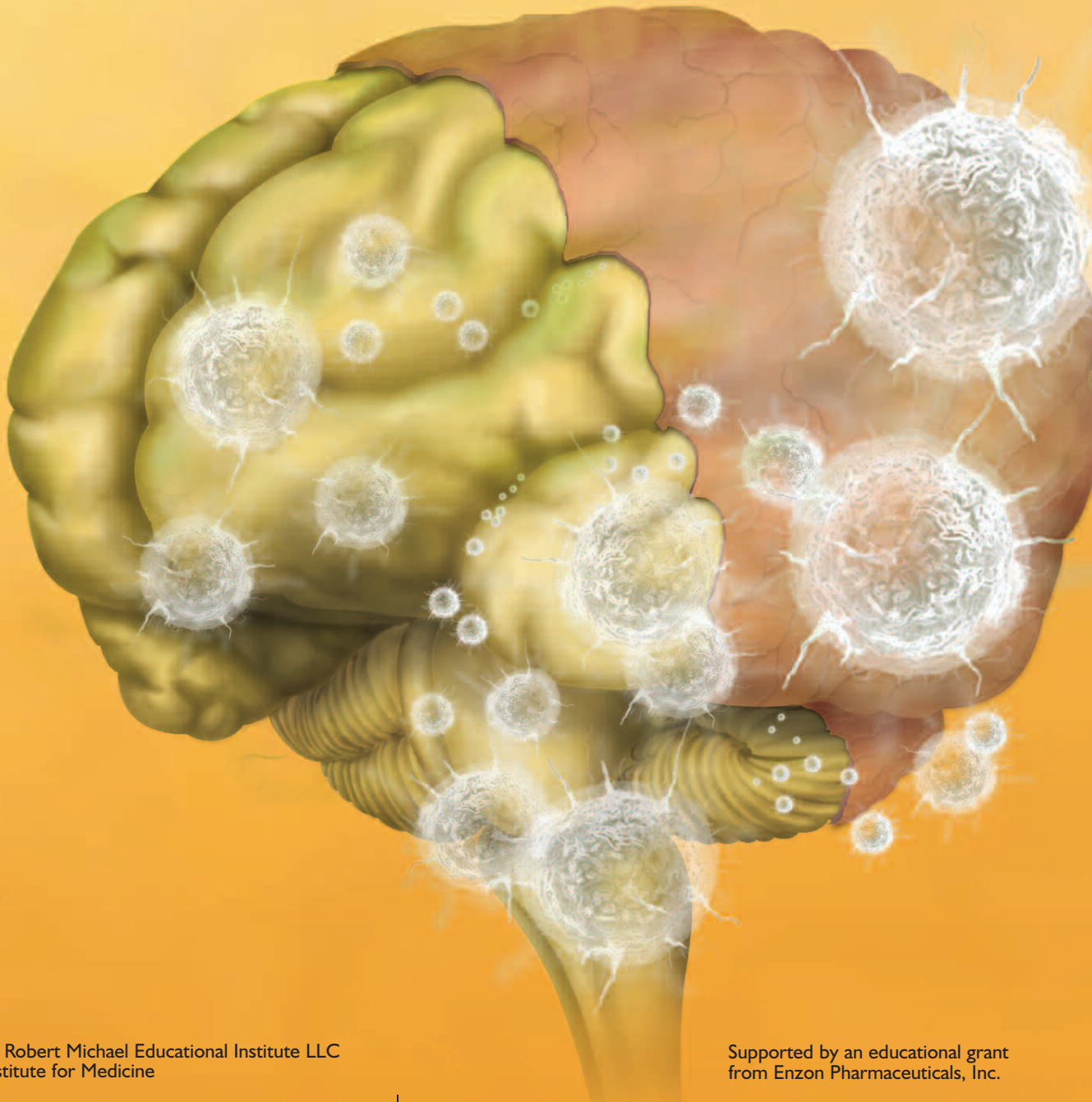
CURRENT CONCEPTS IN
THE DIAGNOSIS AND TREATMENT OF

Neoplastic Meningitis

AN EDUCATIONAL VIRTUAL LECTURE FOR PHYSICIANS, PHARMACISTS AND REGISTERED NURSES

Activity Workbook



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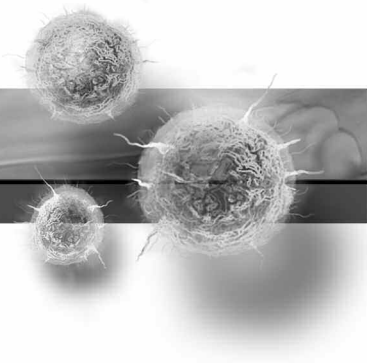
CONTENTS



Target Audience

This virtual lecture has been designated to meet the educational needs of physicians, pharmacists and registered nurses involved in the care of patients with neoplastic meningitis.

Activity Purpose

This virtual lecture is intended to assist clinicians in understanding how to treat and manage patients with neoplastic meningitis.

Statement of Need

Today, more patients are living longer because of effective treatments for cancer. As a result, more patients are at risk for neoplastic meningitis (NM), which occurs when malignant cells enter the cerebrospinal fluid.[1-3] NM is a devastating and ultimately fatal disease.[4] Although treatment remains palliative, it often affords stabilization and protection against further neurological deterioration.[5] When NM is left undiagnosed or untreated, rapid neurological deterioration can occur.[1] Therefore, healthcare professionals should carefully evaluate patients in order to diagnose NM and plan treatment to maximize its effects while minimizing treatment-associated toxicities.[1]

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[1]Armstrong TS, Gilbert MR. The treatment of neoplastic meningitis. *Expert Opin Pharmacother*. 2004;5:1929-1935.
[2]Chamberlain MC, Nolan C, Abrey LE. Leukemic and lymphomatous meningitis: incidence, prognosis and treatment. *J Neurooncol*. 2005;75:71-83.
[3]Chowdhary S, Chamberlain M. Leptomeningeal metastases: current concepts and management guidelines. *J Natl Compr Cancer Netw*. 2005;3:693-703.
[4]Glantz MJ, Jaeckle KA, Chamberlain MC, et al. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. *Clin Cancer Res*. 1999;5:3394-3402.
[5]Chamberlain MC. Neoplastic meningitis. *Neurologist*. 2006;12:179-187.

Educational Objectives

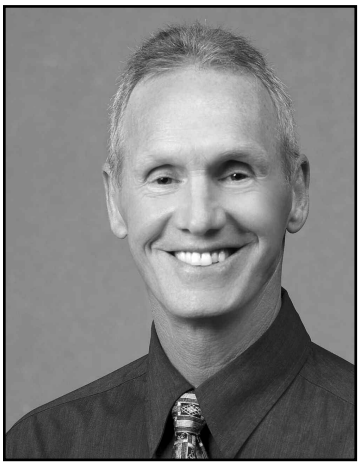
After completing this virtual lecture, the participant should be better able to:

- Describe the epidemiology and pathogenesis of metastatic malignant disease involving the meninges
- Identify signs and symptoms associated with neoplastic meningitis
- Explain methods of diagnosing neoplastic meningitis
- Review existing and emerging treatment options, including intrathecal chemotherapy, systemic chemotherapy and radiation therapy

Marc C. Chamberlain, MD

Professor of Neurology
Department of Neurology
University of Washington

Affiliate Investigator
Fred Hutchinson Cancer Research Center
Seattle, Washington



Marc C. Chamberlain, MD, is Professor of Neurology in the Department of Neurology at the University of Washington and Affiliate Investigator at Fred Hutchinson Cancer Research Center in Seattle, Washington. He is board-certified in both pediatrics and neurology.

After receiving a Bachelor of Arts degree in zoology and a Bachelor of Science degree in biochemistry from the University of California at Berkeley, Dr. Chamberlain earned a medical degree from Columbia University in New York. Subsequently, he completed both an internship and a residency in pediatrics at the Bronx Municipal Hospital Center and a residency in pediatrics at Harbor–UCLA Medical Center in Los Angeles, California. He also completed a fellowship in pediatric neurology at UCLA and an American Cancer Society fellowship.

Dr. Chamberlain is on the editorial boards of *CNS Drugs* and the *American Journal of Cancer* and is a reviewer for numerous journals, including *Cancer*, *Journal of Clinical Oncology, Journal of Neuro-Oncology, Neurology, Archives of Neurology*, and *Lancet Neurology*. He has authored more that 160 articles and 22 book chapters and has presented 200 invited lectures.

Over the years, Dr. Chamberlain developed many of the methods in use today to evaluate and manage neoplastic meningitis. Since 1996, his research has focused increasingly on clinical trials in patients with primary brain tumors.

Physician Continuing Education

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Robert Michael Educational Institute LLC (RMEI) and Postgraduate Institute for Medicine (PIM). PIM is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

Postgraduate Institute for Medicine designates this educational activity for a maximum of *1 AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Accreditation Statement

Postgraduate Institute for Medicine is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Credit Designation

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A statement of credit will be issued only upon receipt of a completed activity Evaluation form and will be mailed to participants within 4 to 6 weeks.

ACPE Release Date: April 25, 2007

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CNA/ANCC

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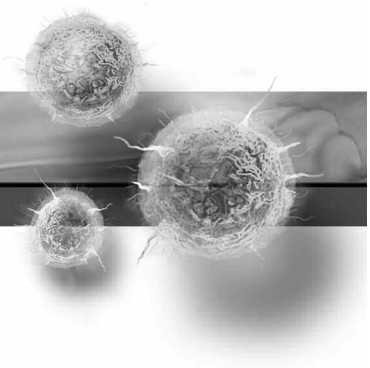
PIM is an approved provider of continuing nursing education by the Colorado Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

California Board of Registered Nursing

Postgraduate Institute for Medicine is approved by the California Board of Registered Nursing, Provider Number 13485 for 1.2 contact hours.



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Dr. Marc C. Chamberlain has asked that we advise participants in this activity that he has an affiliation with Enzon Pharmaceuticals, Inc. and Mundipharma International Limited *(Consultant)*.

The following planners and managers have the following to disclose:

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- **Patricia C. Walter** has no affiliations with commercial interests to disclose.
- **Marie Bialek, PharmD,** has asked that we advise participants in this activity that she has an affiliation with AstraZeneca *(Salary)* and McNeil Consumer & Specialty Pharmaceuticals *(Contractor)*.

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- **Jan Hixon, RN,** has no affiliations with commercial interests to disclose.
- **Linda Graham, RN,** has no affiliations with commercial interests to disclose.
- **Trace Hutchison, PharmD,** has no affiliations with commercial interests to disclose.

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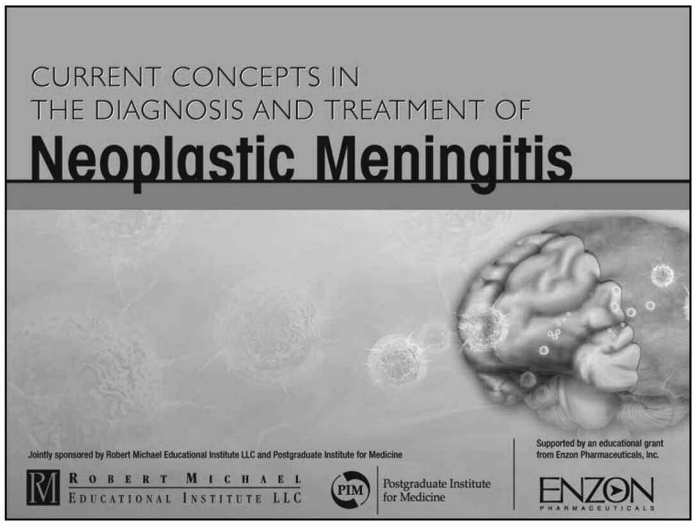
Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without the evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information and comparison with recommendations of other authorities.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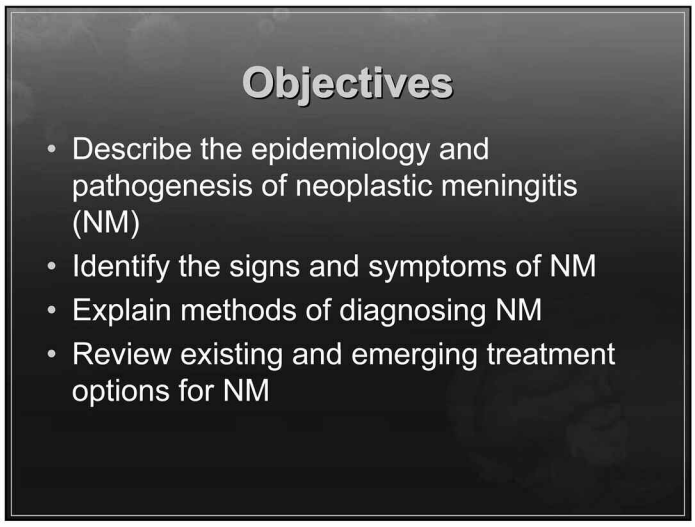
1


Objectives
• Describe the epidemiology and pathogenesis of neoplastic meningitis (NM)
• Identify the signs and symptoms of NM
• Explain methods of diagnosing NM
• Review existing and emerging treatment options for NM

2

Background

- A central nervous system (CNS) metastatic complication in patients with late-stage cancer[1,2]
- Also called leptomeningeal metastasis
  - Carcinomatous meningitis (from solid tumor)[2,3]
  - Lymphomatous meningitis (from systemic lymphoma)[2,3]
  - Leukemic meningitis (from systemic leukemia)
- Malignant cells spread to the leptomeninges and subarachnoid space[1]
- Tumor cells are disseminated within the cerebrospinal fluid (CSF)[1]
- Early diagnosis and treatment are important[1]

1. Gleissner B, Chamberlain MC. *Lancet Neurol.* 2006;5:443-452.
2. Jaeckle KA. *Semin Oncol.* 2006;33:312-323.
3. NCCN Guidelines. V.2.2006. Accessed February 5, 2007.

3

Incidence of Neoplastic Meningitis

- **NM is diagnosed clinically in 3% to 5% of patients with cancer**
- Autopsy studies suggest a higher incidence
  - 4%-15% of solid tumors
  - 5%-15% of leukemia and lymphoma
  - 1%-2% of primary brain tumors

Chamberlain MC. *Neurologist.* 2006;12:179-187.

4

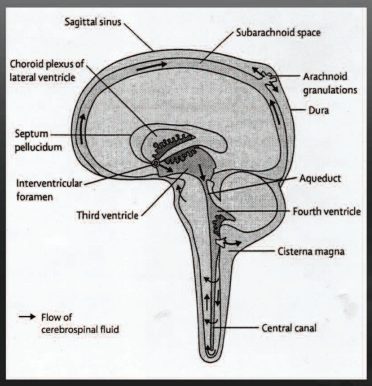
Risk Factors

- Liquid tumors[1,2]
  - Raised lactate dehydrogenase; low serum albumin; <60 years of age
  - Involvement of the testis, breast, or bone marrow
  - More than 2 extranodal sites
  - Brain metastases?
- Solid tumors[3]
  - No risk factors identified
  - HER2-positive breast cancer?
  - Brain metastases?

1. Chamberlain MC. *J Clin Oncol.* 2005;23:3605-3613.
2. Gleissner B, Chamberlain MC. *Lancet Neurol.* 2006;5:443-452.
3. Gabos Z, et al. *J Clin Oncol.* 2006;24:5658-5663.

5

CSF Production and Circulation



Adapted from Gleissner B, Chamberlain MC. *Lancet Neurol.* 2006;5:443-452; with permission.

6

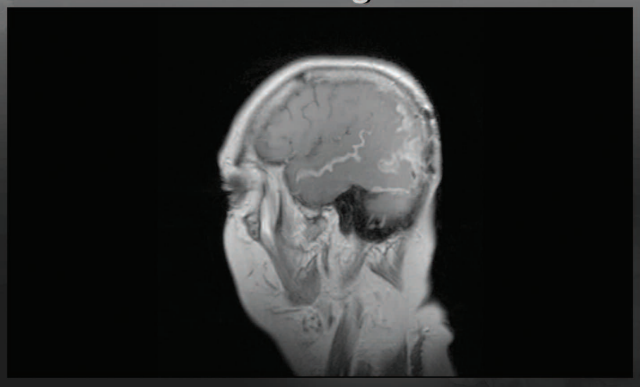
Pathophysiology: Entry of Cancer Cells into the CSF Compartment

- Hematogenous dissemination[1,2]
- Centripetal migration from systemic tumors along perineural or perivascular spaces[1,2]
- Direct extension from contiguous tumor deposits[1-3]
  - Epidural- or dural-based disease
  - Brain parenchyma

1. NCCN Guidelines. V.2.2006. Accessed February 5, 2007.
2. Chamberlain MC. *J Clin Oncol.* 2005;23:3605-3613.
3. Gleissner B, Chamberlain MC. *Lancet Neurol.* 2006;5:443-452.

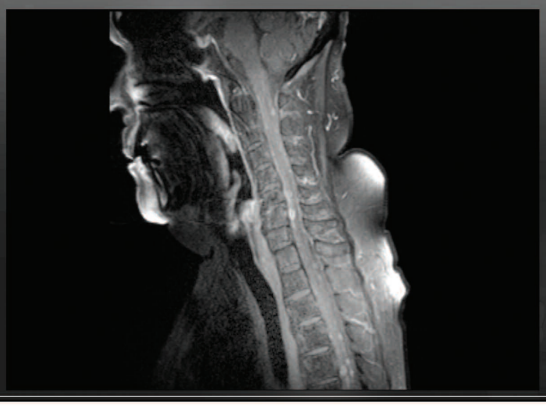
7

Neoplastic Meningitis in Non-Small Cell Lung Cancer: Brain



8

Neoplastic Meningitis in Non-Small Cell Lung Cancer: Spine



9

Signs and Symptoms of NM

	Symptoms	Signs
Cerebral	Headache	Cognitive defects
	Alteration of mentation	Seizures
	Difficulty walking	Gait disturbances
	Nausea and vomiting	Sensory disturbances
	Loss of consciousness	Papilledema
Cranial nerves	Diplopia	Oculomotor paresis III, IV, VI; hypoglossal neuropathy XII
	Hearing loss	
	Visual loss	Trigeminal neuropathy V; diminished gag reflex IX, X; acoustic neuropathy VIII; optic neuropathy II
	Facial numbness	
	Dysphagia	
		Facial paresis VII
Spinal	Focal weakness	Reflex asymmetry
	Paresthesias	Sensory loss
	Back pain	Upper or lower motor neuron weakness
	Radicular pain	Decreased rectal tone
	Bladder and bowel dysfunction	Straight leg raising
		Nuchal rigidity

Adapted from Gleissner B, Chamberlain MC. *Lancet Neurol*. 2006;5:443-452; with permission.

10

Etiology of Signs and Symptoms

- Injury to nerves that traverse the subarachnoid space
- Direct tumor invasion of the brain or spinal cord
- Alteration in the local blood supply
- Obstruction of normal CSF flow pathways

NCCN Guidelines. V.2.2006; Accessed February 5, 2007.

11

Diagnosis of Suspected NM

Symptoms compatible with NM
↓
Cranial and spinal MRI
↓
CSF analysis

- **Diagnosis can be made by[1]**
  - **Clinical signs and symptoms**
  - **Radiology**
  - **Cytology**
- **Cytology is persistently[2] negative in ~50% of patients with NM**

1. Gleissner B, Chamberlain MC. *Lancet Neurol.* 2006;5:443-452.
2. Glass JP, et al. *Neurology.* 1979;29:1369-1375.

12

Findings on CSF Examination

CSF Findings	Initial Examination (%)	Total Examinations (%)
Opening pressure >150 mm H_2O	30-57	61-72
White blood cells >4 mm^3	57-64	72-79
Protein >50 mg/dL	73-86	79-91
Glucose <60 mg/dL	31-55	41-77
Positive cytology	45-73	77-100

A composite from 5 studies in more than 300 patients.

Kaplan JG, et al. *J Neurol Oncol.* 1990;9:225-229.
Wasserstrom WR, et al. *Cancer.* 1982;49:759-772.
Balm M, Hammack L. *Arch Neurol.* 1996;53:626-632.
Theodore WH, Gendelman S. *Arch Neurol.* 1981;38:696-699.
Olson ME, et al. *Arch Neurol.* 1974;30:122-137.

13

Sensitivity of CSF Analysis

- False-negative results are common (40% to 60%)
- Prospective evaluation of 39 patients with NM suggests sample size of at least 10.5 mL required to ensure a 3% false-negative rate

Glantz MJ, et al. *Cancer.* 1998;82:733-739.

14

CSF Analysis in Liquid Tumors

- Another analytic method is flow cytometry together with 2 to 4 fluorescence markers (FACS)[1]
- Polymerase chain reaction (PCR) amplification of IgH genes is useful for lymphomatous meningitis[2]
  - Each clonal lymphoma cell is characterized by a unique rearranged cell surface heavy chain immunoglobulin (IgH) or T-cell receptor

1. Gleissner B, Chamberlain M. *J Neurooncol.* 2007; Feb 28 [Epub ahead of print].
2. Gleissner B, et al. *Neurology.* 2002;58:390-396.

15

Use of Magnetic Resonance Imaging

- Gadolinium (Gd)-enhanced MRI imaging is the technique of choice
- Imaging of the entire CNS axis (brain and spine) is required
- T1-weighted with contrast and T2-weighted images with fat suppression

Chamberlain MC. *Neurologist.* 2006;12:179-187.
Glass JP, et al. *Neurology.* 1979;29:1369-1375.

16

Cranial MRI Findings in NM

Neuroimaging Abnormality	Chamberlain, 1990 (N=14) (%)	Balm, 1996 (N=126) (%)
Parenchymal volume loss	93	
Focal or diffuse enhancement of		
Sulci or convexity	57	
Cisterns	28	
Tentorium	21	
Ependymal	21	
Nodules		
Subarachnoid	36	
Parenchymal	43	
Hydrocephalus	7	16
Communicating		14
Obstructive		2
Parenchymal metastases	43	24
Single		18
Multiple		6

Chamberlain MC, et al. *Neurology*. 1990:40:435-438. Balm M, et al. *Arch Neurol*. 1996;53:626-632.

17

Neuroradiographic Differential Diagnosis

- Inflammatory disease
- Infectious disease
- Granulomatous disease (ie, sarcoid)
- Iatrogenic disease (ie, chemical meningitis)
- Stroke (ie, cortical thrombosis, subarachnoid hemorrhage)
- Intracranial surgery
- Low-pressure syndromes
- Trauma

Gleissner B, Chamberlain MC. *Lancet Neurol*. 2006;5:443-452.

18

Radioisotope CSF Flow Studies (1)

- CSF flow obstruction is common in NM[1-4]
  - Approximately one third of patients with solid tumor NM
  - No data on incidence in liquid tumor NM
  - Blocks are most common at base of skull, spinal canal, and over the cerebral convexities
- CSF flow studies are performed in most nuclear medicine departments
- Technique of choice[4,5]
  - Indium 111-DTPA (only FDA-approved method)
  - ^{99m}Technetium macroaggregated albumin

1. Chamberlain MC. *J Clin Oncol.* 2005;23:3605-3613.
2. Chamberlain MC. *J Neurooncol.* 1995;23:233-238.
3. Glantz MJ, et al. *Cancer.* 1995;75:2919-2931.
4. Trump DL, et al. *Arch Intern Med.* 1982;142:583-586.
5. Chamberlain MC. *J Neurooncol.* 1998;38:135-140.

19

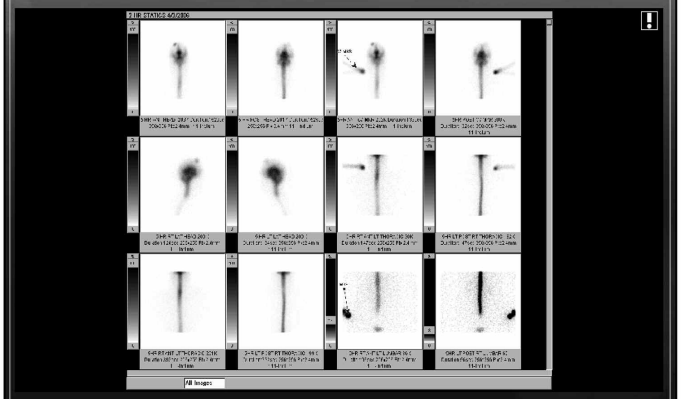
Radioisotope CSF Flow Studies (2)

- Used as an adjunct to treatment planning
- Enable detection of flow abnormalities in patients considered for treatment
  - Risk for toxicity increases in patients with ventricular outlet obstruction
  - Obstruction of CSF flow prevents drug dissemination

Chamberlain MC. *J Clin Oncol.* 2005;23:3605-3613.

20

Indium 111-DTPA CSF Flow Study



21

Treatment of CSF Flow Obstruction

- Radiation therapy to sites of obstructions
  - One third of CSF obstructions are in the brain
    - 50% resolve after radiotherapy[1]
  - Two thirds of CSF obstructions are in the spine
    - 35% resolve after radiotherapy[1]
- May obviate need for CSF shunting

Gleissner B, Chamberlain MC. *Lancet Neurol.* 2006;5:443-452.

22

Treatment Goals

- Maintain neurological quality of life[1]
- Stabilize or improve neurological symptoms[1-3]
- Extend survival[1-3]

1. Chamberlain MC. *Neurologist.* 2006;12:179-187.
2. Gleissner B, Chamberlain MC. *Lancet Neurol.* 2006;5:443-452.
3. NCCN Guidelines. V.2.2006. Accessed February 5, 2007.

23

Stratification for Treatment

Poor Risk Group
- Low KPS
- Multiple, serious, or major neurological deficits
- Extensive systemic disease with few treatment options
- Bulky CNS disease
- NM-related encephalopathy
- CSF block

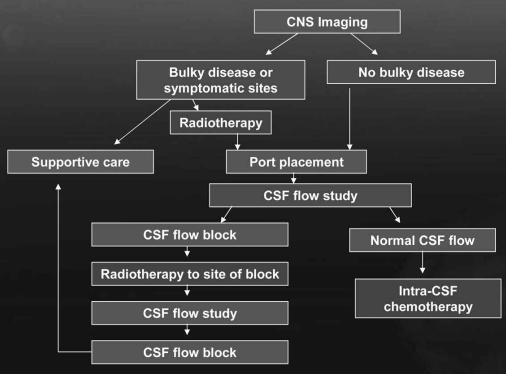
Good Risk Group
- High KPS
- No major neurological deficits
- Minimal systemic disease
- Reasonable systemic treatment options
- No CSF block

KPS = Karnofsky Performance Status.

NCCN Guidelines. V.2.2006. Accessed February 5, 2007.

24

Treatment Algorithm



Adapted from Chamberlain MC. *J Clin Oncol.* 2005;23:3605-3613; with permission.

25

Radiotherapy for NM

- Palliate symptoms
- Treat bulky disease
- Correct CSF flow abnormalities
- Therapy type
  - Involved-field irradiation
  - Craniospinal irradiation

Chamberlain MC. *J Clin Oncol.* 2005;23:3605-3613.

26

Surgery for NM

- Placement of port for intraventricular therapy
- CSF diversion for patients with symptomatic hydrocephalus[1]
- Meningeal biopsy

1. Omuro AM, et al. *Neurology.* 2005;64:1625-1627.

27

Treatment Options for NM

- Regional or intra-CSF chemotherapy
- High-dose systemic chemotherapy
- Craniospinal irradiation

28

Treatment: Intra-CSF Chemotherapy

- Three agents used most often
  - Methotrexate
  - Cytarabine (including the liposomal form)
  - Thiotepa
- Toxicity and complications of treatment
  - Primary toxicity of intra-CSF chemotherapy is transient chemical meningitis
    - May last for 4 to 5 days
    - May be associated with confusion, seizures, fever, stiff neck, photophobia, nausea, vomiting, and headache
  - Device- or port-related complications
    - Failure
    - Infection

Chamberlain MC. *J Clin Oncol.* 2005;23:3605-3613.

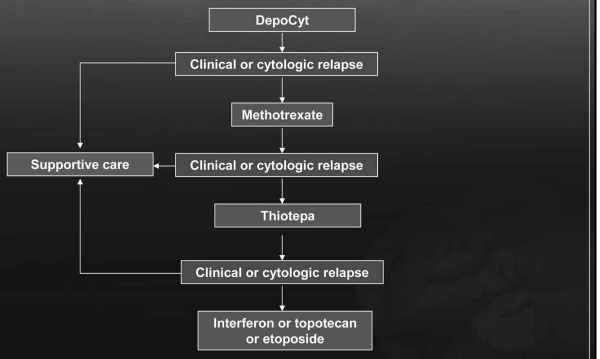
29

	INDUCTION		CONSOLIDATION		MAINTENANCE	
	Bolus	CxT	Bolus	CxT	Bolus	CxT
Methotrexate	10-15 mg 2 x wk x 4wk	2 mg/d x 5d QOW x 8wk	10-15 mg 1 x wk x 4wk	2 mg/d x 5d QOW x 4wk	10-15 mg Qmo	2 mg/d x 5d Qmo
Cytarabine	25-100 mg 2 or 3 x wk x 4wk	25 mg/d x 3d/wk x 4wk	25-100 mg 1 x wk x 4wk	25 mg/d x 3d QOW x 4wk	25-100 mg Qmo	25 mg/d x 3d Qmo
DepoCyt®*	50 mg Q14d for 2 doses		50 mg Q14d for 3 doses plus 1 dose at 13wk		50 mg Q28d for 4 doses	
Thiotepa	10 mg 2 or 3 x wk x 4wk	10 mg/d x 3d/wk x 4wk	10 mg 1 x wk x 4wk	10 mg/d x 3d QOW x 4wk	10 mg Qmo	10 mg/d x 3d Qmo
Alpha-Interferon	1 x 10^6 U 3 x wk x 4wk		1 x 10^6 U 3 x wk QOW x 4wk		1 x 10^6 U 3 x wk x 1wk/mo	
Etoposide		0.5 mg/d x 5d QOW x 8wk				0.5 mg/d x 5 d Qmo
Topotecan	0.4 mg 2 x wk x 4wk		0.4 mg 2 x wk QOW x 4 wk		0.4 mg 2 x wk Qmo	

*Administer concomitantly with dexamethasone 4 mg bid PO or IV for 5 days beginning on first day of DepoCyt injection.
CxT = Concentration x time; QOW = every other week; Qmo = every month.
Chamberlain MC. *Neurologist.* 2006;12:179-187. Chamberlain MC, et al. *Cancer.* 2006;106:2021-2027.

30

Intra-CSF Chemotherapy



Adapted from Chamberlain MC. *Neurologist.* 2006;12:179-187; with permission.

31

Randomized Clinical Trial Data (1)

Study	Design	Response	Toxicity
Shapiro et al. ASCO Annual Meeting Proc. *J Clin Oncol.* 2006;24(June 6 Suppl):1528	Solid tumors (n=103) DepoCyt vs MTX Lymphoma (n=25) DepoCyt vs Ara-C	DepoCyt vs MTX/Ara-C: PFS*: 35 vs 43 d DepoCyt vs MTX: PFS: 35 vs 37.5 DepoCyt vs Ara-C: CR*: 33.3% vs 16.7% PFS: 34 vs 50 d	DepoCyt vs MTX/Ara-C: Drug-related AEs: 48% vs 60% Serious AEs: 86% vs 77%
Boogerd et al. *Eur J Cancer.* 2004;40:2726-2733	N=35 Breast cancer IT vs no IT †	IT vs no IT: Improvement or stabilization: 59% vs 67% TTP: 23 vs 24 wk Median survival: 18.3 vs 30.3 wk	IT vs no IT: Neurological complications: 47% vs 6%
Glantz et al. *J Clin Oncol.* 1999;17:3110-3116	N=28 Lymphoma DepoCyt vs Ara-C	DepoCyt vs Ara-C: TTP*: 78.5 vs 42 d OS*: 99.5 vs 63 d RR: 71% vs 15%	DepoCyt vs Ara-C: Headache: 27% vs 2%; nausea: 9% vs 2%; fever: 8% vs 4%; pain: 5% vs 4%; confusion: 7% vs 0%; somnolence: 8% vs 4%

* No significant differences between groups.
† Appropriate systemic chemotherapy and/or radiotherapy given in both arms.

32

Randomized Clinical Trial Data (2)

Study	Design	Response	Toxicity
Glantz et al. *Clin Cancer Res.* 1999;5:3394-3402	N=61 Solid tumors (eg, breast, SCLC, NSCLC in 52%) DepoCyt vs MTX	DepoCyt vs MTX: RR* 26% vs 20% OS* 105 vs 78 d TTP 58 vs 30 d	DepoCyt vs MTX: Sensory/motor: 4% vs 10%; altered mental status: 5% vs 2%; headache: 4% vs 2%
Grossman et al. *J Clin Oncol.* 1993;11:561-569	N=59 Nonleukemic malignancy (breast, lung, lymphatic in 90%) IT MTX vs thiotepa	IT MTX vs thiotepa: Neurological improvements: none Median survival: 15.9 vs 14.1 wk	IT MTX vs thiotepa: Serious toxicities similar between groups. Mucositis and neurological complications more common in MTX group
Hitchins et al. *J Clin Oncol.* 1987;5:1655-1662	N=44 Nonleukemic malignancy (eg, SCLC, breast cancer, adenocarcinoma unknown primary in 70%) IT MTX vs MTX + Ara-C	IT MTX vs MTX + Ara-C: RR*: 61% vs 45% Median survival*: 12 vs 7 wk	IT MTX vs MTX + Ara-C: N/V: 36% vs 50%; septicemia, neutropenia: 9% vs 15%; mucositis: 14% vs 10%; pancytopenia: 9% vs 10%. AEs related to reservoir: blocked port: 17% vs 0%; intracranial hemorrhage: 11% vs 0%

*No significant differences between groups.

AEs=adverse events; CR=complete response; MTX=methotrexate; NSCLC=non-small cell lung cancer; N/V=nausea/vomiting; OS=overall survival; PFS=progression-free survival; RR=response rate; SCLC=small cell lung cancer; TTP=time to progression.

33

Novel Intra-CSF Chemotherapy

- Etoposide in adults with solid or liquid NM[1]
  - RR of 26% (7/27); reversible arachnoiditis (4/27)
- Topotecan in children and adults with solid or liquid NM
  - RR of 26% (6/23); arachnoiditis DLT (phase I)[2]
  - RR/no change in 16% (5/30); mild toxicity (phase II)[3]
- Mafosfamide in children with brain tumors[4]
  - RR of 42% (11/26) (median follow-up, 26.5 mo)
  - Immediate toxicities manageable

1. Chamberlain MC, et al. *Cancer.* 2006;106:2021-2027.
2. Blaney SM , et al. *J Clin Oncol.* 2003;21:143-147.
3. Groves MD, et al. *Neurology.* 2004;62:475 [Abstract].
4. Slavc I, et al. *J Neurooncol.* 2003;64:239-247.

34

Intra-CSF Biological Agents

- Alpha-interferon[1]
- Rituximab[2]
  - Maximum tolerated dose in one recent, small, Phase I study: 25 mg twice weekly by Ommaya reservoir for a maximum of 9 doses
- Trastuzumab[3]
- Preclinical studies of nonradioactive antibodies[4] or immunoconjugates[5]

1. Chamberlain MC. *Cancer.* 2002;15:2675-2680.
2. Rubenstein JL, et al. *J Clin Oncol.* 2007;25:1350-1356.
3. Laufman LR, Foprsthoefel KF. *Clin Breast Cancer.* 2002;2:316.
4. Bergman I, et al. *Int J Cancer.* 1999;112:538-548.
5. Bigner DD, et al. *Clin Cancer Res.* 1995;1:1545-1555.

35

Radioisotopes and Radioimmunoconjugates

- Unconjugated iodine 131[1]
  - Low toxicity with transient improvements (n=31)
- ^{131}I-radiolabeled monoclonal antibodies
  - Case study reported complete response[2]
  - In neuroectodermal tumors, RR was 53%[3]
- I-conjugated antibody to chondroitin proteoglycan sulfate and tenascin[4]
  - CSF or radiographic response achieved; prolonged survival

Wong F, et al. *Neurology.* 2006;66 [Abstract EV6.002].
Cokgor I, et al. *Cancer.* 2001;91:1809-1813.
Bigner DD, et al. *J Neurooncol.* 1995;24:109-122.
Coakham HB, Kemshead JT. *J Neurooncol.* 1998;38:225-232.

36

Supportive Care

- Radiation to symptomatic and bulky sites
- Anticonvulsants for seizure control
- Adequate analgesia
- Antidepressants, anxiolytics
- Corticosteroids (of limited use)
- Antiemetics
- Psychostimulants

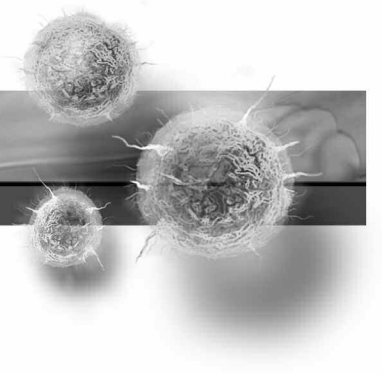
Chamberlain MC. *J Clin Oncol.* 2005;23:3605-3613.
Chamberlain MC. *Neurologist.* 2006;12:179-187.
Chamberlain MC. *Arch Neurol.* 1997;54:16-17.

37

Challenges and Complications (1)

- Does intra-CSF chemotherapy contribute to outcome?
- Does site of drug administration matter (ie, intraventricular vs intralumbar)?
- Does positive CSF cytology have clinical relevance?
- Is extent and progression of neurological disease the most relevant outcome measure?
- Can clinicians reliably distinguish between deaths due to NM compared with systemic disease?

38



Challenges and Complications (2)

- What is the role for intra-CSF chemoprophylaxis aside from ALL?
- Do CSF-negative patients differ from CSF-positive patients?
- What is the role of radioisotope CSF flow studies?
- Is there a preferred intra-CSF drug and schedule?
- What characteristics define a patient for which intra-CSF chemotherapy is reasonable?
- Is there a role for systemic chemotherapy in improving outcomes independent of intra-CSF chemotherapy?

39

Conclusions

- Intra-CSF chemotherapy is the primary therapy for neoplastic meningitis
- Most patients require a combination of intra-CSF chemotherapy and radiotherapy
- Treatment may prolong survival and improve QOL
  - No *significant* survival advantages at this time
- Recommend treatment only for a subset of patients
- Further studies are needed to improve outcomes

40

REFERENCES

Balm M, Hammack J. Leptomeningeal carcinomatosis. Presenting features and prognostic factors. *Arch Neurol*. 1996;53:626-632.

Bergman I, Barmada MA, Heller G, Griffin JA, Cheung N-K. Treatment of neoplastic meningeal xenografts by intraventricular administration of an antiganglioside monoclonal antibody, 3F8. *Int J Cancer.* 1999;82:538-548.

Bigner DD, Archer GE, McLendon RE, Friedman HS, Fuchs HE, Pai LH, Herndon JE II, Pastan IH. Efficacy of compartmental administration of immunotoxin LMB-1 (B3-LysPE38) in a rat model of carcinomatous meningitis. *Clin Cancer Res*. 1995;1:1545-1555.

Bigner DD, Brown M, Coleman RE, Friedman AH, Friedman HS, McLendon RE, Bigner SH, Zhao X-G, Wikstrand CJ, Pegram CN, Kerby T, Zalutsky MR. Phase I studies of treatment of malignant gliomas and neoplastic meningitis with (131)I-radiolabeled monoclonal antibodies anti-tenascin 81C6 and anti-chondroitin proteoglycan sulfate Mel-14 F $(ab')_2$: a preliminary report. *J Neurooncol*. 1995;24:109-122.

Blaney SM, Heideman R, Berg S, Adamson P, Gillespie A, Geyer JR, Packer R, Matthay K, Jaeckle K, Cole D, Kuttesch N, Poplack DG, Balis FM. Phase I clinical trial of intrathecal topotecan in patients with neoplastic meningitis. *J Clin Oncol*. 2003;21:143-147.

Boogerd W, van den Bent MJ, Koehler PJ, Heimans JJ, van der Sande JJ, Aaronson NK, Hart AA, Benraadt J, Vecht ChJ. The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomized study. *Eur J Cancer*. 2004;40:2726-2733.

Chamberlain MC. A phase II trial of intra-cerebrospinal fluid alpha interferon in the treatment of neoplastic meningitis. *Cancer*. 2002;94:2675-2680.

Chamberlain MC. Carcinomatous meningitis. *Arch Neurol*. 1997;54:16-17.

Chamberlain MC. Comparative spine imaging in leptomeningeal metastases. *J Neurooncol*. 1995;23:233-238.

Chamberlain MC. Neoplastic meningitis. *J Clin Oncol*. 2005;23:3605-3613.

Chamberlain MC. Neoplastic meningitis. *Neurologist*. 2006;12:179-187.

Chamberlain MC. Radioisotope CSF flow studies in leptomeningeal metastases. *J Neurooncol*. 1998;38:135-140.

Chamberlain MC, Sandy AD, Press GA. Leptomeningeal metastasis: a comparison of gadolinium-enhanced MR and contrast-enhanced CT of the brain. *Neurology*. 1990; 40:435-438.

Chamberlain MC, Tsao-Wei DD, Groshen S. Phase II trial of intracerebrospinal fluid etoposide in the treatment of neoplastic meningitis. *Cancer*. 2006;106:2021-2027.

Coakham HB, Kemshead JT. Treatment of neoplastic meningitis by targeted radiation using (131)I-radiolabelled monoclonal antibodies. Results of responses and long term follow-up in forty patients. *J Neurooncol*. 1998;38:225-232.

Cokgor I, Akabani G, Friedman HS, Friedman AH, Zalutsky MR, Zehngebot LM, Provenzale JM, Guy CD, Wikstrand CJ, Bigner DD. Long term response in a patient with neoplastic meningitis secondary to melanoma treated with (131)I-radiolabeled antichondroitin proteoglycan sulfate Mel-14 $F(ab')_2$: a case study. *Cancer*. 2001;91:1809-1813.

Gabos Z, Sinha R, Hanson J, Chauhan N, Hugh J, Mackey JR, Abdulkarim B. Prognostic significance of human epidermal growth factor receptor positivity for the development of brain metastasis after newly diagnosed breast cancer. *J Clin Oncol*. 2006;24:5658-5663.

Glantz MJ, Cole BF, Glantz LK, Cobb J, Mills P, Lekos A, Walters BC, Recht LD. Cerebrospinal fluid cytology in patients with cancer: minimizing false-negative results. *Cancer*. 1998;82:733-739.

Glantz MJ, Hall WA, Cole BF, Chozick BS, Shannon CM, Wahlberg L, Akerley W, Marin L, Choy H. Diagnosis, management, and survival of patients with leptomeningeal cancer based on cerebrospinal fluid-flow status. *Cancer*. 1995;75:2919-2931.

Glantz MJ, Jaeckle KA, Chamberlain MC, Phuphanich S, Recht L, Swinnen LJ, Maria B, LaFollette S, Schumann GB, Cole BF, Howell SB. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. *Clin Cancer Res*. 1999; 5:3394-3402.

Glantz MJ, LaFollette S, Jaeckle KA, Shapiro W, Swinnen L, Rozental JR, Phuphanich S, Rogers LR, Gutheil JC, Batchelor T, Lyter D, Chamberlain M, Maria BL, Schiffer C, Bashir R, Thomas D, Cowens W, Howell SB. Randomized trial of a slow-release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. *J Clin Oncol*. 1999;17:3110-3116.

Glass JP, Melamed M, Chernik NL, Posner JB. Malignant cells in cerebrospinal fluid (CSF): the meaning of a positive CSF cytology. *Neurology*. 1979;29:1369-1375.

Gleissner B, Chamberlain M. Treatment of CNS dissemination in systemic lymphoma. *J Neurooncol*. 2007; 84:107-117.

REFERENCES

Gleissner B, Chamberlain MC. Neoplastic meningitis. *Lancet Neurol*. 2006;5:443-452.

Gleissner B, Siehl J, Korfel A, Reinhardt R, Thiel E. CSF evaluation in primary CNS lymphoma patients by PCR of the CDR III IgH genes. *Neurology*. 2002;58:390-396.

Grossman SA, Finkelstein DM, Ruckdeschel JC, Trump DL, Moynihan T, Ettinger DS. Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. Eastern Cooperative Oncology Group. *J Clin Oncol*. 1993; 11:561-569.

Groves MD, Baumgartner KE, Conrad CA, Chamberlain M, Hsu S, Glantz M, Gilbert M, Forman A, Puduvalli V, Colman H, Yung A. A phase II study of intrathecal topotecan in patients with meningeal malignancies. *Neurology*. 2004; 62:475 [Abstract].

Hitchins RN, Bell DR, Woods RL, Levi JA. A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. *J Clin Oncol*. 1987;5:1655-1662.

Jaeckle KA. Neoplastic meningitis from systemic malignancies: diagnosis, prognosis and treatment. *Semin Oncol*. 2006;33:312-323.

Kaplan JG, DeSouza TG, Farkash A, Shafran B, Pack D, Rehman F, Fuks J, Portenoy R. Leptomeningeal metastases: comparison of clinical features and laboratory data of solid tumors, lymphomas and leukemias. *J Neurol Oncol*. 1990; 9:225-229.

Laufman LR, Forsthoefel KF. Use of intrathecal trastuzumab in a patient with carcinomatous meningitis. *Clin Breast Cancer*. 2001;2:235.

NCCN Guidelines. Central and nervous system cancers. V.2.2006; Available at: http://www.nccn.org/professionals/physician_gls/PDF/cns.pdf Accessed February 5, 2007.

Olson ME, Chernik, NL, Posner JB. Infiltration of the leptomeninges by systemic cancer: a clinical and pathologic study. *Arch Neurol*. 1974;30:122-137.

Omuro AM, Lallana EC, Bilsky MH, DeAngelis LM. Ventriculoperitoneal shunt in patients with leptomeningeal metastasis. *Neurology*. 2005;64:1625-1627.

Rubenstein JL, Fridlyand J, Abrey L, Shen A, Karch J, Wang E, Issa S, Damon L, Prados M, McDermott M, O'Brien J, Haqq C, Shuman M. Phase I study of intraventricular administration of rituximab in patients with recurrent CNS and intraocular lymphoma. *J Clin Oncol*. 2007;25:1350-1356.

Shapiro WR, Schmid M, Glantz M, Miller JJ. A randomized phase III/IV study to determine benefit and safety of cytarabine liposome injection for treatment of neoplastic meningitis. 2006 ASCO Annual Meeting Proceedings Part I. *J Clin Oncol*. 2006;24 (June 6 Suppl):1528.

Slavc I, Schuller E, Falger J, Günes M, Pillwein K, Czech T, Dietrich W, Rössler K, Dieckmann K, Prayer D, Hainfellner J. Feasibility of long-term intraventricular therapy with mafosfamide (n=26) and etoposide (n=11): experience in 26 children with disseminated malignant brain tumors. *J Neurooncol*. 2003;64:239-247.

Theodore WH, Gendelman S. Meningeal carcinomatosis. *Arch Neurol*. 1981;38:696-699.

Trump DL, Grossman SA, Thompson G, Murray K. CSF infections complicating the management of neoplastic meningitis: clinical features and results of therapy. *Arch Intern Med*. 1982;142:583-586.

Wasserstrom WR, Glass JP, Posner, JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. *Cancer*. 1982;49:759-772.

Wong F, Groves M, Conrad C, et al. A phase I study of intraventricular injection of I-131 sodium iodide in patients with leptomeningeal metastases. *Neurology*. 2006;66 [Abstract EV 6.002].

NOTES