

Carcinoma Meningitis Secondary to Non–Small Cell Lung Cancer

Combined Modality Therapy

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Background: Leptomeningeal metastases (LM) are increasingly diagnosed as anticancer therapies become more effective and result in prolonged patient survival.

Objective: To evaluate survival, cause of death, and treatment-related toxic effects in patients undergoing combined modality therapy for LM of non–small cell lung cancer.

Patients and Methods: Thirty-two patients (age range, 48–73 years; median, 57 years) with LM attributable to metastatic non–small cell lung cancer were treated prospectively. Neurologic presentation included headache (11 patients), cranial neuropathies (9), ataxia (5), cauda equina syndrome (3), myelopathy (3), meningismus (2), radiculopathy (2), and confusion (1). All patients underwent radiographic evaluation to determine the extent of central nervous system disease followed by radiotherapy (16 patients) and sequential and intraventricular chemotherapy (methotrexate in 32 patients; cytarabine in 16; and thiotepea in 6). Twelve patients received concurrent systemic chemotherapy.

Results: Central nervous system imaging demon-

strated interrupted cerebrospinal fluid flow (13 patients), parenchymal brain metastases (9), subarachnoid nodules (8), hydrocephalus (5), and epidural spinal cord compression (2). Cytological responses were seen in 17 patients to first-line chemotherapy, 8 to second-line chemotherapy, and 2 to third-line chemotherapy. Treatment-related toxic effects included 20 patients with aseptic meningitis (grade 2 in 16; grade 3 in 4) and 12 patients with grade 3 or 5 thrombocytopenia or neutropenia (4 related to intraventricular chemotherapy). Median survival was 5 months (range, 1–12 months). Nineteen patients died of progressive LM or combined LM and systemic disease progression. Patients with persistent interruption of cerebrospinal fluid flow fared worse than patients with normal cerebrospinal fluid flow (median survival, 4 vs 6 months; $P < .05$).

Conclusions: Leptomeningeal metastases in patients with non–small cell lung cancer may be palliated with combined modality therapy; however, therapy and survival is based on the extent of central nervous system disease present at pretreatment evaluation.

Arch Neurol. 1998;55:506–512

LEPTOMENINGEAL metastasis (LM) is an increasingly common complication of non–small cell lung cancer, occurring with an estimated incidence of approximately 5%.^{1–5} As patients with cancer survive longer because of more effective contemporary anticancer treatments, central nervous system (CNS) metastases including LM are becoming increasingly common.^{1–5} Most often LM presents in patients with cancer at a time when systemic disease has recurred and patients have failed one or more prior chemotherapy regimens. Therefore, treatment decisions regarding LM are usually made in the context of a patient with active widespread systemic cancer, CNS metastases, and limited life expectancy. Thus, treatment of LM, if

initiated, is necessarily palliative with the objective of preserving neurologic performance notwithstanding failing function in other organ systems affected by metastatic cancer. Determination of appropriate candidates for treatment of LM is complicated by the lack of a uniform approach and treatment of LM.^{1–5} This prospective study, representing a decade of experience by the University of California, San Diego Neuro-Oncology Service of 32 select patients with LM secondary to metastatic non–small cell lung cancer, presents a standardized evaluation and treatment of LM using contemporary CNS imaging and combined modality radiochemotherapy. Outcome measures evaluated during the course of study included survival, cause of death, and treatment-related toxic effects.

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PATIENTS AND METHODS

STUDY POPULATION

Thirty-two patients (22 men and 10 women) with LM secondary to non-small cell lung cancer, ranging in age from 48 to 73 years (median, 57 years), were prospectively studied. Patients were accrued between July 1986 (study opened) and June 1996 (study closed) at the University of California, San Diego, Gildred Cancer Center. All patients gave informed consent for therapy and entry into the study. Inclusion criteria enabling entry into the study included (1) Karnofsky performance score of 70 or more; (2) expected survival of 3 months or more; (3) a diagnosis of LM made by compatible clinical or neuroradiographic findings with or without a positive cerebrospinal fluid (CSF) cytological finding; (4) no prior intra-CSF therapy; and (5) patients' desire for further therapy. Approximately 50% (34/66) of patients evaluated with carcinomatous meningitis because of non-small cell lung cancer were excluded for failing to meet entry criteria. Exclusion from the study was because of poor performance status (n=18), expected survival of less than 3 months (n=12), and patients declining further therapy (n=4). Karnofsky performance scores at the time of diagnosis of LM ranged from 70 to 100 (median, 90). Twenty-six patients had cytologically documented LM requiring 1 (n=21), 2 (n=4), or 3 (n=1) lumbar punctures for cytological diagnosis. In the remaining 6 patients, LM was documented by CSF abnormalities and a clinical syndrome or neuroradiographic findings consistent with LM. Cerebrospinal fluid abnormalities in patients with cytologically negative results included an elevated protein level (n=5), elevated opening pressure (n=3), leukocytosis (n=2), and a depressed glucose level (n=1). Clinical syndromes in patients with negative CSF cytological findings included cranial neuropathies (n=4), ataxia (n=2), cauda equina syndrome (n=1), and radiculopathy (n=1). Neuroradiographic findings in patients with cytologically negative results included indium-111 CSF flow block (n=3), spinal subarachnoid nodules (n=2), intracranial subarachnoid nodules (n=1), and hydrocephalus (n=1). All patients had LM diagnosed following initial systemic tumor presentation ranging from 3 to 12 months (median, 7 months) after primary tumor presentation. All patients had non-small cell lung cancer with the following histologic diagnoses: adenocarcinoma (24 patients), large cell (6), and squamous cell carcinoma (2).

Presenting neurologic examination included the following findings: headache (11 patients); solitary or multiple cranial neuropathies (9 patients); ataxia (5 patients); cauda equina syndrome (3 patients); myelopathy (3 patients); meningismus (2 patients); radiculopathy (2 patients); and confusion (1 patient) (**Table 1**). The extent of pre-LM treatment of systemic disease was characterized as follows. In 7 patients, the primary tumor was in remission (ie, relapse manifested as isolated LM) and therefore only regional chemotherapy and limited-field CNS radiation were used (Table 1). In the remaining 25 patients, LM occurred in the context of active systemic disease (lung, 25 patients; liver, 9 patients; and bone, 4 patients) in whom a variety of non-small cell lung-specific systemic chemotherapies were used (12 patients) in addition to regional chemotherapy and limited-field CNS radiation. No patient received high-dose systemic methotrexate, cytarabine, or thiotepa, regimens with activity against LM.⁶⁻⁸

IMAGING TECHNIQUES

All patients underwent placement of an intraventricular catheter and reservoir, after which an evaluation of pretreatment extent of disease (CNS staging) was undertaken and included the following:^{1,5,9-16} cranial contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI; all patients); spinal contrast-enhanced MRI if clinically indicated (myelopathy, radiculopathy, or back pain) or if CSF flow studies documented a spinal subarachnoid block; and ¹¹¹In diethylenetriamine pentaacetic acid (DTPA) CSF flow study (all patients).

As previously described,^{1,2,9,11-13} imaging was performed with a gamma camera (Elscent, Tel Aviv, Israel) equipped with a medium-energy collimator. Abnormal results of radionuclide flow studies were categorized according to location of the CSF flow abnormality and defined by the CSF compartment at which blocking of the radionuclide occurred.^{9,11,13-15}

Cranial CT examinations were performed on a scanner (GE 9800 scanner, General Electric, Milwaukee, Wis). Cranial and spinal MRI examinations were performed with a 1.5-T superconducting magnet (Signa, General Electric). After intravenous administration of 0.01 mmol/kg of gadolinium-diethylenetriamine pentaacetic acid dimeglumine (Berlex Laboratories, Cedar Knolls, NJ), coronal and axial T₁-weighted sequences (repetition time, 600 milliseconds; echo time, 25 milliseconds) were performed. All postcontrast images were obtained within 30 minutes of gadolinium infusion.

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RESULTS

The extent of CNS disease evaluation at the time of LM presentation was as follows. Contrast-enhanced cranial MRI and CT results were positive in 17 patients (53%), 9 of whom demonstrated parenchymal brain masses; 5, hydrocephalus; and 3, subarachnoid nodules. Contrast-enhanced spine MRI results were positive in 7 patients (22%), 5 of whom demonstrated subarachnoid nodules and 2, epidural spinal cord compression. Results of ¹¹¹In DTPA CSF flow studies showed abnormalities in 13 patients (41%), 7 of whom had intracranial block (4, base of brain; 3, cerebral convexities); 3, thoracic spine

subarachnoid space block; and 4, lumbar spine subarachnoid space block.

Regions of bulky disease as defined by cranial MRI and CT, spine MRI or symptomatic disease, and areas of CSF compartmental CSF flow block as defined by ¹¹¹In DTPA CSF flow studies were treated with limited-field radiotherapy. In all instances both whole brain and limited spine (defined as a part encompassing 3-5 vertebral bodies) radiotherapy was given before the initiation of regional chemotherapy. In 1% of patients in whom whole brain radiotherapy was administered for either parenchymal brain metastases (n=9) or intracranial subarachnoid nodules (n=3), follow-up cranial MRI demon-

DRUG SCHEDULE

All patients received intra-CSF (regional) chemotherapy according to a fixed sequence. Methotrexate (first-line therapy) was given initially followed by cytosine arabinoside (second-line therapy) if clinically appropriate. Last, patients received thiotepa (third-line therapy), again if clinically appropriate. Clinical appropriateness was determined as patients meeting original entry criteria as defined in the "Study Population" subsection. In only a few patients were either methotrexate or cytosine arabinoside CSF or serum drug levels obtained. Methotrexate was administered intraventricularly in a concentration \times time drug schedule, as previously reported, at the completion of limited-field irradiation in the following manner^{1,2,8-9,15,17,18}: induction, 2 mg of methotrexate in 5 mL of nonbacteriostatic normal saline daily for 5 consecutive days every other week for 8 weeks (20 drug administrations; methotrexate total dose, 40 mg); maintenance, 2 mg of methotrexate in 5 mL of normal saline daily for 5 consecutive days every 4 weeks until disease progression. Maintenance methotrexate was administered only to patients with a cytologically proven complete response (defined below) and stable or improved clinical disease (defined below) following induction of intraventricularly administered methotrexate.

Cytosine arabinoside was administered intraventricularly in a concentration \times time drug schedule as previously reported following cytological relapse after intraventricular administration of methotrexate, or in patients failing to respond to induction of methotrexate, in the following manner^{1,2,8,9,15,17,19}: induction, 25 mg of cytosine arabinoside in 5 mL of normal saline daily for 3 consecutive days every week for 4 weeks (12 drug administrations; cytosine arabinoside total dose, 300 mg). Induction cytosine arabinoside was administered only to patients with cytological relapse, failure of induction of methotrexate or clinical disease progression following intraventricularly administered methotrexate; maintenance, 25 mg of cytosine arabinoside in 5 mL of normal saline daily for 3 consecutive days once every 4 weeks until disease progression. Maintenance cytosine arabinoside was administered only to patients with cytologically proven complete response and stable or improved disease after induction of intraventricularly administered cytosine arabinoside.

Thiotepa was administered intraventricularly in a concentration \times time drug schedule as previously reported following cytologically proven relapse, clinical disease progression, or failure to respond to induction after use of intraventricular methotrexate and cytosine arabinoside in the

following manner^{1,2,8,9,17,20}: induction, 10 mg of thiotepa in 5 mL of normal saline daily for 3 consecutive days every week for 4 weeks (12 drug administrations; thiotepa total dose, 120 mg). Induction of thiotepa was administered only to patients with cytologically proven relapse, failure of induction, or following disease progression after intraventricularly administered methotrexate and cytarabine; maintenance, 10 mg of thiotepa in 5 mL of normal saline daily for 3 consecutive days once every 4 weeks until disease progression. Maintenance thiotepa was administered only to patients with cytologically proven complete response and stable or improved disease after induction of intraventricularly administered thiotepa.

RESPONSE CRITERIA

Cytological response criteria are defined based on CSF cytological findings as follows^{1,2,9}: complete response, 2 consecutive negative CSF (ventricular and lumbar sampling) cytological examinations at least 1 week apart and sustained for at least 1 month on a regimen of stable or decreasing steroid dosage; partial response, conversion from positive to suspicious on 2 consecutive CSF examinations (ventricular and lumbar sampling) at least 1 week apart and sustained for at least 1 month on a regimen of stable or decreasing steroid dosage; and progressive disease, conversion from negative on 2 prior consecutive examinations to positive, or 2 consecutive positive or suspicious cytological findings.

All patients underwent weekly ventricular CSF cytological examinations and at the conclusion of induction therapy they underwent lumbar CSF cytological examination. No biochemical markers (eg, lactate dehydrogenase) were used in evaluating CSF responses. Clinical response criteria are based on sequential neurologic examination as follows: complete response, resolution of all neurologic signs; partial response, incomplete resolution of neurologic signs; stable disease, no change in clinical signs; and progressive disease, worsening of preexisting or new neurologic signs.

In patients with LM defined clinically and with negative CSF cytological findings, clinical response (and when appropriate, neuroradiographic response) served as response criteria. Neuroradiographic responses were defined as follows: complete response, resolution of all neuroradiographic signs; partial response, incomplete resolution of neuroradiographic signs; stable disease, no change in neuroradiographic signs; and progressive disease, worsening of preexisting or new neuroradiographic signs.

strated stable disease. Similarly, in 7 patients treated with spinal irradiation for either spinal subarachnoid nodules (n=5) or epidural spinal cord compression (n=2), follow-up spine MRI demonstrated stable disease. In 7 patients in whom intracranial interruption of CSF flow was documented by radionuclide ventriculography, whole brain radiotherapy (ten 300-Gy fractions) was administered, and 4 (57%) demonstrated restoration of normal CSF flow following radiotherapy. In 3 patients (33%) persistent intracranial CSF block was seen. Limited spine irradiation was used in 7 patients and was given in ten 300-Gy fractions. Of 6 patients with pretreatment CSF block, in 3 (50%) following radiotherapy, spinal sub-

arachnoid CSF flow block was restored to normal; however, in 3 patients (50%) persistent interruption of CSF flow was seen following radiotherapy. In all patients with interruption of CSF flow treated with radiotherapy directed at the site of CSF block, following radiotherapy both CSF cytological (positive in all) and ¹¹¹In DTPA CSF flow studies were performed. Thereafter, all patients were treated with systemic or regional (intra-CSF) chemotherapy.

Intraventricular chemotherapy was administered to all patients of whom 32 received methotrexate as initial therapy, 16 received cytosine arabinoside as second-line therapy, and 6 received thiotepa as third-line che-

Table 1. Lung Leptomeningeal Metastases: Patient Characteristics and Outcome*

Patient/Age, y	Karnofsky Performance Scores at Treatment Initiation	Neurologic Presentation	Pretreatment Extent of Disease, Systemic	Outcome	
				Survival, mo	Cause of Death
1/49†	90	Left abducens	Liver, lung	6	SD
2/63†	100	Meningismus	Lung	7	LM
3/61†	100	Headache	Lung	8	SD
4/58†	90	Headache	Lung, liver	2	LM and SD
5/60†	80	Gait ataxia	Lung	4	LM
6/73†	90	Gait ataxia	...	3	LM
7/59†	100	Headache	...	4	LM and SD
8/62†	90	Facial	Lung	6	SD
9/56†	100	Abducens	Lung	5	SD and LM
10/58†	80	Headache	Bone, lung, liver	6	SD and LM
11/60†	70	Cauda equina syndrome	...	3	SD
12/62†	90	Radiculopathy	Lung	4	LM and SD
13/61†	90	Headache, gait ataxia	Bone, lung	5	SD and LM
14/58†	80	Left abducens	Lung	7	SD
15/54†	70	Headache, myelopathy	...	6	SD
16/56†	90	Left abducens	Bone, lung, liver	5	SD and LM
17/62†	70	Myelopathy	Lung	4	LM
18/65†	70	Cauda equina syndrome	...	1	LM
19/52	100	Headache	Lung	8	SD
20/49	70	Radiculopathy	Bone, lung, liver	4	LM and SD
21/61	100	Left abducens	Bone, lung	10	SD
22/60†	100	Headache	Bone, lung, liver	6	LM
23/58†	90	Gait ataxia	Bone, lung	4	LM
24/56†	70	Myelopathy	Bone, lung	5	SD
25/54†	70	Cauda equina syndrome	...	8	SD
26/64†	90	Left abducens	Bone, lung	2	LM
27/48	100	Left facial	Bone, lung, liver	10	SD
28/51	90	Headache	Bone, lung	7	SD
29/62	90	Meningismus	...	4	SD and LM
30/49	90	Headache, left abducens	Bone, lung	12	SD
31/51	80	Headache, gait ataxia	Bone, lung, liver	3	LM
32/56	70	Headache, confusion	Bone, lung, liver	2	SD and LM

*SD indicates systemic disease progression; LM, leptomeningeal disease progression; SD and LM, combined systemic and leptomeningeal disease progression; and ellipses, not reported.

†Subjects of prior reports of LM and neuroradiographic manifestations.^{11,12,14,15}

motherapy (**Table 2**). No dose modifications of intra-CSF chemotherapy were made in patients with persistent CSF flow blocks. The total dose of intraventricularly administered drugs was as follows, methotrexate: median, 65 mg (range, 20-110 mg); cytosine arabinoside: median, 337 mg (range, 300-675 mg); and thiotepa: median, 120 mg (range, 120-180 mg). Seventeen (43%) of 32 patients responded (cytological examination, 17 patients with complete response; clinical, 17 patients with partial response; and neuroradiographic examination, 17 patients with partial response) to treatment with intraventricular methotrexate with a median time to response of 6 weeks (range, 4-8 weeks). Duration of response ranged from 1 to 7 months (median, 3 months). No difference in response or survival was seen in patients treated with systemic chemotherapy compared with patients not receiving concurrent systemic chemotherapy. Twenty-six (81%) of 32 patients treated with intraventricular methotrexate had normal findings on pretreatment or postradiotherapy CSF flow studies. Duration of response in this cohort ranged from 2 to 11 months (median, 5 months). By contrast, 6 (19%) of 32 patients had an interruption of CSF flow despite therapy (me-

dian duration of response, 2 months; range, 0-3 months) ($P<.001$).

Eight (50%) of 16 patients responded (cytological examination, 8 patients with complete response; clinical, 8 patients with partial response; and neuroradiographic, 3 patients with partial response) to second-line therapy with a time to response to intraventricular cytosine arabinoside therapy ranging from 2 to 4 weeks (median, 3 weeks). In patients responding to cytosine arabinoside, 4 patients failed induction of methotrexate and 4 experienced a relapse with maintenance methotrexate therapy. Median duration of response was 2.5 months (range, 1-6 months). Twelve (75%) of 16 patients treated with intraventricular cytosine arabinoside had normal results of either pretreatment or postradiotherapy CSF flow studies. Duration of response in this cohort ranged from 1 to 6 months (median, 3.5 months). By contrast, 4 (25%) of 16 women had treatment-resistant interruption of CSF flow and their median duration of response to intraventricular cytosine arabinoside was 1 month (range, 1-3 months) ($P<.01$).

Two (33%) of 6 patients responded (cytological examination, 2 patients with complete response; clinical,

Table 2. Treatment of Lung Leptomeningeal Metastases

	No. of Patients
Systemic chemotherapy	
None	20
Cisplatin and vinorelbine tartrate (Navelbine)	8
Taxol and cisplatin	3
Gemcitabine	1
Radiotherapy	
None	16
Whole brain	9
Spine	7
Intraventricular chemotherapy	
Methotrexate	32
Response	17
Cytosine arabinoside	16
Response	8
Thiotepa	6
Response	2

2 patients with partial response; and neuroradiographic, 1 patient with partial response) to third-line thiotepa regional chemotherapy with a median time to response of 3 weeks (range, 2-4 weeks). Both patients responding to thiotepa failed induction of cytosine arabinoside. Median duration of response was 1 month (range, 1-3 months). No differences were seen in a median duration of response to intraventricular thiotepa in patients with normal or restored CSF flow (67% of patients) compared with patients with persistent interruption of CSF flow (33% of patients).

Complications of regional chemotherapy included induction of an aseptic chemical meningitis seen in 40% of 348 cycles of therapy. The incidence of aseptic meningitis was similar in patients with normal or obstructed CSF flow. Manifestations of the chemical meningitis included fever, headache, photophobia, nausea, vomiting, meningismus, and occasionally confusion. These symptoms were easily managed by the coadministration of oral dexamethasone (4 mg orally twice per day for 5 days) and in no instance did patients require hospitalization or delay in initiating the next cycle of therapy because of chemical meningitis. Fourteen cycles of regional chemotherapy complicated by aseptic meningitis (10% of all cycles with chemical meningitis) necessitated outpatient administration of intravenous fluids to mitigate dehydration seen as a consequence of nausea or vomiting. The incidence of aseptic meningitis was similar irrespective of the intra-CSF agent (methotrexate, cytosine arabinoside, or thiotepa). Neither leukoencephalopathy nor myelopathy secondary to intra-CSF chemotherapy was observed.

Two patients (6%) developed bacterial meningitis, in one instance related to neurosurgical placement of the Ommaya system and in another secondary to iatrogenic introduction of bacteria during regional chemotherapy administration. In both episodes, *Staphylococcus epidermidis* was cultured from the CSF. Sterilization of CSF was achieved by a combination of intravenous (vancomycin hydrochloride), oral (rifampin), and intraventricular (vancomycin) antibiotics. In both patients, the Ommaya system was preserved; however, antibiotic therapy necessi-

tated a 2- to 3-week delay in initiating or continuing regional chemotherapy.

Twelve patients (38%) developed grade 3 or 4 myelosuppression (Common Toxicity Scale of the Cancer and Leukemia Group B) of whom 4 patients (5 episodes) had neutropenia, 4 patients had anemia (6 episodes), and 4 patients had thrombocytopenia (6 episodes). Four of 5 episodes of neutropenia were associated with fever; however, body fluid cultures were negative for organisms. None of these episodes were believed to be related to regional chemotherapy and all patients were receiving concomitant systemic chemotherapy. Two of 6 episodes of anemia were thought to be attributable to regional chemotherapy; however, systemic chemotherapy was being coadministered, thus confounding interpretation. All 6 episodes of anemia necessitated packed red blood cell transfusion. Two of 6 episodes of thrombocytopenia were also thought to be secondary to regional chemotherapy (all thiotepa); however, again systemic chemotherapy was coadministered, complicating interpretation of causality. All 6 episodes of thrombocytopenia required platelet transfusion. No treatment-related deaths occurred.

Overall survival from the onset of LM-directed therapy ranged from 1 to 12 months (median, 5 months). In 25 patients with normal CSF flow, either at presentation and initial staging (18 patients) or following documentation of CSF block and subsequent treatment with involved-field radiotherapy (7 patients), survival ranged from 2 to 12 months (median, 6 months). In 7 patients with persistent interruption of CSF flow, survival ranged from 1 to 7 months (median, 4 months). Notwithstanding the small number of patients, these data are consistent with prior studies documenting a survival advantage in patients with normal or corrected CSF flow as determined by ¹¹¹In DTPA CSF flow studies.¹⁵ The cause of death in the entire cohort was as follows: 13 (41%) died of progressive systemic disease with stable leptomeningeal disease; 9 (28%) died of leptomeningeal disease with stable systemic disease; and 10 (31%) died of progressive combined systemic and leptomeningeal disease. The cause of death differed in patients with normal or restored CSF flow (25 patients) with 13 patients (52%) dying of progressive systemic cancer, 9 (36%) dying of combined systemic and leptomeningeal disease, and 3 (12%) dying of progressive leptomeningeal cancer. In patients with persistent interruption of CSF flow (7 patients), 6 (86%) died of progressive leptomeningeal disease and 1 (14%) died of combined systemic and leptomeningeal disease. Again, this difference in cause of death was statistically significant ($P < .001$) by both Mantel-Cox log rank and Breslow-Gehan-Wilcoxon rank tests.

COMMENT

Leptomeningeal metastases is a complicated disease for a variety of reasons.¹⁻⁵ First, most reports concerning LM treat all varieties of carcinomatous meningitis as equivalent with respect to CNS staging, treatment, and outcome. However, clinical trials in oncology are based on specific tumor histologic findings. Comparing responses in patients with carcinomatous meningitis at-

tributable to breast cancer with patients with non-small cell lung cancer outside of investigational new drug trials may be misleading.¹⁻⁵ A general consensus is that breast cancer is inherently more chemosensitive than non-small cell lung cancer and therefore survival following chemotherapy is likely to be different.²¹⁻²⁴ This observation has been substantiated in patients with systemic metastases although comparable data regarding CNS metastases, and in particular LM, are meager. To our knowledge, no prior study regarding LM exclusively discusses carcinomatous meningitis attributable to metastatic non-small cell lung cancer.

The most cited article regarding LM is that of Wasserstrom et al,⁴ a study of 90 patients, of whom 23 had lung cancer as their primary tumor. Among this group of 23 patients with lung cancer primaries, in only 17 was LM secondary to metastatic non-small cell lung cancer. A limitation of that study was in the pretreatment extent of CNS disease evaluation, in part because the study preceded the availability of both CT and MRI, and furthermore the authors did not perform radionuclide ventriculography. Similar to later studies, Wasserstrom et al used intraventricular methotrexate, although not according to a concentration \times time drug schedule as in this study. In addition, no second-line or third-line intraventricular chemotherapy was used. Wasserstrom et al reported a 50% response rate and a median survival of 4 months in patients with both small cell and non-small cell lung primaries. These findings are similar to those of 2 other large studies^{25,26} of carcinomatous meningitis in which 25 and 10 patients with non-small cell lung cancer and LM were reported, respectively; however, median survival in both of these studies (1.5 and 2.5 months, respectively) was considerably shorter. These data, and ours, suggest that patients with non-small cell lung cancer complicated by LM can be palliated with aggressive multimodal therapy; however, determining which patients are candidates for aggressive therapy is problematic. Both studies^{25,26} are retrospective and include all patients with a diagnosis of LM; therefore, they included patients preferentially excluded from the studies of Wasserstrom et al and our own, perhaps accounting for the differing patient survival data.

A second feature of LM that complicates therapy is deciding whom to treat.^{1-5,15,25,27,28} Not all patients necessarily warrant aggressive therapy directed to the CNS; however, few guidelines exist to facilitate the appropriate choice of therapy. Previous studies have indicated that performance status and extent of activity of systemic cancer influence outcome in patients with LM. An additional consideration, partially addressed in this study, is the extent of disease in the CNS. A coassociation with epidural spinal cord compression, parenchymal brain metastases, or bulky subarachnoid nodules may identify patients who are poor candidates for intraventricular chemotherapy, but this issue has yet to be systematically addressed. Another perspective on the extent of CNS disease is reflected in the performance of radionuclide ventriculography that assesses compartmentalization of CSF compartments.^{1,2,5,15,27,29} Blockage of CSF flow as demonstrated by radionuclide ventriculography is a result of leptomeningeal cancerous adhesions that prevent ho-

mogeneous distribution of intraventricularly or intrathecally administered chemotherapy. Additionally, as shown in our study and 2 prior studies,^{15,28} survival is affected wherein patients with medically refractory interrupted CSF flow do poorly compared with patients with normal or restored CSF flow. Radionuclide ventriculography may therefore be useful both for prognosis and treatment of patients with LM.

FINALLY, optimal treatment of LM remains poorly defined. Notwithstanding aggressive therapy, treatment of carcinomatous meningitis attributable to non-small cell lung cancer is palliative with a median survival of 6 months in the most favorable patient subset as defined in this study. A provocative study by Siegal et al¹⁶ suggests a subset of patients with LM, predominantly patients with lymphoma or breast cancer, may respond to standard-dose systemic chemotherapy without the inclusion of intra-CSF therapy. Similar conclusions were reached by others,²³⁻²⁵ suggesting the importance of systemic chemotherapy in treating patients with LM. These studies are sufficiently compelling to suggest a prospective study comparing patients with LM treated with systemic chemotherapy with or without intra-CSF chemotherapy. In our study group, no difference was seen in comparing survival or cause of death in patients treated with or without systemic chemotherapy. This difference may reflect the poor chemosensitivity of non-small cell lung cancer in general. A prospective phase 3 study²⁹ of LM compared the use of intraventricular methotrexate with thiotepa, which did not show any difference with respect to response or survival.²⁹ Another cooperative group study³⁰ compared single-agent methotrexate with triple-agent therapy (methotrexate, cytosine arabinoside, and hydrocortisone) and showed no response or survival advantage with triple-agent therapy. The present study suggests that salvage treatment with single-agent therapy results in diminishing effectiveness both with respect to response (50% response to second-line and 33% response to third-line therapies) and durability of response. Finally, there are no studies that compare intermittent vs a concentration \times time drug schedule such as that used in this study in the treatment of patients with LM. Consequently, it is not clear which method of intra-CSF drug therapy is more effective in palliating patients with LM. These studies suggest new therapies are needed to improve outcomes of patients with LM. DepoFoam (Depotech Corp, La Jolla, Calif) encapsulated cytosine arabinoside is a new agent for the treatment of LM that has shown activity in a limited phase 1 trial and is presently in a multi-institutional phase 3 trial comparing methotrexate with DepoFoam cytosine arabinoside in patients with carcinomatous meningitis.³¹ Results of novel trials such as this will hopefully bring in new and more effective therapies for patients with LM.

In conclusion, comprehensive evaluation of the extent of disease in the CNS and aggressive combined modality therapy of patients with non-small cell lung cancer and LM result in modest improvement in survival. Determining which patients are candidates for these com-

plex treatments is difficult; however, radioisotope ventriculography may assist in the selection of appropriate patients for the treatment of LM.

Accepted for publication September 29, 1997.

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