Overview

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Title: Ventriculolumbar Perfusion Chemotherapy With Methotrexate for Treating Leptomeningeal Carcinomatosis: A Phase II Study

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Author Summary: Abstract and Brief Discussion

Background
The efficacy of ventriculolumbar perfusion (VLP) chemotherapy with methotrexate (MTX) was evaluated for treatment of leptomeningeal carcinomatosis (LMC).

Methods
The primary outcome was the response rate of increased intracranial pressure (ICP), which was available for comparison from historical data on conventional intraventricular chemotherapy. Secondary endpoints were response rates of other LMC symptoms and overall survival of patients. Artificial cerebrospinal fluid (CSF) premixed with MTX was continuously perfused intraventricularly through a preinstalled intraventricular reservoir and drained via lumbar catheter for 72 hours. The VLP was repeated twice at 3-day intervals for each cycle.

Results
Forty-five of 65 patients had increased ICP, and 32 patients (71%) showed response after VLP chemotherapy, including 31 patients with normalization of ICP. Altered mentation improved in 7 of 21 patients (33%). Cauda equina symptoms responded in 5 of 27 patients (19%), including 4 patients who became ambulatory from a bedridden state. Median overall survival was 187 days, and the 1-year survival rate was 27%. All side effects, including nausea, vomiting, confusion, and sleep disturbance, were tolerable and transient except for two cases of CSF infection.

Conclusion
VLP chemotherapy with MTX provided better control of increased ICP, improved symptom response, and prolonged survival at a cost of acceptable toxicity in patients with LMC.

Discussion

The effectiveness of intracerebrospinal fluid chemotherapy for patients with leptomeningeal carcinomatosis (LMC) is doubted, considering marginal survival benefit and poor symptom improvement [1–4]. Cerebrospinal fluid (CSF) flow disturbance, which occurs in more than half of patients with LMC, makes CSF chemotherapy ineffective by hindering even distribution of the injected drug and results in hydrocephalus with increased intracranial pressure (ICP) [5–7].

The potential benefits of ventriculolumbar perfusion (VLP) chemotherapy are uniform drug distribution throughout the CSF space, even under conditions of disturbed CSF flow, and increased cancer-cell killing by enforced drug perfusion [8, 9].

In this phase II study, the primary endpoint was a controlled rate of increased ICP, which was an objective measurement for comparison. VLP chemotherapy with methotrexate (MTX) showed remarkable improvement of increased ICP (71%), altered mentation (33%), and cauda equina symptoms (19%) at a cost of a few, usually transient complications. Wasserstrom et al. reported improvement of increased ICP in 15 of 64 LMC patients (23%) after radiation plus intraventricular chemotherapy [10]. In our previous study of patients with LMC from non-small cell lung cancer (NSCLC) treated by intraventricular chemotherapy, 20 of 69 patients (29%) with increased ICP achieved normal ICP [11]. In this phase II trial, 31 of 41 patients (76%) with increased ICP at the start of VLP were normalized (Fig. 1), and the superiority of VLP in terms of ICP control was statistically significant (chi-square test, $p < .001$).

The survival of patients with LMC is affected greatly by the primary cancer diagnosis [10–15]. We were able to retrieve institutional data of overall survival for LMC from NSCLC patients treated with a median of five rounds of conventional intraventricular chemotherapy [11]. In comparison, VLP treatment significantly prolonged patient survival from a median of 89 days with conventional intraventricular chemotherapy to a median of 187 days for NSCLC patients with VLP (Fig. 2).

The technical complexities of VLP and the high incidence of side effects limit its widespread use. Our technical advances included use of a noncollapsible Chemoport, instead of an Ommaya reservoir, to ensure stable needle position with the designated hooked needle [16], and a reduced perfusion rate of 20 mL/hour resulted in more tolerable constitutional side effects than the previously used perfusion rate of 40 mL/hour [17].

Trial Information

Disease	Advanced cancer/solid tumor only
Disease	Brain cancer – metastatic
Disease	Lung cancer – NSCLC
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	None
Type of study - 1	Phase II
Type of study - 2	Single Arm
Primary Endpoint	Overall Response Rate
Secondary Endpoint	Overall Survival
Additional Details of Endpoints or Study Design	The primary endpoint was the response rate of increased ICP, which was available for comparison from historical data [11]. Secondary endpoints were response rates of other LMC-related symptoms including altered mentation and cauda equina symptoms. Overall survival of patients was compared with that of conventional chemotherapy in limited primary cancer (non-small cell lung cancer).
Investigator's Analysis	Active and should be pursued further

Drug Information

Drug 1 **Generic/Working name**	Methotrexate
Trade name	DBL Methotrexate
Company name	Korea DB Pharm

Drug type	Biological
Drug class	Antimetabolite
Dose	24 mg per day for 3 consecutive days milligrams (mg) per flat dose
Route	Other
Schedule of Administration	Artificial CSF premixed with MTX was continuously perfused intraventricularly through preinstalled intraventricular reservoir at 20 ml/h of a daily 24 mg MTX and drained via lumbar catheter for 72 h (3 days). The VLP was repeated twice at 3-day intervals for each cycle.

Patient Characteristics

Number of patients, male	31
Number of patients, female	34
Stage	IV
Age	Median (range): 54 years (30–77)
Number of prior systemic therapies	Not Collected
Performance Status:	ECOG 0 — 4 1 — 35 2 — 25 3 — 1 unknown — 0
Other	Not Collected
Cancer Types or Histologic Subtypes	Non-small cell lung cancer 51 Breast cancer 6 Malignant glioma 2 Bladder cancer 1 Esophageal cancer 1 Ovarian cancer 1 Small cell lung cancer 1 Thyroid cancer 1 Adenocarcinoma of Unknown Origin 1

Primary Assessment Method

Experimental Arm: Total Patient Population

Number of patients enrolled:	65
Number of patients evaluable for toxicity:	65
Number of patients evaluated for efficacy:	65
Evaluation method:	For increased ICP, the 3 level grading system was as follows: within normal limits (＜15 cm H2O) and no need for intervention; increased ICP and/ or necessary intermittent aspiration; and increased ICP and need for continuous drainage or shunt. Response was defined as improvement by one or more grades.
Response assessment other:	71%
(Median) duration assessments OS:	187 days, CI: 116-258
(Median) duration assessments response duration:	104 days
(Median) duration assessments duration of treatment:	10 days

Secondary Assessment Method

Experimental Arm: Total Patient Population

Number of patients enrolled:	65
Number of patients evaluable for toxicity:	65

Number of patients evaluated for efficacy:	65
Evaluation method:	Altered mentation was graded as follows: normal; communicable but confused; and unable to communicate. For cauda equina symptoms, we defined three components of motor, sensory, and bladder/ anal control and evaluated for each component as follows: normal; incomplete function or intermittent need for intervention; complete loss of function or definite need for intervention. Response was defined as improvement by one or more grades for altered mentation, whereas the sum of all changes was used for cauda equina symptoms.
Response assessment other:	33%

Adverse Events

Name	*NC/NA	1	2	3	4	5	All Grades
Nausea	13%	23%	61%	1%	0%	0%	86%
Insomnia	50%	40%	9%	0%	0%	0%	49%
Confusion	66%	10%	16%	6%	0%	0%	33%
Seizure	89%	0%	9%	1%	0%	0%	10%
Infections and infestations - Other, specify	96%	0%	0%	3%	0%	0%	3%

*No change from baseline/no adverse event.

Serious Adverse Events

Name	Grade 1	Attribution
CSF infection	3	Definite
Vomiting	3	Definite
Confusion	3	Probable
Seizure	3	Unlikely

Assessment, Analysis, and Discussion

Completion:	Study completed
Pharmacokinetics / Pharmacodynamics:	Not Collected
Investigator's Assessment:	Active and should be pursued further

Discussion

The concept of ventricular perfusion of a chemotherapeutic agent in artificial cerebrospinal fluid (CSF) was described by Rubin et al. in 1966 for the purpose of both reducing systemic absorption and achieving effective concentrations of the drug to control brain tumor or central nervous system leukemia [8]. They did not report tumor response in modern oncologic terms but observed side effects such as fever and meningitis. Later, Nakagawa et al. tried a modified method of so-called ventriculolumbar perfusion (VLP) chemotherapy, in which the drug was injected into the ventricle as a bolus while the perfusion of artificial CSF from the ventricle to lumbar drainage continued for 3 days, for patients with leptomeningeal carcinomatosis (LMC) from solid tumors [18]. Despite of a surprising result of 3 of 6 bedridden patients recovering ambulatory function, the authors stated that VLP toxicity was unacceptable when compared with that of conventional intrathecal chemotherapy. However, determination of the cause of side effects was not possible because they provided neither the CSF methotrexate (MTX) concentrations nor the detailed dosages of individual patients showing those side effects, including encephalopathy.

In our pilot study (unpublished data), we found that CSF MTX concentration is predictable because the clearance is a sum of that in the conventional ventricular injection and the perfusion rate [19, 20]. In addition, we noticed some constitutional side effects, such as nausea and vomiting, that occurred at preinjection artificial CSF perfusion itself and that were related to the perfusion rate. Consequently, we planned to have two parameters, perfusion rate and daily MTX dose, for toxicity evaluation in a previous phase I study [17]. A perfusion rate of 20 mL/hour and daily MTX dose of 24 mg were tolerable and caused only

transient side effects in the phase I study. We also simulated steady-state concentration (Css) of continuous intraventricular infusion, which was obtained in nonhuman primates (*Macaca mulatta*) by Bails et al. [21] and expected that Css of our regimen would be in a range of 10–100 μM. Accompanying pharmacokinetics of phase I revealed that the clearance rate is a sum of the perfusion rate and the physiologic CSF flow rate, and Css of continuous infusion was 49.6 μM ($\pm$7.1 μM) at perfusion of 20 mL/hour daily with 24 mg MTX [17].

In the present phase II study, we demonstrated that VLP chemotherapy with MTX showed remarkable improvement of increased ICP (71%), altered mentation (33%), and cauda equina symptoms (19%) and significant prolongation of overall survival (median: 187 days) at a cost of acceptable side effects. Studies reporting the symptom "improvement" rate for individual LMC-related symptoms are rare, and the definitions of symptom improvement have been vague and subjective, except for changes in CSF profiles [22–24]. In this context, ICP was an objective measurement for evaluating efficacy of this palliative treatment. Wasserstrom et al. reported improvement of increased ICP ($>$16 cm H_2O) in 15 of 64 patients with LMC (23%) after radiation plus intraventricular chemotherapy [10]. However, they did not define their criterion for favorable response of increased ICP. In our previous study of patients with LMC from non-small cell lung cancer (NSCLC) treated by conventional intraventricular chemotherapy, 20 of 69 patients (29%) with increased ICP ($>$15 cm H_2O) achieved normal ICP [11]. In our phase II trial reported in this paper, 31 of 41 patients (76%) with increased ICP at the start of VLP were normalized. The superiority of VLP to conventional intraventricular chemotherapy in terms of ICP control was statistically significant (chi-square test, $p < .001$). Although 3 of 6 bedridden patients became ambulatory in the study by Nakagawa et al. [2], in our study, only 4 of 16 bedridden patients showed this response. The possible difference in the symptom response rate according to different VLP modes (i.e., bolus injection vs. continuous infusion) requires investigation in future clinical trials. Other difficulties in evaluating efficacy of CSF chemotherapy are lack of pharmacodynamics markers and inconsistent CSF cytology results [13, 25]. LMC itself is a disease without radiological response criteria, and quantitative measurement of LMC has never been tried. We analyzed CSF protein concentration; drug absorption rate of VLP; and, in some patients, CSF tumor-specific antigen concentration (i.e., carcinoembryonic antigen in NSCLC patients). By far, the above-listed parameters did not reveal any quantitative relationship or threshold level for symptom response (unpublished data). We tried to develop pharmacodynamic markers for patients with LMC, including metabolome, microRNA, or DNA. A specific biomarker for LMC cancer cells may be identified by comparing the CSF of patients with LMC to the CSF of healthy controls or cancer patients without LMC through in vitro experiments and a pilot study.

Primary cancer is one of factors affecting the survival of patients with LMC receiving intraventricular chemotherapy [10, 11, 13–16]. Chamberlain and Kormanik reported treatment results of intraventricular chemotherapy for 32 patients with LMC from NSCLC, and median survival was 5 months [13]. This improvement of survival could be attributed to the intensive "concentration $\times$ time" schedule of administration (2 mg/day MTX for 5 consecutive days every other week for 8 weeks; median total dosage of 65 mg). In that study, MTX treatment-resistant patients were treated with second-line (cytosine arabinoside) and third-line (thiotepa) salvage intraventricular chemotherapies. Fortunately, we were able to retrieve institutional data to compare the survival of patients treated with VLP and those treated with a median of five rounds of conventional intraventricular chemotherapy for LMC from NSCLC [11]. In comparison, VLP treatment significantly doubled patient survival from a median of 89 days with conventional intraventricular chemotherapy to 187 days with VLP. This result should be interpreted based on a well-defined cause of death to ascertain whether prolonged survival in the VLP group resulted from preventing patients' neurologic death.

The technical complexities of VLP and the high incidence of side effects limit its widespread use. One technical advance that we achieved was using a Chemoport instead of an Ommaya reservoir [16]. The noncollapsible Chemoport chamber prevents possible backflow of chemotherapeutic agents through the pericatheter space, confirming the utility of pressing the Ommaya reservoir after drug injection. Furthermore, the hooked needle not only ensures stable needle position but also makes use of sterile closed dressing easier than does the straight needle that is inserted into the plastic dome of Ommaya reservoir.

Fever was an unavoidable constitutional side effect reported in previous studies by other groups [8, 18]. However, we did not observe overt fever during VLP through both phase I and II studies, probably because we used advanced sterile and pyrogen-free artificial CSF preparations. Cases of CSF infection in our study were clinically silent, and early detection was possible through routine daily CSF examination. The other improvement of VLP technique in our study was reduced perfusion rate. Our phase I study proved that a reduced perfusion rate of 20 mL/hour resulted in much more tolerable constitutional side effects than the previous perfusion rate of 40 mL/hour used by Nakagawa et al. [18]. However, 40 of 65 patients in the phase II trial still suffered from grade 2 nausea and vomiting during perfusion. Based on the promising results of the present trial, we have launched a noninferiority study of continuous-infusion VLP with a reduced perfusion rate of 15 mL/hour. Our goal is to optimize VLP methods and, ultimately, to perform a randomized study to determine overall efficacy.

References

1. Chamberlain MC, Kormanik PA, Barba D. Complications associated with intraventricular chemotherapy in patients with leptomeningeal metastases. J Neurosurg 1997;87:694–699.
2. Bokstein F, Lossos A, Siegal T. Leptomeningeal metastases from solid tumors: A comparison of two prospective series treated with and without intra-cerebrospinal fluid chemotherapy. Cancer 1998;82:1756–1763.
3. Boogerd W, van den Bent MJ, Koehler PJ et al. The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: A randomised study. Eur J Cancer 2004;40:2726–2733.
4. Bleyer WA. Neurologic sequelae of methotrexate and ionizing radiation: A new classification. Cancer treatment reports 1981;65. Suppl 1: 89–98.
5. Grossman SA, Trump DL, Chen DC et al. Cerebrospinal fluid flow abnormalities in patients with neoplastic meningitis. An evaluation using 111indium-dtpa ventriculography. The American journal of medicine 1982;73:641–647.
6. Chamberlain MC. Radioisotope csf flow studies in leptomeningeal metastases. Journal of neuro-oncology 1998;38:135–140.
7. Taillibert S, Laigle-Donadey F, Chodkiewicz C et al. Leptomeningeal metastases from solid malignancy: A review. Journal of neuro-oncology 2005;75:85–99.
8. Rubin RC, Ommaya AK, Henderson ES et al. Cerebrospinal fluid perfusion for central nervous system neoplasms. Neurology 1966;16:680–692.
9. Fleischhack G, Jaehde U, Bode U. Pharmacokinetics following intraventricular administration of chemotherapy in patients with neoplastic meningitis. Clinical pharmacokinetics 2005;44:1–31.
10. Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: Experience with 90 patients. Cancer 1982;49:759–772.
11. Gwak HS, Joo J, Kim S et al. Analysis of treatment outcomes of intraventricular chemotherapy in 105 patients for leptomeningeal carcinomatosis from non-small-cell lung cancer. J Thorac Oncol 2013;8:599–605.
12. Chamberlain MC, Kormanik PA. Prognostic significance of 111indium-dtpa csf flow studies in leptomeningeal metastases. Neurology 1996;46: 1674–1677.
13. Chamberlain MC, Kormanik P. Carcinoma meningitis secondary to non-small cell lung cancer: Combined modality therapy. Archives of neurology 1998;55:506–512.
14. Bruna J, Gonzalez L, Miro J et al. Leptomeningeal carcinomatosis: Prognostic implications of clinical and cerebrospinal fluid features. Cancer 2009;115:381–389.
15. Park JH, Kim YJ, Lee JO et al. Clinical outcomes of leptomeningeal metastasis in patients with non-small cell lung cancer in the modern chemotherapy era. Lung cancer (Amsterdam, Netherlands) 2012;76:387–392.
16. Gwak HS LC, Yang HS et al. Chemoport with a non-collapsible chamber as a replacement for an ommaya reservoir in the treatment of leptomeningeal carcinomatosis. Acta Neurochir 2011;153:1971–1978.
17. Gwak HS, Lim HS, Shin SH et al. Ventriculolumbar perfusion chemotherapy for the treatment of leptomeningeal carcinomatosis: A phase I study with pharmacokinetic data. Am J Clin Oncol 2013;36:491–499.
18. Nakagawa H, Fujita T, Kubo S et al. Ventriculolumbar perfusion chemotherapy with methotrexate and cytosine arabinoside for meningeal carcinomatosis: A pilot study in 13 patients. Surgical neurology 1996;45:256–264.
19. Blasberg RG, Patlak CS, Shapiro WR. Distribution of methotrexate in the cerebrospinal fluid and brain after intraventricular administration. Cancer treatment reports 1977;61:633–641.
20. Shapiro WR, Young DF, Mehta BM. Methotrexate: Distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. The New England journal of medicine 1975;293:161–166.
21. Balis FM, Blaney SM, McCully CL et al. Methotrexate distribution within the subarachnoid space after intraventricular and intravenous administration. Cancer chemotherapy and pharmacology 2000;45:259–264.
22. Ongerboer de Visser BW, Somers R, Nooyen WH et al. Intraventricular methotrexate therapy of leptomeningeal metastasis from breast carcinoma. Neurology 1983;33:1565–1572.
23. Schabet M, Kloeter I, Adam T et al. Diagnosis and treatment of meningeal carcinomatosis in ten patients with breast cancer. European neurology 1986;25:403–411.
24. Hitchins RN, Bell DR, Woods RL et al. A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. J Clin Oncol 1987;5:1655–1662.
25. Freilich RJ, Krol G, DeAngelis LM. Neuroimaging and cerebrospinal fluid cytology in the diagnosis of leptomeningeal metastasis. Annals of neurology 1995;38:51–57.

Figures and Tables

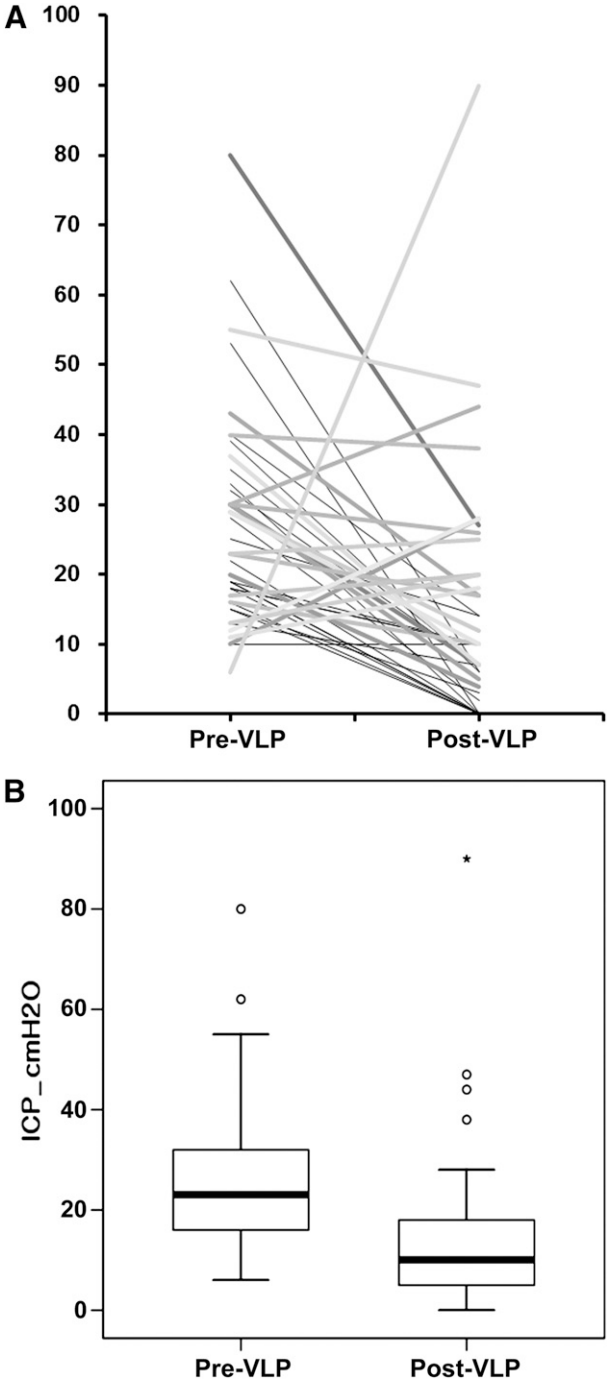

Figure 1. Distribution of intracranial pressure. **(A):** The distribution of individual patients' intracranial pressure (cm H2O) is shown before (left) and after (right) the ventriculolumbar perfusion chemotherapy with methotrexate. Gray scales differentiate individual patients. **(B):** Box plot shows significant reduction of median intracranial pressure (thick line) from 23 cm H2O to 10 cm H2O (Wilcoxon signed rank test, $p < .0001$). Box shows range of quartile and error bars simulate 95% confidence interval.

Abbreviations: ICP, intracranial pressure; VLP, ventriculolumbar perfusion.

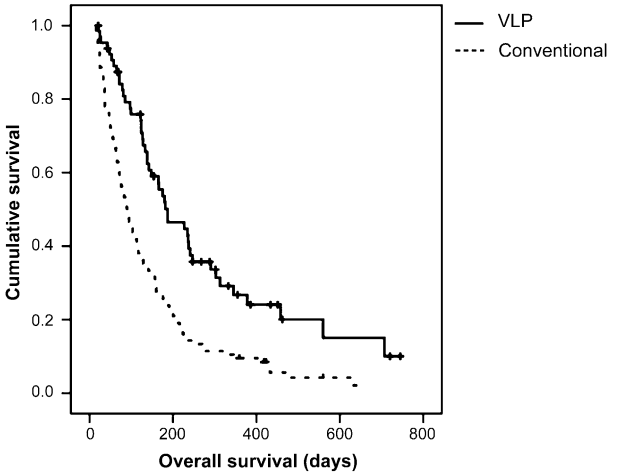

Figure 2. Comparison of overall survival time of VLP-treated non-small cell lung cancer patients ($n = 51$) versus conventional intraventricular chemotherapy-treated patients ($n = 105$). Data published in [11].

Abbreviation: VLP, ventriculolumbar perfusion.

Table 1. Increased ICP symptom response of VLP chemotherapy

		Post-VLP ICP grade		
		0	1	2
Pre-VLP ICP grade	0	3	1	10
	1	0	6	21
	2	0	4	20

Grading system for ICP is as follows: 2 = within normal limit (<15 cm H_2O); 1 = increased and needs intermittent aspiration (15~30 cm H_2O); 0 = increased and needs continuous drainage or shunt (>30 cm H_2O).

Improved.

No change.

Worse.

Abbreviations: ICP, intracranial pressure; VLP, ventriculolumbar perfusion.

Table 2. Altered mentation symptom response of VLP chemotherapy

		Post-VLP mentality score		
		0	1	2
Pre-VLP mentality score	0	4	1	
	1	2	6	6
	2	2	0	44

Grading system for altered mentation is as follows: 2 = normal, communicates fully; 1 = communicates but response is inappropriate; 0 = unable to communicate.

Improved.

No change.

Worse.

Abbreviation: VLP, ventriculolumbar perfusion.

Table 3. Cauda equina symptom response of VLP chemotherapy

		Post-VLP CES score						
		0	0.5	1	1.5	2	2.5	3
Pre-VLP CES score	0							
	0.5		1		1			
	1							
	1.5			1	7		1	
	2				2	2	1	
	2.5						6	2
	3		1			1	1	38

CES score is a sum of three components (motor, sensory, and bladder/anal control). Each score is as follows: motor weakness; 1 = ambulatory, 0 = paraplegia, otherwise = 0.5; sensory; 1 = normal, 0 = complete loss, otherwise = 0.5; bladder/ anal control; 1 = normal, 0.5 = intermittent catheterization or diaper/constipation, 0 = indwelling catheter/loss of anal tone.

Improved.

No change.

Worse.

Abbreviations: CES, cauda equina symptom; VLP, ventriculolumbar perfusion.