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ORIGINAL ARTICLE

The efficacy of slow-rate ventriculolumbar perfusion chemotherapy for leptomeningeal carcinomatosis: a phase II study

Soojin Jang[1] · Ho-Shin Gwak[2] · Jungnam Joo[3] · Yoon-Sik Doh[4] · Sang-Hoon Shin[4] · Heon Yoo[4] · Kyu-Chang Wang[4]

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Abstract

Purpose This study aimed to evaluate the symptomatic response and side effects of ventriculolumbar perfusion (VLP) methotrexate chemotherapy with a low perfusion rate in patients with leptomeningeal metastasis.

Methods Patients in a single-arm, two-stage phase II trial based on Simon's minimax design received VLP with a reduced (15 cc/h) perfusion rate with the purpose of decreasing constitutional side effects such as nausea/vomiting, insomnia, and confusion. The primary outcome was control of increased intracranial pressure (ICP). The secondary outcome was an occurrence of side effects. The results were compared with those of a previous trial of VLP with a 20-cc/h perfusion rate.

Results Total 90 patients were enrolled. Out of 65 patients with increased ICP, 32 achieved normalized ICP after VLP chemotherapy (bias-adjusted response rate = 51%). The incidence of moderate-to-severe nausea/vomiting was reduced to 46% from 64% in the previous study, and that of sleep disturbance was increased to 13% from 9%, but both failed to reach statistical significance. The incidence of moderate-to-severe confusion was significantly reduced to 12% from 23% in the previous study ($p = 0.04$). Median overall survival was better among patients with controlled ICP than among those who remained with increased ICP (193 days vs. 94 days, $p = 0.013$).

Conclusion Compared with a higher perfusion rate, the low perfusion rate failed to provide non-inferior ICP control or improved side effects, except for confusion. The relationship between VLP perfusion rate and ICP control needs to be evaluated in future trials adjusting for bias from uncompleted protocol due to poor general condition.

Keywords Cerebrospinal fluid · Chemotherapy · Leptomeningeal metastasis · Methotrexate · Perfusion

Introduction

Leptomeningeal metastasis (LM), also known as leptomeningeal carcinomatosis, is a condition in which tumor cells disseminate into the cerebrospinal fluid (CSF) or invade the leptomeninges [7, 30]. LM is considered to be an incurable, terminal-stage disease with limited treatment options and low response rate [5]. LM occurs in 5–8% of advanced cancers, especially breast cancer (12–35%), lung cancer (10–26%), and melanoma (5–25%), and its incidence is increasing with advancements in neuroimaging diagnosis and improved patient survival due to systemic cancer control [8, 14, 25].

Therapeutic options for LM include radiotherapy, systemic chemotherapy, and intraventricular CSF (intra-CSF) chemotherapy [28]. Among these modalities, intra-CSF chemotherapy with agents such as methotrexate (MTX), cytosine arabinoside, and thiotepa delivered by repeated lumbar puncture or ventricular reservoir is widely used, but this provides only a marginal survival benefit of 4–9 months [2, 3, 23, 26]. Furthermore, the distribution of intra-CSF chemotherapy into the CSF space can be limited by CSF flow disturbance, which presents in up to 50% of patients with LM [12–14]. CSF flow disturbance leads to hydrocephalus combined with increased intracranial pressure (ICP), which can cause encephalopathy due to transependymal

✉ Ho-Shin Gwak
nsghs@ncc.re.kr

1 Department of Neurosurgery, Seoul National University College of Medicine, Seoul, Korea

2 Department of Cancer Control, Graduate School of Cancer Science and Policy, National Cancer Center, 323 Ilsan-Ro, Ilsandong-Gu, Goyang, Korea

3 Biometric Research Branch, National Heart, Lung and Blood Institute, Bethesda, USA

4 Neuro-Oncology Clinic, National Cancer Center, Goyang, Korea

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drug penetration into the brain parenchyma [13, 16, 17, 21, 29].

To overcome the limitations of intra-CSF chemotherapy, ventriculolumbar perfusion (VLP) chemotherapy has been tried since 1996 [10, 16, 27]. In VLP, drug is administered either as a bolus or continuously by an intraventricular infusion pump at a designated flow rate, and hydrostatic pressure is relieved by simultaneous lumbar drainage at an approximately equal rate. In addition to providing enforced intra-CSF drug distribution in patients with CSF flow disturbance, VLP chemotherapy has shown a similar or slightly better response rate compared with conventional intra-CSF chemotherapy.

In our previous phase I and II studies of VLP MTX chemotherapy, up to 60% of patients displayed moderate or worse (grade ≥ 2, based on the Common Terminology Criteria for Adverse Events) constitutional side effects, including nausea/vomiting, sleep disturbance, and confusion. We assumed these side effects might be related to the VLP rather than to MTX specifically because they occurred previously with bolus injections of MTX on artificial CSF infusion, and in the phase I study, they were more severe in patients with a higher perfusion rate (40 cc/h) than in patients with a lower perfusion rate (20 cc/h). Therefore, we hypothesized that a lower perfusion rate might reduce these constitutional side effects and make VLP therapy more tolerable for patients with LM.

In the current study, we applied VLP therapy at a reduced perfusion rate of 15 cc/h (VLP 15 cc/h), compared with the 20 cc/h perfusion rate in the previous phase II study (VLP 20 cc/h). The primary outcome was the rate of control of increased ICP, and the secondary outcome was the occurrence of moderate-to-severe (grade ≥ 2) side effects.

Methods

All patients provided written informed consent prior to enrollment. The protocol was reviewed and approved by the Institutional Review Board of the National Cancer Center of Korea (NCC2014-0061). The trial was registered on the government-owned official trial registration site (http://cris.nih.go.kr) before patient enrollment (KCT0000082) and was conducted according to the guidelines of the Declaration of Helsinki for biomedical research.

Eligibility criteria

Inclusion criteria were a diagnosis of LM by positive CSF cytology or definitive MRI findings [13], > 18 years of age, and at least one of the following LM-related symptoms: increased ICP (> 15 cm H_2O), altered mentality due to hydrocephalus, or cauda equina symptoms or cranial neuropathy. Exclusion criteria were CSF pathway blockage evidenced by whole-spine MRI or radioisotope cisternography; presence of space-occupying brain lesion that might cause herniation; diagnosis of hemorrhagic central nervous system metastases; ≥ grade 3 leukopenia (leukocyte count < 2,000), neutropenia (absolute neutrophil count < 1,000/mm^3), or thrombocytopenia (platelet count < 50 K); or previous history of VLP chemotherapy.

Ventriculolumbar perfusion procedures

The VLP procedures were the same as those used in our previous phase II study except for the reduced perfusion rate [16]. As illustrated in Fig. 1, a ventricular catheter was installed stereotactically or by a navigation-guided method and connected to either a Chemoport (Celsite®, ST205, B. Braun, Boulogne Cedex, France) or a V-port (INSUNG Medical Co., Ltd, Wonju, Korea) as previously described [11]. Artificial CSF premixed with MTX was perfused at 15 cc/h (0.96 mg MTX per hour) by an infusion pump with a warming kit (37.5 °C) via a designated 21-gauge hooked needle that was inserted into the ventricular port and maintained in position with a sterile closed dressing. A lumbar drainage catheter was inserted into the thecal sac at the time of VLP, and CSF drainage was achieved by hydrostatic pressure. The lumbar drainage rate was checked on an hourly basis, and the drainage set height was adjusted so that the drainage rate equaled the infusion rate.

Treatment protocol

The standard protocol of VLP MTX chemotherapy consisted of two 72 h continuous infusions performed 3 days apart, as previously described [9, 16]. We refer to these two initial consecutive infusions as "induction" VLP and consider them a complete VLP treatment. If the patients still presented LM symptoms after induction VLP, we performed a "maintenance" VLP cycle in which a 72-h VLP infusion was given every 28 days until the patient experienced progression or refused to undergo further chemotherapy. A schematic of the treatment protocol is illustrated in Fig. 2.

CSF samples were taken every morning on the days of perfusion to ensure the MTX plateau level and to check the CSF profile for possible infection. Serum MTX concentration was also checked daily, and if it was above 0.15 μM, a 30-mg leucovorin rescue was administered intravenously every 6 h.

Response evaluation

Pre-VLP ICP was defined as the highest ICP measured during the related procedures of reservoir installation, lumbar puncture, and needle insertion at the reservoir before the start of

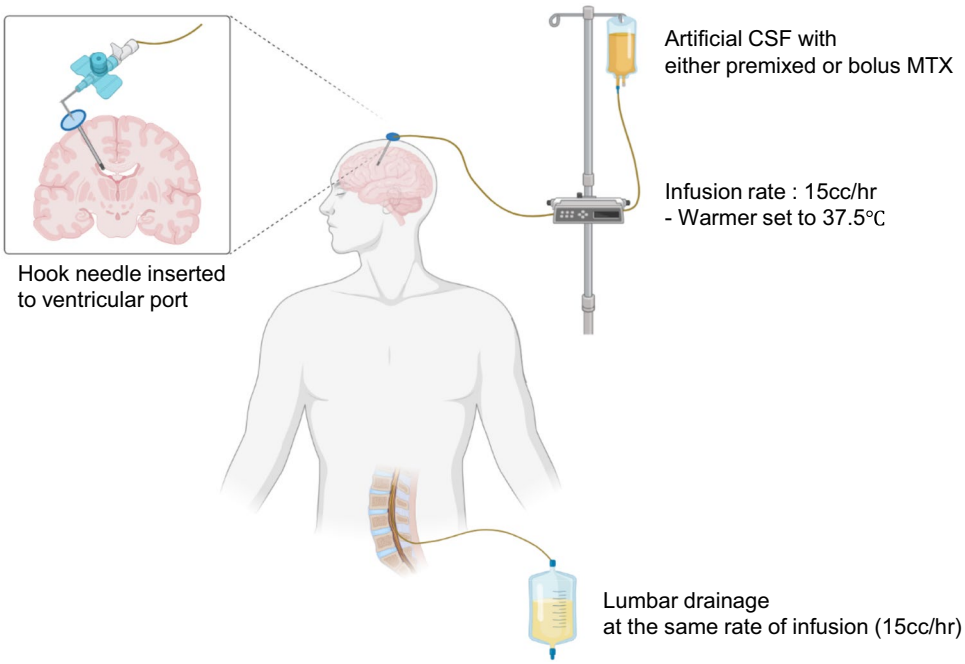

Fig. 1 Illustration of ventriculolumbar perfusion chemotherapy. Abbreviations: CSF, cerebrospinal fluid; MTX, methotrexate

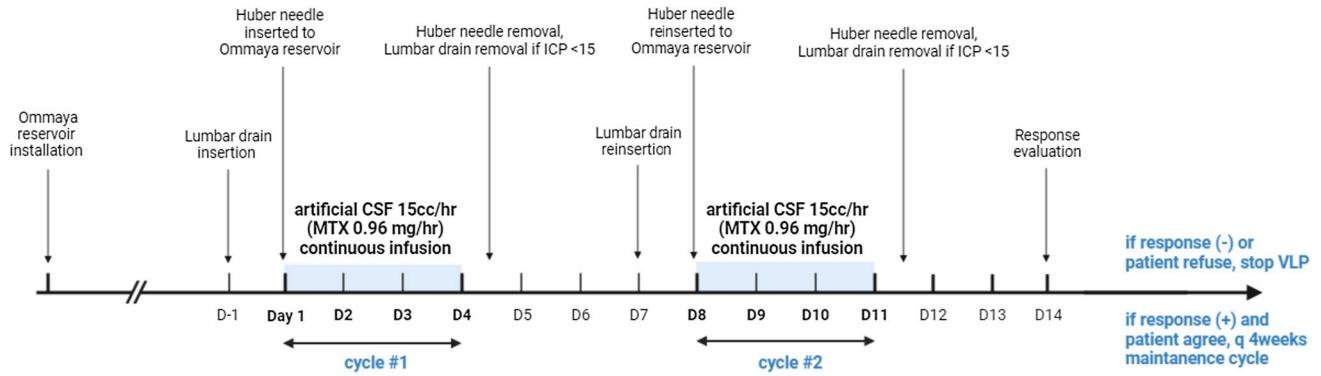

Fig. 2 Treatment schema of ventriculolumbar perfusion methotrexate chemotherapy. Abbreviations: CSF, cerebrospinal fluid; ICP, intracranial pressure; MTX, methotrexate; RI, radioisotope

VLP. If ICP was ≥ 15 cm H_2O, we considered the patients to have increased ICP. Post-VLP ICP was measured on the last day of VLP induction 6 h after the last VLP and before lumbar drainage removal (D11, Fig. 2). Normalization (< 15 cm H_2O) of increased ICP was counted as a response. Patient mentality was graded as normal, communicable but confused, or unable to communicate. For cauda equina symptoms, we defined three components (i.e., motor, sensory, and bladder/anal control) and evaluated each component as normal, incomplete function or intermittent need for intervention, or complete loss of function or definite need for intervention. The response to these symptoms was defined as improved if the grade was increased by one or more levels at the end of VLP induction (D14) or patient discharge.

Toxicity evaluation

The possible VLP side effects of nausea/vomiting, sleep disturbance, and encephalopathy (confusion) were closely monitored and recorded daily. These side effects were graded using the Common Terminology Criteria for Adverse Events (CTCAE, version 3.0) and assessed for equality to those in our previous phase II study of VLP 20 cc/h [29]. The most severe grade determined for a given side effect in a given patient during the VLP chemotherapy was used as the grade for that side effect in the patient.

Study design and statistical analysis

The study was designed as a single-arm phase II study with Simon's minimax two-stage design [27]. The primary endpoint was the rate of control of increased ICP, which was compared to that in our previous phase II trial of VLP 20 cc/h [16]. Based on a review of historical data, we considered a 50% positive response rate as a non-inferior response rate compared to that achieved with VLP 20 cc/h in the previous trial. Thus, we considered a null response rate (p_0) of 50% compared with an increased response rate (p_1) of 65%. With 20% power and a one-sided type-I error rate of 0.1, the number of patients required at stage one was 22. As the interim analysis revealed that increased ICP was normalized in 13 out of 22 patients (positive response rate of 59%) [9], 28 additional patients were to be included at stage 2, for a total of 50 evaluable patients among which 30 or more positive responses were expected.

Comparison of moderate-to-severe side effects (the secondary end point) between VLP 15 cc/h and VLP 20 cc/h was determined by chi-square test with continuity correction from all enrolled patients. Overall survival (OS) data were defined as the time from LM diagnosis to the end of the observation period or patient death, whichever occurred first. The survival rates were estimated using the Kaplan–Meier method, and the differences in survival between the investigated factors were compared using the log-rank test. We considered a p-value < 0.05 to indicate a statistically significant difference for these analyses. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) (version 18.0, Chicago, IL).

Results

Patients and ventriculolumbar perfusion chemotherapy

From May 2014 to April 2022, 90 consecutive patients were enrolled in this phase II trial. The clinical characteristics of the patients and their results after VLP chemotherapy are summarized in Table 1. Fifty-nine patients were female, and 31 patients were male. The median patient age was 58 (range 31–82) years. Fifty-five patients (61%) had non-small cell lung cancer (NSCLC), and 20 patients (22%) had breast cancer. The median Karnofsky Performance Status (KPS) score at the time of enrollment was 70 (range 40–100). Forty-one patients (46%) had KPS scores below 70 (KPS = 60 in 16 patients, KPS = 50 in 14 patients, and KPS = 40 in 10 patients).

Sixty-five out of 90 total patients (72%) completed the two consecutive infusions of VLP induction chemotherapy, whereas the remaining 25 patients (28%) failed to complete the induction therapy and dropped out due to progression of LM, intolerance to side effects, lumbar drain malfunction, treatment-related meningitis, or other medical problems (Supplementary Table 1). Thirty-seven patients received further maintenance VLP chemotherapy for a median of two (range 1–7) rounds after the induction chemotherapy.

Table 1 Clinical characteristics and results of the patients who underwent VLP chemotherapy

Characteristics	Number of patients ($n = 90$)	
Gender (male/female)	31/59	
Median age (range)	58 years (31–82)	
Primary cancer		
Non-small cell lung cancer		55 (61%)
Breast cancer		20 (22%)
Others		15 (17%)
Ovarian cancer		5
Small cell lung cancer		3
Malignant melanoma		2
Cervical cancer		1
Malignant glioma		1
Pancreatic cancer		1
AUO		2
Median KPS (range)		70 (40–100)
≥ 70		49 (54%)
< 70		41 (46%)
LM Symptoms and sign		(responded/ presented)
Increased ICP (> 15 cm H_2O)		32/ 65
Altered mentality		4/ 23
Cauda equina involvement		9/ 60
Constitutional side effects		
Nausea/Vomiting		74 (82%)
Grade 1	28 (31%)	
Grade 2	44 (49%)	
Grade 3	2 (2%)	
Sleep disturbance		33 (37%)
Grade 1	22 (24%)	
Grade 2	8 (9%)	
Grade 3	3 (3%)	
Confusion		21 (23%)
Grade 1	10 (11%)	
Grade 2	4 (4%)	
Grade 3	7 (8%)	

AUO adenocarcinoma of unknown origin, *KPS* Karnofski Performance Status, *VLP* ventriculolumbar perfusion

Response to increased intracranial pressure

The change in ICP before and after the VLP induction therapy is depicted in Fig. 3. Briefly, the median ICP among

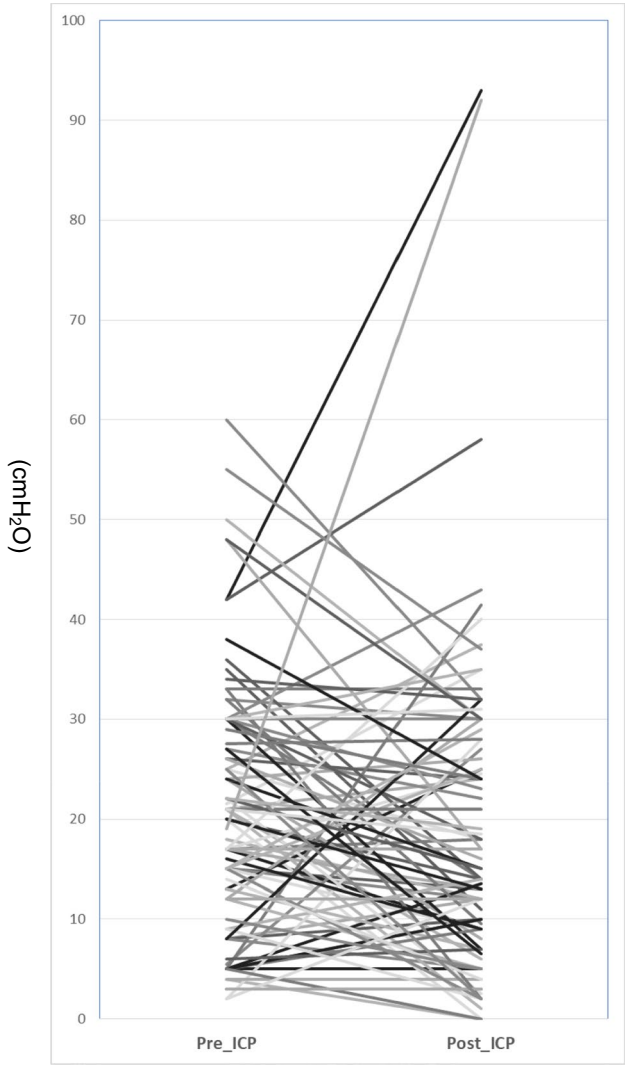

Fig. 3 Change of intracranial pressure (cm H_2O) before (left) and after (right) ventriculolumbar perfusion methotrexate chemotherapy. Gray scales differentiate individual patients

all patients before VLP was 20.0 (range 2–60) cm H_2O. ICP after VLP was decreased in 54 patients, increased in 27 patients, and remained the same as before VLP (change < 1 cm H_2O) in nine patients. Overall, the median ICP was significantly reduced after VLP to 14.5 cm H_2O (range 0–93; $p < 0.01$, Wilcoxon signed-rank test).

The study recruited 15 more patients than planned, resulting in a total of 65 enrolled patients. The number of positive responses required at the end of the study after the excess recruitment was therefore 39 [20]; however, the primary end point of ICP normalization was only observed in 32 patients, indicating that VLP 15 cc/h failed to show a non-inferior response rate compared with VLP 20 cc/h. The bias-corrected response rate of increased ICP was 51.3% [18] (90% one-sided confidence interval, 0.42–1).

Nine patients with normal ICP at the time of enrollment showed increased ICP during the study period, but this increased ICP returned to normal in four of these patients by the end of the study period.

Response to other leptomeningeal metastasis–related symptoms

Among 23 patients who had symptoms of altered mentality before VLP, only 13 were able to complete the VLP induction cycle, and the symptoms improved after VLP in 4 (17%) of these patients. Sixty patients had at least one symptom of cauda equina involvement at the time of enrollment. Forty of these patients completed the induction cycle, and nine (15%) had improved symptoms after VLP. The other 20 patients with cauda equina involvement were unable to complete the VLP induction cycle, and none of them showed improvement in their cauda equine symptoms.

Side effects of ventriculolumbar perfusion therapy

Sixteen patients (18%) had no additional nausea, whereas 28 patients (31%) experienced mild (grade 1) nausea, 44 patients (49%) experienced grade 2 nausea resulting in reduced oral intake but no significant malnutrition or dehydration, and two patients (2%) experienced severe (grade 3) nausea resulting in inadequate oral intake and requiring further treatment with total parenteral nutrition (TPN) or tube feeding. Thirty-three patients (37%) experienced sleep disturbance, which was mild (grade 1) and did not require further medication in 22 patients (24%), moderate (grade 2) in 8 patients, and severe (grade 3) in three patients who were unable to sleep for more than an hour and had difficulty being awake during daytime. Confusion as a manifestation of encephalopathy was observed in 21 patients (23%). Ten of these patients experienced only transient disorientation that could be corrected by verbal intervention (grade 1), whereas four experienced sustained disorientation but remained fully communicable (grade 2), and another seven experienced severe disorientation and delirium and needed medication or, in one patient, physical restraint to control their behavior during VLP (grade 3).

To compare the occurrence of constitutional side effects of VLP 15 cc/h to that of VLP 20 cc/h (Supplementary Table 2), we grouped the side effects into two groups: "nil to mild" (grade 0–1) and "moderate to severe" (grade ≥ 2). The rate of moderate-to-severe nausea/vomiting tended to decrease in patients who received VLP 15 cc/h (51%) compared with that in patients who received VLP 20 cc/h (63%), but the difference failed to reach statistical significance ($p = 0.086$). The rate of moderate-to-severe insomnia was not significantly different between the patients who received VLP 15 cc/h (13%) and the patients who received

VLP 20 cc/h (9%). By contrast, moderate-to-severe confusion was significantly reduced in the patients who received VLP 15 cc/h (12%) compared with that in patients who received VLP 20 cc/h (23%; $p=0.04$).

Overall patient survival

All but one patient had expired by the end of the observation period in August 2023. The median OS was 162 days (95% confidence interval, 136.4–187.6; Fig. 4a). Fifty-two patients (58%) achieved controlled ICP, including patients who received a CSF shunting operation, whereas 38 patients (42%) remained with increased ICP. Control of ICP affected OS significantly (193 days vs. 94 days, $p=0.013$; Fig. 4b). The 39 patients who received maintenance VLP chemotherapy after induction VLP chemotherapy had significantly prolonged median OS compared with the 51 patients who received only induction VLP chemotherapy (216 days vs. 104 days, $p=0.020$, Log-rank test; Supplementary Fig. 1a). However, completion of the VLP induction protocol did not affect patient OS significantly (171 days vs. 104 days, $p=0.32$; Supplementary Fig. 1b).

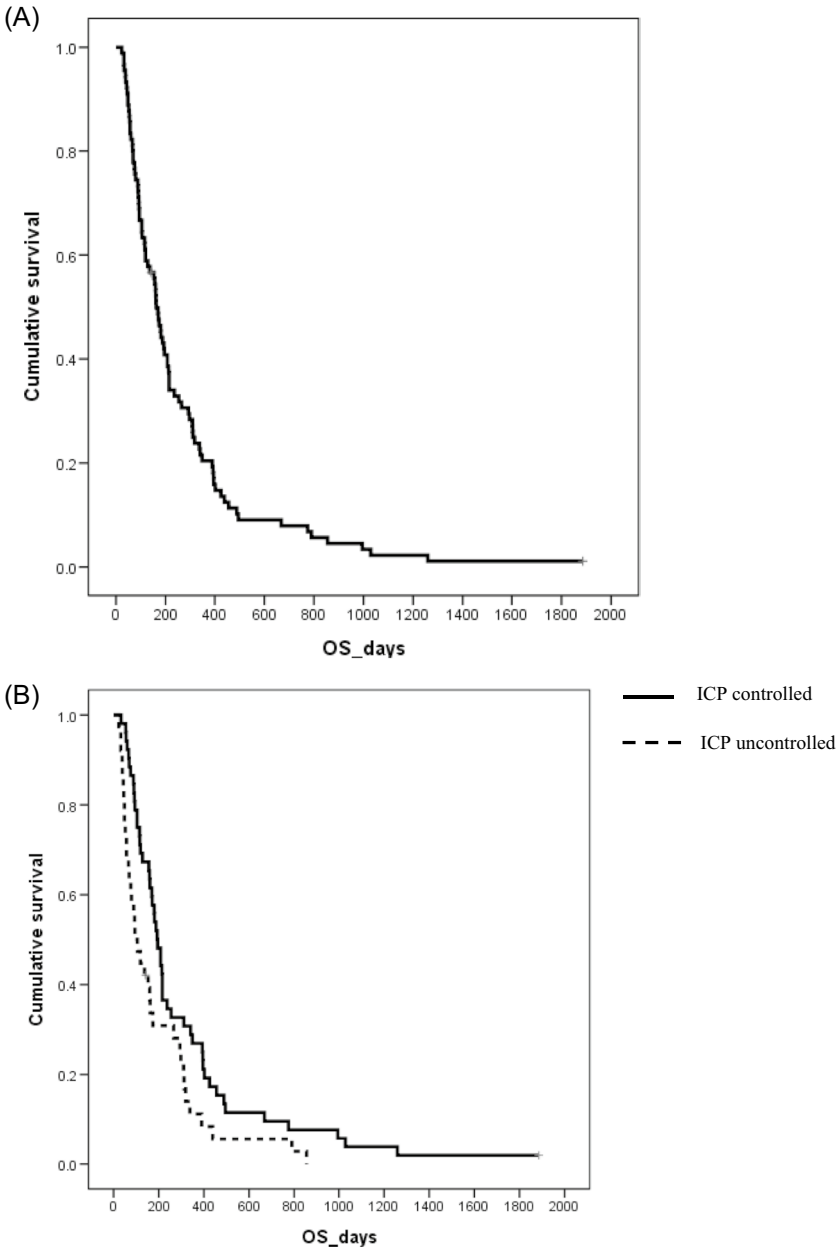

Fig. 4 **A** Kaplan–Meier overall survival curve of all 90 patients who were "intention-to-treat" with ventriculolumbar perfusion. (**B**) Comparison of overall survival time of patients who achieved controlled ICP versus patients who remained with increased ICP (193 days vs. 94 days, Log-rank test, $p=0.013$)

Discussion

As LM is still considered incurable with an expected patient median OS of only a few months, the primary goal of LM treatment is not only to prolong survival but also to maintain the quality of life as much as possible. In this context, the reduced perfusion rate of VLP MTX chemotherapy is worth evaluating, given that it is expected to maintain symptom palliation with less severe side effects than VLP with a higher perfusion rate.

Intracranial pressure control rate in ventriculolumbar perfusion chemotherapy

Among the common LM-related symptoms and signs, increased ICP from CSF flow disturbance is one of the most significant manifestations of LM that affect both quality of life and OS [6, 8, 16, 19]. Furthermore, CSF flow disturbance hinders the normal distribution of intraventricularly or intrathecally injected chemotherapeutics and is thought to increase the toxicity from transependymal drug penetration into the brain parenchyma [1, 12, 17]. In our previous study of patients with LM from NSCLC who received conventional intraventricular chemotherapy, 20/69 patients (29%) with increased ICP (> 15 cm H_2O) achieved normal ICP [15], whereas in our previous phase II clinical trial of VLP 20 cc/h, 32/45 patients (71%) with increased ICP at the start of VLP had normalized ICP at the end of the trial. The superior ICP control rate was one of the advantages of VLP over conventional intraventricular chemotherapy, making it essential that the primary endpoint in the current study of VLP 15 cc/h was a non-inferior response rate of increased ICP compared to that in the previous study of VLP 20 cc/h (p_0 = 50%). Although the bias-corrected ICP control rate of 51% with VLP 15 cc/h failed to reach the threshold for a non-inferior response rate, there were a number of differences in clinical factors between the two trials. One is the KPS scores at the time of entry into the trial, as 10/90 patients in this VLP 15 cc/h trial had KPS scores of 40, whereas only 1/65 patients in the VLP 20 cc/h trial had a KPS score of 40. Patients with poor KPS scores often failed to complete induction VLP chemotherapy and had a significantly low ICP control rate (5/18, 28%). When we re-calculated the ICP response rate for the patients who completed induction VLP chemotherapy, the response rate increased to 57% (27/47).

Decreased side effects of ventriculolumbar perfusion chemotherapy with reduced perfusion rate

During our phase I study, patients complained of nausea/vomiting and sleep disturbance during artificial CSF perfusion before bolus MTX injection, and more severe side effects were reported after VLP with a perfusion rate of 40 cc/h [17]. Based on pharmacokinetic indexes from the phase I trial, the CSF flow rate of VLP 20 cc/h calculated from MTX clearance was 43 ml/h (± 0.006), which was a sum of the normal CSF flow rate and the artificial CSF infusion rate. We assumed that this relatively rapid CSF flow might cause constitutional side effects due to disruption of normal neuropeptide transmission or continuous stimulation of the chemo-receptor trigger zone around the 4th ventricle floor. Compared with VLP 20 cc/h, VLP 15 cc/h resulted in significantly reduced confusion and marginally reduced nausea/vomiting. Sleep disturbance in patients undergoing VLP chemotherapy can be attributable to disruption of the "melatonin surge" for induction of sleep [11]. We postulate that mere reduction of the perfusion rate to 15 cc/h failed to restore the physiological melatonin surge, which remained similarly disrupted as it was with VLP 20 cc/h. Future studies of CSF melatonin levels will show if our assumption of VLP-induced sleep disturbance is correct.

Prolonged overall survival after ventriculolumbar perfusion chemotherapy

As intraventricular chemotherapy is still not recommended as standard therapy for LM, various clinical factors such as patient performance, presenting symptoms, systemic disease status, increased ICP, and primary cancer type affect the OS of patients with LM undergoing intraventricular chemotherapy [4, 5, 15, 22, 30]. Previously, we compared OS between patients treated with VLP and those treated with conventional intraventricular chemotherapy with the same primary cancer of NSCLC [16]. VLP treatment significantly prolonged patient OS from a median of 89 days with conventional intraventricular chemotherapy to a median of 187 days with VLP [16]. In the current study, the median OS was 162 days (5.0 months), which is comparable to that in the previous phase II study of VLP 20 cc/h. Among the evaluated variables, control of increased ICP was a significant prognostic factor for patient OS (193 days vs. 94 days, $p = 0.013$), and patients who received maintenance VLP chemotherapy after induction VLP chemotherapy also had significantly prolonged median OS (216 days vs. 104 days, $p = 0.020$). We need to perform another clinical trial to confirm that various clinical factors can affect the OS of patients with LM in poor medical/general conditions, making these patients unlikely to be able to endure continued chemotherapy.

Limitations.

As some important clinical variables such as KPS scores and primary cancer types were not controlled between the current study of VLP 15 cc/h and the previous study of VLP 20 cc/h used for comparison, the results must be interpreted with caution. Another limitation of the current study is the low

response rate of the patients who did not complete the VLP induction treatment. A future trial should balance these variables to draw needed conclusions.

Conclusion

VLP chemotherapy is a useful for LM patients with increased ICP. However, a reduced perfusion rate (15 cc/h) failed to show non-inferior control of increased ICP compared with previous trial of VLP chemotherapy with a 20-cc/h perfusion rate (51% vs. 71%). Furthermore, the reduced perfusion rate did not significantly lower the moderate-to-severe side effects, except for confusion. Based on OS, which was similarly prolonged by VLP with either perfusion rate; VLP still could be provided to LM patients, who need to achieve control of increased ICP.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00701-024-05989-0.

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Data availability All data supporting the findings of this study are available within the paper and its Supplementary Information.

Code availability Not applicable.

Declarations

Ethics approval All the procedures involving human participants were performed in accordance with the Institutional Review Board of the National Cancer Center of Korea (NCC2014-0061). The trial was registered on the government-owned official trial registration site (http://cris.nih.go.kr) before patient enrollment (KCT0000082) and was conducted according to the guidelines of the Declaration of Helsinki for biomedical research.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

Disclaimer The sponsor had no role in the design or conduct of this research.

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