3. Eight patients accepted the serial CSF samples collection, and 62.5% (5/8) of them reached the peak concentration at 2 to 4 hours, which was significantly different between the patients with a maximum concentration of

Table 3 The Treatment-related AEs Observed in the Whole Cohort

No.	Dosage (mg)	Toxicity	Grade	Time Point
P2	40	Myelosuppression (Leucopenia)	2	After C2
		Anaemia	2	After C2
		Epilepsy	3	After C3
P3	50	Localized scalp infection associated with reservoir	2	Before C1
		Anaemia	1	After C1
		Myelosuppression (Leucopenia)	2	After C2
		Elevation of ALT and AST	3	After C3
P4	50	Myelosuppression (Leucopenia)	3	After C4
		Anaemia	2	After C2
		Epilepsy	2	After C5
P5	50	Myelosuppression (Leucopenia)	3	After C3
		Anaemia	2	After C3
P6	50/30	Myelosuppression (Leucopenia)	4	After C2
		Elevation of AST	1	After C1
P9	30	Elevation of ALT	1	After C2
P10	30	Myelosuppression (Leucopenia)	1	After C1
		Elevation of ALT and AST	1	After C4
P11	30	Myelosuppression (Leucopenia)	3	After C5
P19	30	Elevation of ALT	1	After C3
P21	30	Myelosuppression (Leucopenia)	1	After C1
		Elevation of AST	1	After C1

ALT, alanine transaminase; AST, aspartate transaminase.

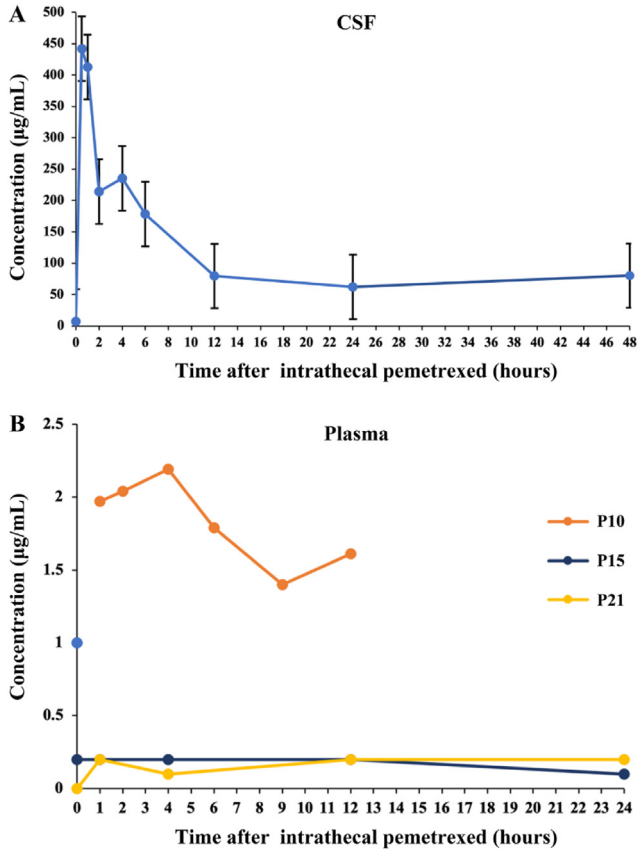
2417.53 μg/mL. At 24 hours after IC, pemetrexed still maintained effective concentration levels in CSF, with an average of 93.44 μg/mL. In the mean concentration-time curve, a minor rise was observed at 6 hours, displaying a biphasic elimination pattern of pemetrexed. Among the patients above, 5 patients (P15, P17, P19, P20, and P21) with adequate CSF samples at each time node were used for further pharmacokinetic analysis. The half-lives of pemetrexed in CSF were 1.53 h, 1.50 h, 1.70 h, 5.65 h, and 0.25 h respectively. The terminal half-lives for the distribution elimination phase were 12.99 h, 31.20 h, 15.64 h, 8.95 h, and 8.97 h. The predicted maximal concentrations (Cmax) were 262.1, 195.4, 532.4, 1211.7, and 2417.5 μg/mL. The areas under the concentration versus time curve (AUC) of pemetrexed were 3263.36, 4848.83, 3259.30, 12860.88, and 9707.24 mg/L*h, respectively. In addition, a series of plasma samples from 3 patients (P10, P15, and P21) were also collected, and pemetrexed showed extremely low concentrations in plasma, which was consistent with previous studies.[11]

Discussion

IC is an efficient local treatment for LM, and intra-lumbar injection is the most commonly used route. However, repeated LP has some deficiencies in common that significantly limit the clinical practice of IC[6,11]: (1) local pain; (2) special operating position that is difficult to coordinate for patients with terminal cancer; (3) risk of infection and hemorrhage; (4) risk of unsuccessful LP; (5) risk of chemical arachnoiditis or neurotoxicity; and (6) inadequate delivery and uneven distribution of the drug. To overcome the deficiencies mentioned above, we applied Ommaya reservoirs to the treatment of LUAD-LM. The Ommaya capsule, a reservoir in the form of a dome with a diameter of 3.45 cm, is the preferred choice for IC due to many practical and technological benefits.[5,7,10] To compare the safety and efficacy of Ommaya capsule and LP in intrathecal pemetrexed for LUAD-LM, we reviewed prior studies related to IC administration of pemetrexed by LP. The findings, which included 2 prospective clinical studies and 2 retrospective studies, are presented in Table 4.[6,9,15,16]

Among them, Pan et al. demonstrated that intralumbar pemetrexed at a dose of 10 mg was efficient and safe for LUAD-LM, revealing an ORR of 31%, DCR of 54%, median PFS of 2.5 months and median OS of 3.8 months.[6] Fan et al. found that 50 mg intralumbar pemetrexed was more effective, with a median OS of 9.0 months.[9] The substantial variation in suggested doses between these 2 trials may be attributable to disparities in patient cohorts or study design. Two retrospective investigations found that pemetrexed intrathecal dosages of 10 mg to 40 mg resulted in an OS of 3.5 months and a DCR of 82.6% to 85.3%, despite the fact that treatment regimens were not uniform between patients in these trials.[15-16] It is also worth noting that in the above 2 retrospective studies, patients were treated with IC in parallel with systemic therapy changes in most of the patients, which would largely affect the assessment of the efficacy of intrathecal chemotherapy. Comparing these findings with ours, PFS and OS were further improved by intraventricular pemetrexed via Ommaya reservoirs.

Figure 3 The CSF and plasma concentration–time curves



In addition to its better efficacy, Ommaya capsule also shows advantages in terms of IC safety. The major serious adverse effects of pemetrexed IC in previous studies include myelosuppression, radiculitis, elevation of hepatic aminotransferases, and headache. Severe AEs were encountered in 30.4% to 31% of the cases.[6,9,15,16] The incidence of severe AEs was significantly lower in this study compared to previous studies, suggesting that Ommaya reservoirs might be a safer route to implement intrathecal pemetrexed.

Up to now, there are no studies to confirm the specific mechanism of toxicity occurrence associated with intrathecal pemetrexed. Drug toxicity is closely related to the mode of administration, dose, duration of action and concomitant use of other drugs. Therefore, we speculate that these adverse effects may be related to 2 reasons: on the one hand, although the intrathecal pemetrexed is administered in small amounts, the half-life of the drug in the CSF is prolonged compared to that in the peripheral blood due to the "reservoir" effect, and thus may have a sustained impairment of bone marrow function and hepatic function. On the other hand, patients with LUAD-LM have received multiple lines of antitumor therapy prior to IC, which may cause potential cumulative bone marrow and liver damage. Moreover, some patients combine other systemic therapies with IC, which may result in a superimposed effect of drug toxicity. Although some adverse effects exist, most of them are mild and may resolve on their own or with symptomatic treatment. The incidence of adverse reactions can be reduced to some extent by choosing the appropriate dose of the drug and by the use of adjuvant treatments, such as folic acid and vitamin B12, among others.

In terms of pemetrexed concentration, the peak CSF concentration of intravenous pemetrexed was 182.5 ng/mL at a regular dose of 500 mg/m^2, and 813.6 ng/mL at a higher dose of 1050 mg/m.[2,18] The CSF concentrations distributed from the plasma were only 5% within 1 to 4 hours. Thus, limited antitumour activity against LM might be due to low CSF concentrations, not drug resistance.[18,19] Consistent with this presumption, our results showed that in the 18 patients who had a history of intravenous pemetrexed, the DCR and ORR were 77.8% (95% CI, 52.4%-93.6%) and 44.4% (95% CI, 21.4%-67.4%), respectively. In addition, the CSF drug concentration of intralumbar pemetrexed was ≤19.2 ng/mL after the fourth IP, which was also obviously lower than that of intraventricularly administered pemetrexed via Ommaya reservoirs. Our pharmacokinetic results and earlier research showed that higher drug concentrations could be obtained using Ommaya reservoirs in the CSF and at relatively higher levels in the leptomeninges but not in the plasma.[11] This partially explains the high efficiency and low toxicity

Table 4 Summary of Previous Studies of Intrathecal Pemetrexed by LP for NSCLC-LM

Name	Pan et al. [6]	Fan et al. [9]	Miao et al. [15]	Geng et al. [16]
Type	Phase I	Phase I/II	Retrospective study	Retrospective study
Number	13	26	23	34
Population	EGFR-mutant (10) ALK-mutant (1) Not detected (2)	EGFR-mutant (26)	EGFR-mutant (16) ALK-mutant (2) ROS1-mutant (1) ERBB2-mutant (1) Not detected (3)	EGFR-mutant (27) ALK-mutant (4) Not detected (3)
Dosage	10 mg to 20 mg	15 mg to 80 mg	10mg	15mg to 40mg
Recommended dose	10mg	50mg	-	-
Drug Delivery mode	Twice IP per week for 4 times in 2 weeks, followed by consolidation therapy once per week for up to 4 times in 4 weeks	IP twice per week for one week (day 1 and day 5) followed by once every 3 weeks until PD was observed, then once every 4 weeks as maintenance therapy	Once a week until: two consecutive negative CSF cytology results were achieved, the side effects were not tolerated, or the disease progressed	IP twice per week, 3 to 4 days for a one-time administration, and 2 to 4 times for successive administrations every month
PFS (months)	2.5 (0.3-12.5)	-	-	-
OS (months)	3.8 (0.3-14)	9.0 (6.6-11.4)	-	3.5
ORR	31%	-	34.8%	76%
DCR	54%	84.6%	82.6%	85.3%
Severe adverse events	Two with grade 4-5 hematological toxicities, and two with grade 4 radiculitis, and one with grade 4 EHA	Two patients experienced grade 4 myelosuppression. Two patients experienced grade 3 limb pain, and one patient had grade 3 headache	Grade 3 or higher AEs occurred in seven patients, including six cases of myelosuppression and one case of headache	No grade 3 or grade 4 AEs occurred
Other important results	After the fourth IP, 8 patients displayed a CSF drug concentration of $\leq$ 19.2 ng/ml. After the fifth IP, the CSF drug concentration in the 8 individuals was of $\leq$9.16 ng/ml. After the sixth IP, 6 patients had CSF drug concentration of $\leq$6.75 ng/ml	Four patients did not survive for four weeks, therefore efficacy could not be determined	On the basis of IP therapy, 19 patients were retreated with TKIs, while 10 patients received systemic chemotherapy. Thirteen patients received two or more modalities of combination therapy	Depending on the severity of their illness, 20 patients switched to anticancer medications

PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DCR, disease control rate; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, ROS proto-oncogene 1; ERBB2, Erb-B2 receptor tyrosine kinase 2; IP, intrathecal pemetrexed; PD, progressive disease; CSF, cerebrospinal fluid; EHA, elevation of hepatic aminotransferases; AEs, adverse events; TKIs, tyrosine kinase inhibitors.

of IC by the Ommaya reservoir route from a pharmacological point of view.

In addition to locally enhanced therapy, systemic antitumor treatment is also essential in the treatment of LM.[1,2,20] TKIs show reliable antitumor activity for LUAD with targetable mutations, but cannot control stubborn neurological symptoms of end-stage LM and improve the poor prognosis. As a result, it is reasonable to combine IC with TKIs against target gene-mutated LUAD-LM to relieve symptoms and improve survival further when TKIs are insufficient or fail. In this clinical trial, TKIs were kept to control extracranial lesions in the process of IC, and could have a synergistic effect with IC in the treatment of intracranial metastasis. Osimertinib and lorlatinib, third-generation TKIs, showed good antitumor effects when combined with IC. Although there was no significant difference between TKIs in our cohort, this combination therapy is still a crucial tactic to take into account according to some prior research.[15,16]

The current study has some limitations. First, the sample number was relatively small, and there was only one patient in the 40 mg dose group, the safety of which could not be adequately evaluated. Second, many patients refused to draw blood frequently due to pain from haemospasia and their weakness in the terminal stage of lung cancer. Only a limited number of serial plasma samples in the IC process were collected, thus more cases and matched samples of CSF and blood were needed.

Despite some limitations, the current study first applied intrathecal pemetrexed via the Ommaya reservoir to LUAD-LM therapy. Effective drug concentrations, reliable antitumor effect and survival benefits were achieved by this treatment. Furthermore, it was well-tolerated by these frail terminal patients who had experienced multiline treatment failures. This research still has much to explore, such as optimized treatment models and more suitable united TKIs. Moreover, based on relevant studies,[21] we are trying to apply some new antineoplastic agents to IC, such as bevacizumab and

nivolumab, to further expand the application of the Ommaya reservoir in lung cancer with LM.

Conclusions

Overall, our study demonstrated the safety and the efficacy of intrathecal pemetrexed at a dose of 30 mg via Ommaya reservoir on Days 1 and 8 every 21 days in patients with LUAD-LM who had progressed after at least 2 prior antitumor therapies, providing a feasible and effective option. A prospective multicenter clinical trial with a larger cohort is necessary to further confirm our findings.

Clinical Practice Points

- The treatment of LUAD-LM is particularly challenging and intrathecal pemetrexed is a potential therapeutic strategy for it, but still faces many obstacles caused by repeated lumbar puncture.
- We performed a prospective phase I study on 33 refractory LUAD-LM patients, aimed at assessing the safety, pharmacokinetic and clinical activity of intrathecal pemetrexed via an Ommaya reservoir for the first time.
- The results show that intrathecal pemetrexed at a dose of 30 mg via the Ommaya reservoirs on Days 1 and 8 every 21 days could achieve promising disease control and satisfactory survival with moderate toxicities in resistant LUAD-LM.
- Our findings provide a feasible and effective option of intrathecal chemotherapy in LUAD-LM, especially for the patients who cannot tolerate lumbar puncture.

Authors' contributions

HL, XQ, and **ZY**. contributed to the study design. **HL** and **SZ**. contributed to the data collection. **HL, SZ**, and **YL.** performed the statistical analyses and interpretation and drafted the manuscript. **TY, YX, CJ**. and **XL**. revised the manuscript. All authors contributed to the critical revision of the manuscript and approved its final version. Financial support and study supervision were provided by **HL, YX**, and **ZY**.

Ethical Statement

All procedures were in accordance with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all the participants included in the study.

Consent for Publication

We obtained consent to publish from all the participant.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2022.11.011.

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