

Diagnostic Tools for Neoplastic Meningitis: Detecting Disease, Identifying Patient Risk, and Determining Benefit of Treatment

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Three methods are routinely used to diagnose neoplastic meningitis (NM): clinical signs and symptoms, cerebrospinal fluid (CSF) cytology, and magnetic resonance imaging (MRI) of the brain and spine. Clinical manifestations are often subtle or may be ascribed to other cancer complications, eg, treatment-related disorders or brain parenchymal metastases. CSF cytology has a high specificity (>95%), but its sensitivity is generally less than 50%. MRI sensitivity and specificity vary with the type of primary cancer; overall, MRI findings consistent with leptomeningeal disease are detected in fewer than 50% of NM patients. While most clinicians evaluate CSF cytology along with MRI and the clinical examination, underdiagnosis is a major problem, since many patients are both cytologically and radiographically negative. Failure to consider NM in the differential diagnosis magnifies the problem of underdiagnosis. CSF flow cytometry is particularly promising for evaluating NM from hematologic cancers, with a diagnostic sensitivity many fold greater than conventional cytology. Research has focused on identifying biochemical markers of tumor cells in the CSF. For example, molecules involved in CNS penetration (eg, matrix metalloproteinases and cathepsins), tumor cell tropism (eg, chemokines CXCL8 and CCL18), and angiogenesis (eg, vascular endothelial growth factor) are elevated in the CSF of patients with NM. Evidence that some tumor types are more likely to infiltrate the CNS also has stimulated research into primary tumor markers predictive of CNS metastases. At present, there is no tumor marker or patient characteristic that reliably predicts the development of NM, and diagnosis still relies on suggestive signs and symptoms, positive CSF cytology, or a consistent MRI—all late manifestations of NM. Until techniques capable of detecting NM early are developed, increased awareness of the disease and standardized evaluation are likely to have the greatest impact on improving diagnosis and implementing earlier treatment. *Semin Oncol* 36 (Suppl 2):S35-S45 © 2009 Elsevier Inc. All rights reserved.

Neoplastic meningitis (NM) is a devastating neurologic complication of cancer that is clinically diagnosed in 4% to 15% of patients with solid tumors, 5% to 15% of patients with leukemia and lym-

phoma, and 1% to 2% of patients with primary brain tumors.^{1,2} However, NM remains underdiagnosed, as postmortem estimates of the true incidence of the disease across all cancers approach 5%.^{2,3} Currently, three independent methods are used to diagnose NM: clinical presentation (ie, neurological signs and symptoms), cerebral spinal fluid (CSF) cytology and flow cytometry, and central nervous system (CNS) neuroradiographic examination with magnetic resonance imaging (MRI).^{2,4} Nonetheless, each of these methods is limited by either suboptimal sensitivity or specificity. For example, CNS signs and symptoms, which are the first indication of NM in the majority (>90%) of patients, are often subtle, unrecognized, and may be difficult to distinguish from manifestations of the primary disease or the neurological side effects of cancer treatment.² In contrast, the often touted standard for NM diagnosis, cytological detection of malignant cells in the CSF, is highly specific for NM but has a low sensitivity (<50%), based on the only autopsy study comparing pre- and postmortem diagnosis.³ The neuroradiographic method of choice, contrast-enhanced brain

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Table 1. Problems Associated With the End Points Currently Used to Assess Treatment Response in Patients With Neoplastic Meningitis

End Point	NM-Specific Examples	Confounders and Concerns
Tumor response	CSF cytologic clearing Resolution of MRI abnormalities	Lack of correlation with other measures Test imprecision Ignores quality of survival
Survival	Time from diagnosis to death Time from first treatment to death	Variation in subsequent care Death from non-CNS cancer Ignores quality of survival
Cause of death	NM-specific death	Variation in subsequent care Lack of reliable criteria Poor correlation with other end points Usually unblended
Surrogate markers	Change in CSF markers Quantitative CSF cytology	Restricted availability Lack of correlation with other measures Ignores quality of survival
Time to tumor progression (laboratory)	MRI improvement Quantitative change in cytology	Lack of correlation with other measures Test imprecision
Time to tumor progression (clinical)	Measures of performance (KPS, etc) Quality-of-life assessment Change in cognitive performance	Usually unblinded Often cumbersome Test imprecision

Abbreviations: NM, neoplastic meningitis; CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; KPS, Karnofsky performance score.

and spine MRI, is limited to detecting NM in approximately 40% to 60% of cases.⁵

The lack of sensitive and specific diagnostic tools has presented difficulties for the diagnosis and treatment of patients with NM, as well as for the design of clinical trials evaluating new treatments (Table 1).⁶ To date, all clinical trials evaluating the treatment of NM have relied upon either the demonstration of positive CSF cytology or neuroradiography consistent with a diagnosis of NM. Furthermore, there are limited data comparing outcomes in patients diagnosed with NM by positive CSF cytology and negative neuroradiography versus patients with negative (or positive) CSF cytology and positive neuroradiography.⁷ Some authors have proposed that patients with NM and radiographic bulky disease, as defined by MRI of the brain and spine, represent a population of NM patients in whom outcome is poor,^{6,8,9} although the one study evaluating this hypothesis found that tumor burden did not inversely correlate with survival outcome.⁹ Suboptimal diagnostic sensitivity presents a challenge when defining appropriate treatment group assignment in clinical trials, and reduces the reliability of treatment end points. Also, not all patients with NM are appropriate candidates for treatment, and risk stratification of patients with NM would likely improve outcome in good-prog-

nosis patients by allowing NM-directed therapy to be more appropriately utilized.^{5,8,10-12} Regardless, there is an urgent need for new, clinically applicable diagnostic and monitoring laboratory tests of NM with increased sensitivity and specificity. This review discusses the limitations of current NM diagnostic methodologies and looks at some of the more promising recent innovations for NM diagnosis.

CSF CYTOLOGY AND MRI

Any one of the three standard methods (neurological examination, CSF cytology, and MRI) can accurately diagnose NM. However, the clinical presentation is challenging, as neurological symptoms and signs may be subtle, may not be elicited from the patient's medical history unless a specific neurologic record is obtained, and often are attributable to other aspects of the patient's cancer (eg, coexisting brain or spine metastases, metabolic encephalopathy, or treatment-related neuropathy).^{2,6} Consequently, if lumbar puncture is feasible, CSF examination including cytological evaluation for malignant cells should be performed in all cases of suspected NM. CSF cytology is estimated to have a >95% specificity for NM.⁴ However, it has a relatively low sensitivity (<50%) and consequently is often

falsely negative. A retrospective analysis of cytology results across 18 studies (N = 874) reported sensitivities of CSF cytology ranging from 45% to 100% depending on how many times the lumbar puncture was repeated.⁴ Perhaps most importantly, these studies defined NM by either positive CSF cytology or neuroradiographic finding consistent with NM, and therefore do not clarify the frequency with which patients with NM have negative CSF cytology.¹²

The lack of standardized techniques for obtaining and evaluating CSF cytology may in part contribute to the high false-negative rates. The sensitivity of cytology may be improved by ensuring optimal conditions for CSF sampling and evaluation. In one prospective analysis of 39 untreated patients with NM, four sources of error were identified, including insufficient sample volume, delayed processing, obtaining CSF distant from the site of symptoms, and acquiring fewer than two samples.¹³ The initial diagnosis of NM is most reliably established when: (1) the CSF sample volume is at least 10.5 mL; (2) CSF is obtained near the site of clinical or radiological disease; (3) the specimen is processed immediately; and (4) at least two CSF samples are obtained.^{4,13,14} Because the shedding of malignant cells into the CSF may occur intermittently and in low numbers, CSF specimens may fail to capture malignant cells. Other CSF indices, such as opening pressure during lumbar puncture, white blood cell (WBC) count, and protein and glucose levels may be abnormal in patients with NM but are nonspecific and likely do not occur in patients with very low volume disease.^{2,4} Still controversial is whether patients with suspected NM can be diagnosed with negative CSF cytology and neuroradiography based on nonspecific CSF abnormalities, a history of cancer, and a clinical syndrome consistent with NM.⁷

Gadolinium-enhanced brain and spine MRI is a preferred radiographic method for establishing a diagnosis of NM.^{2,15} Findings that are indicative of NM include enhancement and/or enlargement of cranial nerves, nodular or linear leptomeningeal enhancement extending into sulci or basal cisterns, and intradural-enhancing nodules, especially in the cauda equina.² The sensitivity of MRI for NM depends on the type of primary cancer. One study found that MRI was capable of detecting 100% of cases of NM from solid tumors (n = 14) but only 44% of those from B-cell acute lymphoblastic leukemia (n = 5) and 48% from non-Hodgkin lymphoma (NHL; n = 20).¹⁶ The average specificity of MRI across all malignancies was 93%, ranging from 89% for acute myelogenous leukemia to 100% for solid tumors.¹⁶ Therefore, the potential for false-negative rates as high as 65% and false-positive rates approaching 10% limit the use of MRI as a stand-alone diagnostic tool.^{4,6,12,16}

FLOW CYTOMETRY AND POLYMERASE CHAIN REACTION

To ensure optimal treatment and reduce unnecessary prophylactic treatment, there has been a strong drive to develop and validate sensitive analytical methods for occult NM in patients with aggressive B-cell lymphomas.¹⁷⁻¹⁹ (See also the article in this supplement by Drs Pui and Thiel.) Flow cytometry is an extremely sensitive method capable of detecting abnormal monoclonal B-cells, which comprise as little as 0.01% of total lymphocytes.^{19,20} The diagnostic utility of flow cytometry for detecting aberrant B cells in the CSF was evaluated in a study of 51 newly diagnosed and nine previously treated patients with diffuse large B-cell lymphoma (DLBCL) at risk for CNS involvement.¹⁹ Multi-color flow cytometry conducted within 1 to 2 hours of CSF sampling (1.2–5.0 mL sample volumes) used multiple antibody panels for light chains and B- and T-cell antigens. The sensitivity of CSF flow cytometry was found to greatly exceed that of conventional CSF cytology. While cytology was positive in only one (2%) of the 51 newly diagnosed high-risk patients, flow cytometry markers were positive in 11 (22%) of these same patients ($P = .002$).¹⁹ The low detection rate of standard cytology likely reflects the low median tumor cell percentage in these patients (median, 7%; range, 0.2%–99%), as quantified by flow cytometry. Not surprisingly, the single patient for whom CNS involvement was detected by both methods had the highest percentage of tumor cells in the CSF (99%).¹⁹ As for the nine previously treated patients with relapsed DLBCL, only one (11%) had positive cytology results, while three (33%) were positive for CNS lymphoma by flow cytometry. The median percent of tumor cells in this patient group was similar to the larger, untreated population (6%; range, 3%–45%).¹⁹

CSF chemistry and cell counts also were evaluated in the study by Hegde et al and were similar for patients with and without lymphomatous meningitis.¹⁹ There were no differences in total protein ($P = .35$), WBC count ($P = .06$), red blood cell count ($P = .29$), or flow cytometry lymphocytes ($P = .96$) for the newly diagnosed NHL patients with positive (n = 11) versus negative (n = 40) CSF cytology. However, as expected, there was a significant difference in flow cytometry percent tumor cells ($P < .001$). Additional analyses evaluated whether previously identified risk factors for CNS relapse correlated with positive flow cytometry. Only the presence of more than two extranodal sites of disease was significantly correlated with positive flow cytometry results ($P = .0057$).¹⁹ This correlation is suggestive of a biologic phenotype that bestows upon certain tumor cells the ability to thrive outside of the lymph node microenvironment and allows for colonization of extranodal sites and CNS spread.

After CSF evaluation by cytology and flow cytometry, all patients were staged and treated with dose-adjusted EPOCH (infusional etoposide, vincristine, and doxorubicin, with bolus prednisone and cyclophosphamide) with or without rituximab.¹⁹ Newly diagnosed patients considered at risk for CNS lymphoma, but with no CSF evidence of disease, received prophylactic intrathecal methotrexate (MTX; 12 mg on days 1 and 5 of cycles 3 to 6 for a total of 8 doses), whereas patients with leptomeningeal lymphoma were actively treated for CNS disease (12 mg of MTX given intrathecally twice weekly until 2 weeks after CSF clearance, followed by a consolidation of six weekly treatments and maintenance of four monthly treatments). All 40 patients who were negative for CNS lymphomas by flow cytometry were treated prophylactically, and only three (8%) experienced CNS relapse and death. Of the 11 patients diagnosed by flow cytometry, nine were treated with the active disease regimen, one was treated with the prophylactic regimen, and one withdrew from the study. Despite receiving early active treatment for CNS disease, five (45%) of these 11 patients had CNS relapse and died. Therefore, even though flow cytometry facilitated earlier detection of CNS disease than had previously been possible, survival rates did not improve. This might be due to the suboptimal CNS-directed therapy used in this study (intrathecal MTX alone).

More recently, the diagnostic sensitivity of flow cytometry was found to be more than twice that of conventional cytology in a study that included 60 patients with NM caused by hematological malignancies.²¹ With the first CSF sample, flow cytometry was positive in 44 (73%) of these patients, whereas cytology identified only 19 (32%). Because of its increased sensitivity, the National Comprehensive Cancer Network now recommends the routine use of flow cytometry for the diagnosis of CNS lymphoma.²² However, because the Bromberg study also found that some false-negatives by flow cytometry are detectable by conventional cytology,²¹ it is recommended that cytomorphologic examination of the CSF still be performed in conjunction with flow cytometry.

Polymerase chain reaction (PCR) also has the potential to improve sensitivity in detecting CSF malignancy. However, PCR requires the selection of primers specific for tumor cell-derived DNA. Two approaches to selecting primers for detecting NM have been evaluated thus far. One study in lymphoma patients (N = 21) used clonal rearrangements of the immunoglobulin gene as DNA markers for CSF malignancy.²³ The use of consensus primers from the immunoglobulin V and J regions allowed for the detection of CNS lymphoma in five of seven specimens from patients with negative cytology and suspected CNS malignancy.²³ However, false-negatives did occur with PCR, as two of the four

specimens that were positive by conventional cytology were negative by PCR.²³ A second study used nested PCR of the complementarity determining region III.²⁴ Using this approach, PCR results and CSF cytology were discordant in 10 of 17 patients with primary CNS lymphoma.²⁴ However, patients in this study had been treated already, and further analysis of CSF samples obtained immediately after diagnosis would be required for a true evaluation of diagnostic utility. It is important to note that the PCR primers used in both of these studies were specific for lymphoma B-cell mutations.^{23,24} For a PCR test to be applicable to the diagnosis of NM derived from a range of primary cancers, the use of primers for DNA sequences common to all metastatic cells would be ideal, but the use of sequences for specific primary cancer histopathologies might provide a more practical option, as many are known already. There also is a need for more broad-spectrum tumor cell-specific antigens that could be labeled for flow cytometric detection of CNS malignancy. This will first require improved understanding of the biology of metastases in general and, perhaps more specifically, the process of CSF penetration by tumor cells.

BIOLOGICAL MARKERS FOR DIAGNOSING AND MONITORING RESPONSE OF NM

Numerous biochemical markers of tumor cells in the CSF have been evaluated for their accuracy in detecting NM, including β_2 -microglobulin, lactic dehydrogenase, α -fetoprotein, and human chorionic gonadotropin, among others.²⁵⁻²⁸ However, their use generally has been limited by their low sensitivity.² Furthermore, these biomarkers are of little clinical significance without a thorough understanding of the biology of metastatic disease in general and brain metastasis in particular.²⁹ Studying the biology of disease progression and the molecular processes of tumor metastasis may identify new biomarkers with increased sensitivity and specificity for NM that also could serve as surrogates of CSF tumor burden and response to therapy (Table 2) (M.D. Groves, personal communication).²⁹⁻³⁷ Ideally, such markers would allow for an earlier diagnosis and carry some prognostic value, thus helping to select therapy.

During the metastatic process, cells from primary tumors develop motility and invasive potential, allowing for penetration into capillaries, venules, and lymphatic channels. Tumor cell extravasation and penetration of the CNS also involve migration through endothelial or other basement membranes to reach the CSF and meninges.²⁹ Some molecules involved in this process, such as matrix metalloproteinases (MMP) and cathepsins, have been evaluated in the CSF of patients with NM. For example, MMP-2 and MMP-9, which digest portions of the extracellular matrix, have been

Table 2. Currently Identified Cerebrospinal Fluid Biomarkers That May Be Indicative of CSF Malignancy

First Author, Year	n	Cancer(s)	Marker(s)	AUC-ROC (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Brandsma, 2006 ³⁰	57	BC, NHL, LC, M, GI, OC	Protein, glucose, IL-8 (CXCL-8), PARC (CCL18), IP-10 (CXCL10)	0.95 (0.9–0.99)				
van de Langerijt, 2006 ³¹	19	LC, M, urothelial, unknown	Log VEGF index/log tPA index		100 (79–100)	73 (57–86)	54 (33–74)	100 (91–100)
Reijneveld, 2005 ³²	53	BC, LC, NHL, M, unknown, GI, OC	CSF VEGF, CSF uPA					
Friedberg, 1998 ³³	5	SCLC, BC, M	MMP2, MMP9					
Herrlinger, 2004 ³⁴	39	BC, LC, M, CUP, OC, other	CSF VEGF		51	98		
Stockhammer, 2000 ³⁵	11	BC, LC, OC	CSF VEGF					
Nagai, 2003 ³⁶	10	Prostate, LC, pharynx, GI	CSF cathepsin B, H cystatin C					
Groves, personal communication	7+/24–	BC	CXCL12, ER status/protein/WBC count	0.97 (0.88–1.00)				
Groves, personal communication	7+/24–	BC	VEGF >20 pg/mL		57	100	100	89
			CXCL12 (>950 pg/mL)		86	97	86	97
Groves, personal communication	15+/22–	LC	VEGF		69	100	100	83
			CXCL12		38	95	83	72
Groves, personal communication	4+/8–	M	VEGF		50	100	100	75
			CXCL12		75	100	100	88
Roy, 2008 ³⁷	24+/77–	NHL	Antithrombin III	0.912	75	98.7		

Abbreviations: CSF, cerebrospinal fluid; AUC-ROC, area under curve-receiver operating curve; BC, breast cancer; CI, confidence interval; CUP, cancer of unknown primary; ER, estrogen receptor; GI, gastrointestinal; IL, interleukin; LC, lung cancer; M, melanoma; MMP, matrix metalloproteinases; NHL, non-Hodgkin lymphoma; NPV, negative predictive value; OC, ovarian cancer; PPV, positive predictive value; SCLC, small-cell lung cancer; tPA, tissue-type plasminogen activator; VEGF, vascular endothelial growth factor; WBC, white blood cell.

detected in the CSF of patients with metastatic brain tumors and positive CSF cytology.³³ Other proteases (cathepsin B and H) and protease inhibitors (cystatin C) also may be useful indicators of NM.³⁶ High activities of cathepsins B and H, along with decreased cystatin C concentrations, have been observed in the CSF of patients with NM as compared with cancer patients who did not have CNS disease.³⁶

Molecules linked to tumor cell tropism for specific organs also may be useful for diagnosing and monitoring NM. Some success in this regard has been achieved with the chemokine markers CXCL-8, CXCL-10, and CCL18 (Table 2). Brandsma and colleagues found that when assayed together with protein and glucose levels, CXCL-8, CXCL-10, and CCL18 levels could accurately predict the presence of CNS disease (0.95 area under curve [AUC]-receiver operating curve [ROC]; 95% confidence interval [CI], 0.9–0.99).³⁰ Another chemokine, CXCL12, a homing ligand for leukocytes and tumor cells, had a high diagnostic accuracy when combined with others markers, including WBC count, protein level, and estrogen receptor status (0.97 AUC-ROC; 95% CI, 0.88–1.00) in breast cancer patients (M.D. Groves, personal communication; Table 2).

Molecules involved in angiogenesis are also important in the metastatic process. Although angiogenesis has not been established as essential for the progression of NM,²⁹ several molecules involved in angiogenesis (eg, vascular endothelial growth factor [VEGF], urokinase-type plasminogen activator, tissue-type plasminogen activator [tPA], and antithrombin III) appear to have diagnostic value (Table 2). Elevated VEGF levels, in particular, have been repeatedly demonstrated in the CSF of patients with NM compared with cancer patients without NM (M.D. Groves, personal communication).^{31,32,34,35} However, the diagnostic specificity and sensitivity and the threshold VEGF concentrations used vary from study to study. For example, Herrlinger et al observed a 98.3% diagnostic specificity but a relatively low sensitivity of 51.4% for NM using threshold VEGF levels of 250 pg/mL (73% sensitivity for a threshold of 100 pg/mL).³⁴ A similarly low sensitivity (50%–69%) but high specificity (100%) using a threshold VEGF level of 20 pg/mL was observed in three other recent studies (Table 2). Another study identifying decreases in tPA in the CSF of patients with NM, which used a combination index of the log of VEGF and tPA, obtained a sensitivity of 100% but a substantially lower specificity (73%) than observed in previous VEGF studies.³¹

Even as the diagnostic utility of VEGF remains to be established, some studies suggest that it has prognostic value. Herrlinger et al observed that VEGF levels mirror the clinical course in some patients, appearing markedly reduced following therapy and increased upon relapse.³⁴ Likewise, Stockhammer and colleagues re-

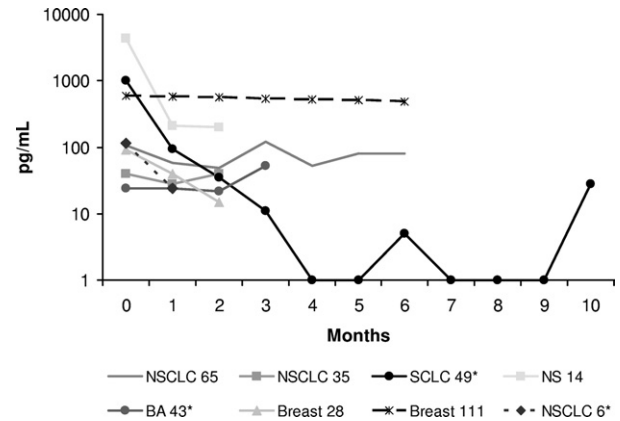


Figure 1. Levels of vascular endothelial growth factor in the cerebrospinal fluid over time.

ported a drop in CSF VEGF levels in response to treatment in four of five patients with various primary cancers.³⁵ We have observed similar trends in our experience (Figure 1). Although further extensive study is required, tracking of VEGF levels over time may prove a useful tool for monitoring the response of NM to therapy.

The use of CSF biomarkers is subject to several inherent problems that must be carefully considered when developing new diagnostic tests. First, assay standardization between institutions is essential. Additionally, CSF flow abnormalities are common in patients with NM, and uneven CSF flow can alter biomarker concentrations in areas of low flow, leading to highly variable measurements at different sampling sites.^{38,39} Sampling of CSF from a lumbar versus a ventricular source also can alter biomarker levels, depending on the location of metastases along the neuraxis.¹⁴ Different tumor histologies are likely to be associated with different levels of certain biomarkers as well, although the more generic markers of malignancy (eg, VEGF) may allow for more consistency. The time point of CSF sampling is also important, since molecular expression may change with disease progression.

DESIGNING CLINICAL TRIALS TO ASSESS BIOMARKERS AND TREATMENT OUTCOME

The clinical relevance of novel CSF biomarkers remains to be firmly established. Patients with microscopic involvement may be least likely to have positive biomarkers. Even if biomarkers allow for higher detection rates or earlier detection, they need to be highly specific, and the natural history of those newly diagnosable cases must be documented. Will such patients ultimately develop symptomatic NM? Is the natural history of such cases the same as for cytologically diagnosed NM? Are effective treatments available? These questions require careful evaluation in future clinical trials. A plausible design for such a clinical trial

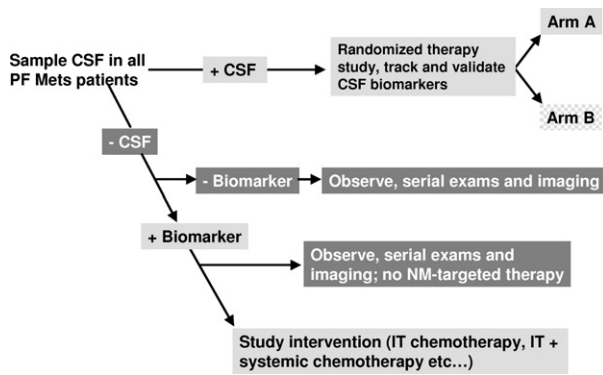


Figure 2. Proposed clinical trial design for assessing the diagnostic utility of biomarkers in patients at high risk for developing neoplastic meningitis (NM). CSF, cerebrospinal fluid; IT, intrathecal; PF Mets, posterior fossa metastasis.

is outlined in Figure 2. Important considerations for trial design include: (1) selection of a validated biomarker; (2) determination of a gold standard for disease detection (flow cytometry/cytology—no standard established yet); (3) whether to exclude from treatment patients who are negative by the gold standard but positive by the biomarker; (4) the choice of treatment intervention for biomarker-positive patients; (5) biomarker sampling location (ie, ventricular *v* lumbar); (6) end point selection; and (7) consideration that the therapeutic intervention and/or biomarker may fail. At the same time, any trial assessing biomarker utility and NM therapy also must include conventional diagnostic response measures, ie, clinical status, cytology, and MRI.

A number of outcome measures have been used to assess treatment response in patients with NM, many of which are inherently problematic (Table 1). Given the high specificity of flow cytometry for the detection of NM in hematologic cancers,^{19,21} it is likely that flow cytometric monitoring of CSF clearance will become a standard measure of treatment outcome in patients with other underlying tumors. Nevertheless, most treatment response determinations in clinical trials have conventionally been based on, in rank of importance, standard CSF cytology, imaging results, and clinical outcome/survival. A strong case can be made that the importance of these end points should be reversed, with patient status viewed as a primary end point, in part because this is the most clinically meaningful outcome and in part because of the inherent problems with CSF cytology and neuro-imaging in patients with NM (Table 1).⁶ Some success has been achieved using patient status as a primary end point in studies using a blinded external review committee to evaluate neurological and neurocognitive progression.⁴⁰⁻⁴²

Another approach to assess neurologic progression as a treatment end point, one that could be easily applied by any clinician, is a short checklist grading cognitive, motor, and cranial nerve functions pertinent

to the NM process on a scale of 1 to 5 (Table 3). This type of survey has been evaluated by Glantz and Jaeckle in pilot studies, and results obtained have correlated well with traditional methods for determining progression, such as survival and CSF cytology (M. Glantz, personal communication). While these tools offer an alternative approach to assessing neurological function, they do not provide an assessment of the actual tumor burden. Also, clinical manifestations often do not appear until late in the disease process. To optimally guide treatment decisions and assess treatment outcome, patients with NM must be identified much earlier, even before the appearance of clinical signs, cytology, or imaging.

DIAGNOSTICALLY DISTINCT SUBCATEGORIES OF NM

Some clinicians have observed that the relative incidences of positive results from cytology versus MRI versus neurological examination are suggestive of three distinct diagnostic categories of NM. For example, it has been estimated that roughly 25% of all patients with NM present with a clinical syndrome consistent with NM irrespective of CSF cytology or neuroradiology results, whereas about 50% have positive CSF cytology regardless of the clinical syndrome or MRI findings, and about 40% present with positive radiology irrespective of clinical syndrome or CSF cytology.^{43,44}

There has been some speculation that differences in the features by which NM is diagnosed may be indicative of inherently distinct forms of NM associated with different prognostic outcomes. However, few studies have evaluated clinical response based on the method of diagnosis. Data from a recent phase II study evaluating NM treatment with intra-CSF topotecan (400 μ g, twice weekly) suggest that clinical response may indeed vary with the diagnostic method.⁴⁵ In this study, 80% of the topotecan-treated patients who had positive CSF cytology but negative MRI findings at diagnosis were stable or improved after a 6-week induction period (Table 4; M.D. Groves, personal communication). Patients with negative cytology and positive imaging had a lower response rate, with only 55% stable or improved. The poorest prognosis was observed in patients who had both positive cytology and MRI results at diagnosis: only 29% were stable or improved after 6 weeks of topotecan treatment (Table 4).⁴⁵ However, it should be noted that despite these apparent differences in response rate depending on CSF and MRI status, overall survival rates were nearly identical in all groups.

Additional data from a single-investigator institutional data set suggest that patients diagnosed by cytology versus MRI also differ in terms of primary systemic cancer and other specific NM disease characteristics

Table 3. Grading Scale of Clinical Indicators of Neurologic Progression

Indicator	Grade 0	Grade 1	Grade 2	Grade 3
<i>Pain</i>				
A Headache	None	Requiring non-opiate analgesics	Requiring use of opiate analgesics (oral, transcutaneous bolus IV, SC)	Requires continuous parenteral opiates
Back/radicular neck pain	None	Requiring non-opiate analgesics	Requiring use of opiate analgesics (oral, transcutaneous bolus IV, SC)	Requires continuous parenteral opiates
B Motor	None	Mild motor loss not affecting function; minor assistance required	Loss affects function, moderate assistance required	Loss severely impairs function, requires near full-time/major assistance
C Ambulation	Normal	Mild impairment, walks without assistance	Moderate instability, requires assistance, cane or walker	Non-ambulatory, requires wheelchair
D Alertness	Normal	Mild alterations not impairing function or requiring minimal assistance or supervision	Moderate, affects function, requiring moderate assistance or supervision	Severe impairment preventing function and requiring nearly full-time assistance and supervision
E Ataxia (truncal or appendicular)	None	Mild, not impairing function	Moderate, impairs function	Severe impairment preventing function
<i>Cranial nerves (changes may be uni- or bilateral)</i>				
F Corrected visual acuity, CN (II)	Normal	Deficit present, does not interfere with function	NA	Significant deficit (finger-counting, light perception, blindness)
Eye movement abnormality, CN (III, IV, VI)	None	Present but stable	NA	New or additional abnormality
Facial CN (VII)	None	Some paresis present but stable	NA	New or additional deficit
Dysphagia/dysarthria, CN (X, XI, XII)	None	Some loss present, does not interfere with function	NA	Significant deficit, interferes with function
Hearing, CN (VIII)	Normal	Some loss present, does not interfere with function	Significant deficit, interferes with function	NA
G Nausea/vomiting	None	Requires oral or parenteral antiemetics	Requires IV hydration or hospitalization	NA
H Sensory	None	Sensory loss not affecting function	Loss impairs function	NA
I Urinary/fecal incontinence or retention	None	Minor, not requiring medication or intervention	Requirement for catheterization	NA
J Mental status	Normal, score of 30 on MMSE	Score of 29-20 on MMSE	Score of <20 on MMSE	NA

Abbreviations: CN, cranial nerve; IV, intravenous; NA, not applicable; MMSE, Mini-Mental State Examination; SC, subcutaneous.

(Table 5) (M.C. Chamberlain, unpublished data).¹² For example, 90% of patients with NM from NHL had positive CSF cytology, but only 10% were diagnosed by MRI alone. In contrast, only 60% of NM cases from melanoma had positive cytology results, and as many as 40% were diagnosed only by MRI (Table 5). Treatment response also varied across patient groups. The highest

rates of CSF cytology conversion from positive to negative were observed in NHL patients (38%), the lowest rates in melanoma patients (18%). These observations are suggestive of distinct biological forms of leptomeningeal disease that differ in the relative degree of cell shedding into the CSF as well as in treatment response.^{7,46-48} However, a recent report of 110 mela-

Table 4. Patient Outcome Varies With the Diagnostic Modality by Which Neoplastic Meningitis Was Diagnosed (M.D. Groves, personal communication)

	Stable Disease or Improved, n (%)	Median Survival (wk)	Range (wk)
CSF-positive MRI-negative	12/15 (80)	12.5	4-70
CSF-negative MRI-positive	6/11 (55)	15.1	3-128
CSF-positive MRI-positive	10/35 (29)	12	2-82

Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

Table 5. Diagnostic and Response Characteristics of Neoplastic Meningitis in Patients With Different Primary Cancers (M.C. Chamberlain, unpublished data)

	Breast Cancer	Melanoma	Non-Small Cell Lung Cancer	NHL
No. of patients	66	30	50	40
Positive cytology	75%	60%	80%	90%
Positive radiology alone	25%	40%	20%	10%
Active systemic disease	70%	80%	80%	90%
CSF cytology conversion from positive to negative	30%	18%	28%	38%
Median survival (range)	7 mo (0.25–19)	2.8 mo (0.25–6)	3 mo (0.25–7)	7 mo (0.25–27)
Cause of death				
LMD	30%	40%	20%	15%
LMD + systemic disease	30%	40%	40%	25%
Systemic disease	40%	20%	40%	60%

Abbreviations: CSF, cerebrospinal fluid; LMD, leptomeningeal disease.

noma patients with NM reported that disease burden of NM, based on CSF and MRI as measures of extent of disease, did not have an impact on survival outcomes,⁹ suggesting that, at least in melanoma patients, segregating good-prognosis and poor-prognosis patients based on evidence of disease burden of NM may not be very useful.

SYSTEMIC TUMOR MARKERS PREDICTIVE OF CNS DISEASE

Evidence that some tumor types are more likely than others to infiltrate the CNS and develop into active CNS disease has stimulated research into biomarkers of these tumors that might be used to identify patient groups that would benefit from CNS prophylaxis. One potentially useful marker identified in breast cancer patients, overexpression of the human epidermal growth factor receptor 2 (HER2), occurs in about 20% to 25% of invasive breast cancers and has been linked to an increased risk for brain metastases.^{49,50} A retrospective study of 664 breast cancer patients found that brain metastases occurred in significantly more patients with HER2 overexpression (HER2⁺: 9%, 27/301) than in patients with normal HER2 expression (HER2⁻: 1.9%, 7/363; hazard ratio, 4.23; CI, 1.84–9.74; *P* = .0007) after a median follow-up of 3.9 years. Five-year event-free survival (EFS) and overall survival rates were also significantly lower for HER2⁺ than for HER2⁻ patients (5-year EFS: 64% *v* 85%, *P* < .001; 5-year overall survival: 73% *v* 87%, *P* < .001). The use of HER2-directed therapy, ie, trastuzumab, has improved systemic control in HER2⁺ breast cancer patients, but the CNS appears to remain a sanctuary site for disease, perhaps because of the limited blood-brain barrier (BBB) penetration of intravenous trastuzumab.^{50,51} Newer drugs

that disrupt the HER2 pathway and can penetrate the BBB may improve CNS control in HER2⁺ breast cancer patients.^{52,53} Therefore, while HER2 positivity has not provided an ideal marker for selecting patients to target with standard CNS-directed prophylaxis (only 9% of HER2⁺ patients at the time of diagnosis ultimately developed CNS disease),⁴⁹ it has provided a rationale for developing and using targeted therapies that penetrate the CNS. Further study into the biology of CNS penetration by tumor cells may provide additional insight into risk factors for CNS disease and perhaps allow for molecular profiling of newly diagnosed cancer patients to predict which patients will develop brain metastases.⁵⁴

TREATMENT-RELATED FACTORS PREDICTIVE OF NM

Cancer patients who develop posterior fossa brain metastases may be susceptible to the later development of NM.⁵⁵ A recent retrospective study of 379 patients with posterior fossa brain metastases found that those who underwent a piecemeal resection of lesions had a 2.45 relative risk of the later development of NM (14% of patients developed NM) compared with patients who underwent en bloc resection or were treated with stereotactic radiosurgery (6% in each group later developed NM).⁵⁶ Therefore, it is uncertain whether patients with posterior fossa brain metastases are a group at increased risk for NM and therefore require closer surveillance for NM, or possibly, if combined with other predictive CSF biomarkers or tumor markers, even considered for prophylactic NM-directed treatments.

CONCLUSIONS

Although current diagnostic and monitoring tools lack sensitivity and/or specificity for NM, these studies nonetheless should continue to be used when evaluating patients for NM-directed treatment. Newer tools, such as flow cytometry and biomarkers of tumor cells in the CSF, may offer increased sensitivity and specificity and allow for earlier identification of CNS involvement. CSF flow cytometry and novel CSF biomarkers could enable earlier treatment of NM and may provide a rationale for CNS-directed prophylaxis before symptomatic disease and fixed neurological deficits become established. However, further validation of these tools, in particular novel CSF biomarkers, in clinical trials is warranted.

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