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Diagnosis and outcome measures in trials for neoplastic meningitis: a review of the literature and clinical experience

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Innovative approaches to the treatment of neoplastic meningitis are being widely tested. Unfortunately, research on diagnostic strategies and outcome measures on which any advances in treatment ultimately depend, has not been avidly pursued.

A critical review of the literature on neoplastic meningitis published since 1978 was undertaken by using MEDLINE and other English language databases. All articles addressing the issues of diagnostic or response criteria were included. Randomized clinical trials (RCTs) were emphasized. Prospectively collected data from the authors' institution correlating the results of cerebrospinal fluid (CSF) cytological examinations with Karnofsky Performance Scale (KPS) score are also discussed.

Twenty-six studies (representing 1208 patients) fulfilled search criteria. Only three were RCTs. Cerebrospinal fluid cytology was the sole diagnostic criterion in two-thirds of studies. The results of CSF cytological examination alone or in combination with other clinical or laboratory endpoints constituted the primary outcome measure in 85%. Few studies attempted to address known deficiencies in the reliability and validity of these measures, and correlation between measures was poor. Quality of life was never used as a primary outcome measure.

All currently available measurements, including CSF cytology, biochemistry, immunological, and molecular markers, neuroimaging studies, clinical examination, and survival, suffer from poor sensitivity and/or specificity, and often correlate poorly with each other. Although CSF cytological examination, performed according to a rigorous, research-supported protocol, may be the optimum diagnostic and outcome measure at this time, additional research is a prerequisite for any further advances in the clinical care of patients with neoplastic meningitis.

Key Words * neoplastic meningitis * outcome measure * cerebrospinal fluid * cytology * diagnosis

The first pathological description of neoplastic meningitis was published 130 years ago,[20] and nearly a century ago, Saenger[62] provided the first clinical description of this disease. In 1904, Dufour[51] first identified malignant cells in the cerebrospinal fluid (CSF). The first two of these events now hold our interest only as historical landmarks. The third study, however, describes a laboratory procedure that remains the gold standard for diagnosing neoplastic meningitis and evaluating the outcome of therapeutic interventions.[22,25,32,37,57,74]

Despite increasing interest and an increasing frequency of the disease,[39,42,74,76] important innovations in disease staging,[10,13,34,41,42] and promising new therapeutic approaches,[6,33,36] neoplastic meningitis continues to be defined by the detection of malignant cells in the CSF, and novel treatments continue to be evaluated based on their ability to convert a positive CSF cytological examination to a negative one. The purpose of this study is to review the diagnostic and response criteria that have been applied in clinical trials of treatment for

solid tumor neoplastic meningitis over the last 20 years. Cerebrospinal fluid cytological examination is emphasized because of its pivotal role, but other diagnostic and outcome measures including biochemical markers, neuroimaging studies, clinical examination, and functional measures, are also discussed. From this review, recommendations for current practice are made.

CLINICAL MATERIAL AND METHODS

Review of Literature

This study has two purposes: the first is an attempt to thoroughly review the literature on neoplastic meningitis to establish the context of current practice. For this, all observational and analytical clinical trials of treatment for neoplastic meningitis published in English since 1978, that primarily focused on outcome rather than prognostic factors, and that provided sufficient data to determine the diagnostic and outcome measures used, were reviewed. Pertinent studies were identified by using MEDLINE searches of the years 1978 through April of 1998. Additional studies were obtained by review of the reference lists of these articles, and of abstracts appearing in the abstract books of the American Society of Clinical Oncology and American Association of Neurology since 1992.

Karnofsky Performance Scale Scores and CSF Cytology

The second purpose is to report our own experience comparing Karnofsky Performance Scale (KPS) scores with the results of CSF cytological examination in 30 patients known to have neoplastic meningitis. These patients were participants in institutional review board-approved clinical trials conducted by the Neuro-Oncology Service at the Brown University School of Medicine from 1992 through 1995.

RESULTS

Since 1978, 26 studies comprising 1247 patients were identified that provided information on diagnostic and response criteria in patients with solid tumor neoplastic meningitis.[4,5,11,14,18,21,23,29,31,33,36,38,40,42,46,53,56,61,63,66,67,69,70,74-76] Only three of these studies (with a total of 154 patients) were randomized clinical trials,[36,40,42] and one of these has, as yet, been published only in abstract form. The remainder are phase I or phase II trials (9), case control studies (3), or case series (11).

Diagnostic Criteria

Of the 26 studies, 16 (62%), including two of the three randomized clinical trials, relied solely on a positive CSF cytology as the diagnostic entry criterion.[4,5,11,18,31-33,38,40,46,56,63,66,69,75,76] One additional study required both positive CSF cytology and the presence of multifocal neurological deficits compatible with the diagnosis of neoplastic meningitis.[53] In the remaining nine studies (35%)[21,23,29,39,42,61,67,70,74] abnormalities of CSF biochemistry or cell count, clinical examination, or neuroimaging studies (myelography, computerized tomography, or magnetic resonance [MR] imaging), alone or in various combinations, were accepted in some patients as sufficient evidence of neoplastic meningitis in the absence of a positive CSF cytology (Table 1).

TABLE 1
REVIEW OF DIAGNOSTIC CRITERIA AND OUTCOME MEASURES IN CLINICAL TRIALS IN SOLID TUMOR NEOPLASTIC MENINGITIS BETWEEN 1978 AND 1998*

Authors and Year	Diagnostic Criteria				Outcome Measures			
	No. of Patients	Cytology Alone	Additional Study Entry Criteria	Cytology Not Used	No. of Patients	Cytology Alone	Additional Study Response Criteria	Cytology Not Used
Yap, et al., 1978	25	25			25	cytology alone		
Edwards, et al., 1981		13		positive CSF cytology & characteristic myelogram	13		+ CSF chem + exam	
Theodore & Gendelman, 1981	33	33			33		+ exam	
Fulton, et al., 1982	32	16		CT or myelography	32		+ exam	
Rosen, et al., 1982	60	37		23 at autopsy	60		+ exam	
Trump, et al., 1982	25	23	2 CSF chem, x-ray, exam		25		+ exam	
Wasserstrom, et al., 1982	90	82		8 exams + x-ray	90		+ exam	
Yap, et al., 1982	40	40			39		+ CSF chem + exam	
de Visser, et al., 1983	33	33			33		+ exam	
Giannone, et al., 1986	22	22			22		+ exam	
Hitchins, et al., 1987	44	33	11 CSF chem, x-ray, exam		41		+ exam	
Stewart, et al., 1987	23	17		5 exams + x-ray	22		+ CSF chem + exam	
Pfeffer, et al., 1988	98	98			71		+ exam	
Sause, et al., 1988	27	27			26		+ exam	
Boogerd, et al., 1991	44	44			31		+ exam	
Berg, et al., 1992	39	39			39	cytology alone		
Nakagawa, et al., 1992	34	34	+ multifocal neurological deficits		34			survival only
Grossman, et al., 1993	52	52			52		+ exam + x-ray	
Grant, et al., 1994	36	36			36			survival only exam only
Jayson, et al., 1994	35	35			35			
Siegal, et al., 1994	137	137			137		+ exam	
Balm & Hammack, 1996	126	126			126			exam only
Fizazi, et al., 1996	68	61	7 CSF protein + CT		62		+ exam	
Glantz, et al., 1996	61	61			60		+ exam	
Glantz, et al., 1998	31	31			31	cytology & exam assessed separately		
Chamberlin & Komarik, 1998	32	26	6 CSF chem, x-ray, exam		32		+ exam	6 exam + x-ray

* Chem = evaluation using biochemical markers; CT = computerized tomography evaluation; exam = clinical examination. Numbers of patients are fewer in the "Outcomes" column because not all patients were available for follow-up.

Despite widespread acceptance of CSF cytology as a diagnostic gold standard for neoplastic meningitis, serious doubts about the validity and reliability of this technique have recently been raised.[4] Whereas false-positive studies are rare or nonexistent in cases of solid tumor neoplastic meningitis,[2,9,22,37,50,74] false-negative results are common, particularly when small CSF volumes (< 10.5 cm³) are submitted, when specimens are not processed by the cytology laboratory immediately, when CSF is obtained from a site distant from the location of active CSF disease (that is, from the lumbar region in patients with cranial nerve or cerebral signs and symptoms or from a

ventricular reservoir in patients with predominantly spinal disease), or when a second CSF specimen is not obtained after an initial specimen is cytologically negative.[32] In addition, inadequate communication between clinician and cytopathologist, as well as inadequacies in cytopreparatory technique, may also contribute substantially to false-negative results. Many of these pitfalls are obvious, and all have been explicitly described, but adherence to strategies for avoiding them in clinical practice is probably quite low.[32,73]

In an attempt to avoid underdiagnosis based on the results of CSF cytological examination alone, many authors have advocated the use of supplementary or alternative diagnostic techniques, including clinical examination, MR imaging;[15,25,68] CSF leukocyte count, glucose and protein studies; assays for tumor markers;[3,26,45,49,54,64,71,74] DNA amplification procedures;[59,60] flow cytometry;[16,19,52] and monoclonal antibody staining.[7,8,43,72] Of these techniques, MR imaging has been the most widely embraced. Some investigators have suggested that a secure diagnosis of neoplastic meningitis can be made based on characteristic MR and clinical findings in the absence of a positive CSF cytological examination.[25,28] Such a claim resonates with many clinicians, who have on occasion encountered cancer patients in whom is found the compelling clinical and radiographic evidence of neoplastic meningitis but a persistently negative CSF cytology. When specific MR criteria have been applied, several studies have demonstrated moderate correlations between the results of cytological examination and MR imaging either in small groups of patients with known neoplastic meningitis[15,68,77] or in larger groups with a clinical suspicion of neoplastic meningitis.[25] Unfortunately, reliance on MR imaging alone is associated with frequent false-negative and false-positive results, and many conditions, some common in cancer patients, have been described that mimic "diagnostic" MR findings.[1,24,48,55,58,65] In our own prospective comparison of the results of CSF cytological examination, MR imaging, and clinical examination in patients with gliomas when the results of CSF cytological examination were used as the reference study, the false-negative and false-positive rates for MR imaging (65% and 8%, respectively) and clinical examination (48% and 48%, respectively) were unacceptably high.[44]

A large number of biochemical and molecular markers derived from tumor cells and measurable in the CSF have also been evaluated as diagnostic tools for neoplastic meningitis.[3,26,45,49,54,64,71,74] Whereas some studies have shown good correlation between the presence of malignant cells, as documented by conventional CSF cytological examination, and one or more biochemical markers, no marker or panel of markers has been sensitive and specific enough to gain widespread acceptance. The same can be said for the routine CSF parameters, including leukocyte count, glucose, and protein.[47,49,74] Although neoplastic meningitis produces typical abnormalities in one or more of these parameters in most patients, these changes are very nonspecific. Similarly, whereas polymerase chain reaction and immunohistochemical techniques have proven very useful in classifying malignant cells found in the CSF, they cannot substitute for the diagnosis of neoplastic meningitis by standard cytological procedures.[7,8,43,59,60,72]

Outcome Measures

In most clinical trials, response determinations, like diagnostic criteria, have depended heavily on the results of CSF cytological examination. Two of the 26 studies reviewed here used these results as the sole outcome measure.[5,75] In one study, CSF cytological and clinical examination were reported separately,[31] and in another study the results of CSF cytological examination was the sole response criterion in 26 of 32 patients with positive cytologies at study entry.[13] Eighteen studies (69%) combined changes in CSF cytology with the results of clinical examination (14 studies),[11,18,23,29,31,35,42,56,61,63,69,70,74] clinical examination combined with CSF biochemistry (3 studies),[21,67,75] or neuroradiographic studies (1 study),[39] to develop specific formulas for determining response. Four studies used as their sole outcome measure either survival (two studies)[38,53] or clinical examination (two studies).[4,46] In those studies relying partly or wholly on the results of CSF cytological examination as the primary response measure, the definition of cytologic clearing (number of requisite samples, duration of clearing, location of sampling, CSF volume, techniques for CSF examination) varied widely. Some studies included partial as well as complete cytological response categories. Similar variability applied to the criteria used for clinical and radiographic responses in those studies for which these were used. In 24 of the 26 studies, survival was also used as an outcome measure (Table 1).

The same limitations that affect cytology as a diagnostic measure apply to the use of cytology as a response measure.[32] Several recent studies have correlated cytological response with neurological improvement or overall survival. Fizazi, et al.,[23] reported clinical improvement in 10 (67%) of 15 cytological responders compared with seven (27%) of 26 cytological nonresponders in their study of intrathecal methotrexate; however, the difference between groups diminished when patients who were clinically improved and stable were combined (93% compared with 65%). Glantz, et al.,[36] found that a single negative CSF cytology following entry into their randomized clinical trial was strongly predictive of prolonged survival compared with patients who never had negative cytology results (60 days compared with 140 days; log rank p value = 0.0024). In contrast, others have found no correlation between survival and the results of CSF cytological examination following the onset of treatment.[11,66] Whereas these authors were rigorous in evaluating CSF cytology, inadequate sampling techniques and treatment-induced cytological atypia may explain some instances of poor correlation between the results of CSF cytology and survival in other studies.

A second confounding problem is the frequency of death from causes unrelated to neoplastic meningitis. Because most patients with neoplastic meningitis also have progressive systemic cancer,[22,35,39,40,42,57] it is not surprising that systemic cancer is the primary or a major contributing cause of death in 39 to 88% (mean 46%) of patients.[18,23,36,56,69,74,76] As a result, even well-controlled leptomeningeal cancer, as evidenced by a negative CSF cytology result and stable neurological examination, may not be predictive of prolonged survival. Thus cause of death (neoplastic meningitis compared with systemic cancer) is another endpoint that some investigators have used to evaluate the effect of various treatments. Because treatment, compared with supportive care alone, seems to shift the cause of death substantially from neoplastic meningitis to systemic cancer, an argument can be made for the utility of this outcome measure.[18,56,69] Unfortunately, determination of cause of death in this setting is difficult. No published study has used prospectively defined criteria and blinded raters, and therefore this outcome measure remains inadequately explored.

A similar lack of consistency can be found in attempts to use clinical status (as indicated either by the neurological examination or KPS score) as a measure of successful therapy. Two studies have reported improved survival in patients who responded clinically compared with those without clinical improvement,[46,67] but most investigators have found that neurological deficits present when treatment is initiated rarely improve even if treatment successfully eliminates malignant cells from the CSF and prolongs survival.[38,40,57,74] In our own recent experience in 30 patients with neoplastic meningitis for whom survival times and serial cytological and KPS data were available, three patterns of correlation or noncorrelation between these parameters were seen. In 25 patients (83%), there was no discernible association between KPS score and the presence of malignant cells in the CSF. In 16 of these 25 patients, the KPS score declined despite persistently negative cytology results (Fig. 1 upper). In nine, the KPS score remained stable despite the continuing presence of malignant cells (Fig. 1 center). Finally, in only five patients (17%) was there good correlation between the KPS score and CSF cytology results (Fig. 1 lower).

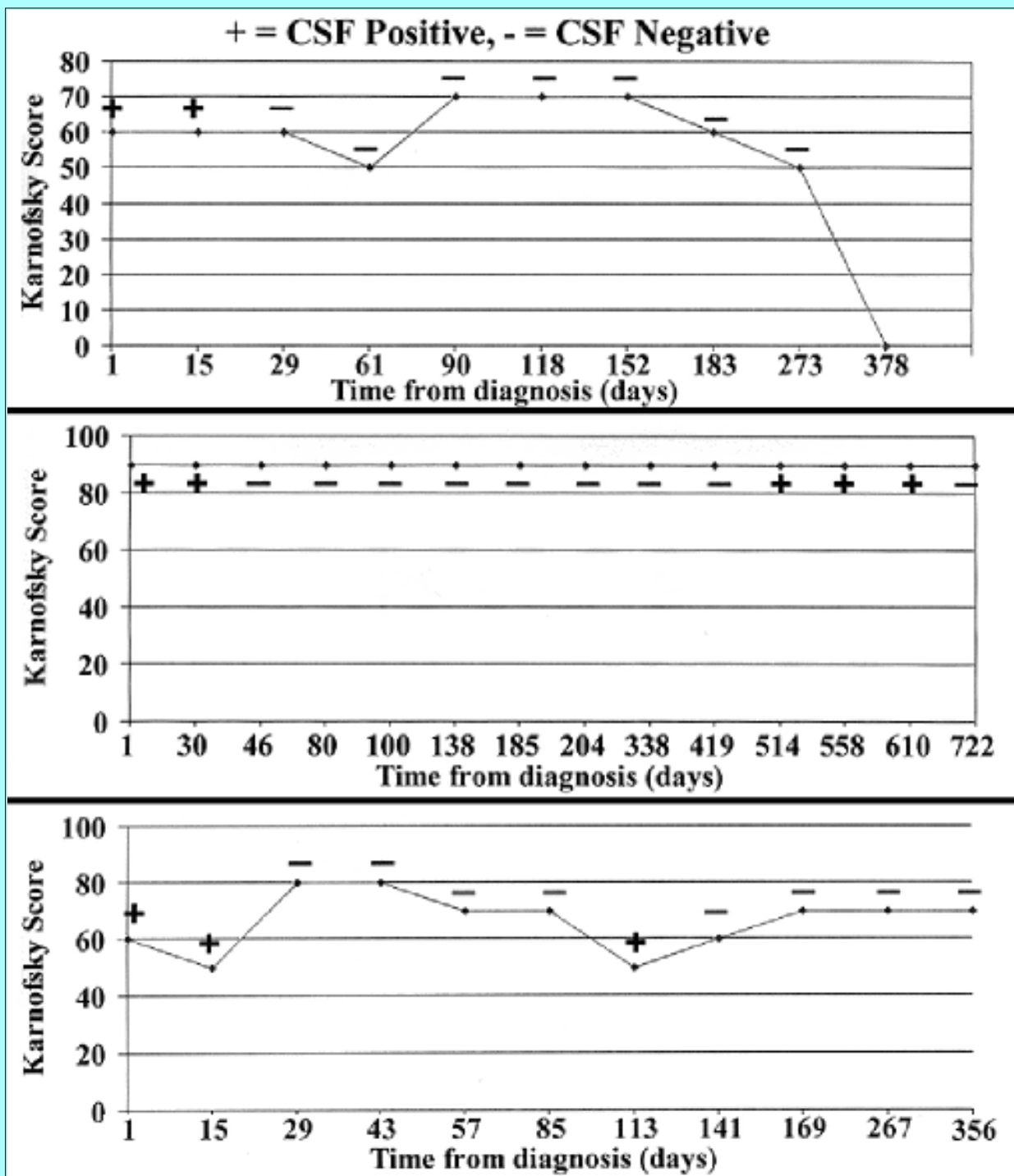


Fig. 1. Graph illustrating the relationship of the results of CSF cytological examination to KPS score. Upper: Plot of CSF cytology results and KPS scores compared with time demonstrating progressive deterioration in KPS score and ultimately death from neoplastic meningitis despite a persistently negative CSF cytology result. Center: Plot of CSF cytology results and KPS scores compared with time demonstrating unwaveringly high KPS score over time and prolonged survival despite reappearance of malignant cells in the CSF. Lower: Plot of CSF cytology results and KPS scores compared with time demonstrating falls in KPS score with reappearance of malignant cells in the CSF and improvement in KPS score with disappearance of malignant cells.

Given the inadequacy of single outcome measures such as survival, neurological examination, or cytological examination, many investigators have attempted to use response definitions combining cytological and clinical information. A number of studies have demonstrated improved survival in patients who responded compared with those who did not respond to treatment, where response was defined as various combinations of cytological and

clinical improvement.[11,36,42,75] Similarly, one trial has evaluated "integrated" measures of quality of life as potentially valuable endpoints in neoplastic meningitis.[35] In this trial, both the functional assessment of cancer therapy-central nervous system (FACT-CNS)[12] and Quality-Adjusted Time Without Symptoms and Toxicity (Q-TWiST) methodology[17,30] were used. Although there was no difference in pre- and posttreatment FACT-CNS scores between the two treatment arms in this study, when responding patients were compared to nonresponders (regardless of treatment arm), responders demonstrated an improved quality of life. A similar and more impressive difference in "TWiST" was seen between responders and nonresponders.

CONCLUSIONS

A century after the first clinical and pathological recognition of neoplastic meningitis as a disease entity, our ability to diagnose this disease and reliably measure response to treatment is still inadequate. Cerebrospinal fluid cytological examination remains the diagnostic gold standard, but its sensitivity is strongly dependent on a set of operator-controlled test specifications, most of which are now well known but are rarely adhered to.[32,73] In addition, the importance of other test parameters such as communication between clinician and cytopathologist remains unexplored. The role of ancillary CSF markers is also uncertain. Measurement of biochemical markers of tumor growth may provide strong supportive evidence of the presence of neoplastic meningitis. More important, these markers may provide information on prognosis and tumor behavior and may even serve as early indicators of tumor recurrence. Ultimately, this should result in a better understanding of the biology of neoplastic meningitis and thus more astute timing and selection of available therapies. At this time, however, there is insufficient evidence to allow any biochemical or molecular biological marker in the CSF to serve as a diagnostic alternative to CSF cytological examination. Similarly, CSF immunohistochemical techniques dramatically enhance the cytopathologist's ability to identify the tissue of origin of malignant cells in the CSF, but these techniques cannot substitute for conventional CSF cytological examination in establishing the diagnosis of cancer. Neuroimaging studies, in particular MR imaging of the neuraxis, have also been advocated, in combination with the clinical examination, as sufficient for the diagnosis of neoplastic meningitis in the absence of a positive CSF cytology result. Although some studies do show moderate correlation between CSF cytology results and specific MR findings, the use of MR imaging as an alternative to CSF cytological examination presents significant problems. Because no prospective trials or case series have been published in which outcome and other characteristics of patients with MR imaging-defined neoplastic meningitis are examined, it remains unclear whether this group of patients has the same disease as those with positive CSF cytology results. Magnetic resonance imaging abnormalities may identify a subgroup of patients with neoplastic meningitis whose disease behavior, response to treatment, and survival differ from those without MR findings. In addition, because our ability to treat bulky subarachnoid tumor with intrathecal chemotherapy is limited, serial MR imaging may not be helpful in monitoring the success of this type of therapy.

The assessment of treatment outcome in patients with neoplastic meningitis is even less securely defined. Cerebrospinal fluid cytology, even when precisely sampled, is probably inadequate as a single outcome measure. Some patients clearly progress neurologically and die from neoplastic meningitis in the absence of persistent, identifiable malignant cells in the CSF. In part, this may reflect the limitations described for the use of cytology in the diagnosis of neoplastic meningitis. In addition, monitoring of CSF cytology results during therapy is complicated by the possibility of sterilizing only the portion of the subarachnoid space from which the CSF sample is obtained (for example, ventricular CSF when intrathecal chemotherapy is administered through an intraventricular reservoir) and by the presence of treatment-related cytological changes that may mimic or obscure the presence of malignant cells. Finally, because most patients have progressive cancer outside of the CSF, clinical outcome is often independent of the course of disease within the CSF.

The sometimes overriding clinical importance of extra-CSF malignancy in patients with neoplastic meningitis may also degrade the usefulness of clinical measures of response such as the neurological examination, KPS score, and global quality of life measures. Moreover, neoplastic meningitis-related deficits present at the time of diagnosis often fail to resolve despite apparently successful therapy as measured by CSF cytology results, radiographic tumor burden, CSF marker studies, and patient survival. As a result of this lack of resilience of the central nervous system,

successful therapy usually can do no more than maintain clinical status at the level present when therapy began. Although this provides a strong rationale for early diagnosis and treatment, it complicates the use of clinical response measures for assessing outcome. Despite these shortcomings, some measure of clinical response or quality of life is important, lest treatments be adopted that simply prolong survival at an undesirably low level of function or intolerably high level of suffering.[27,35] Similarly, the relationship of cause of death to neoplastic meningitis is also, potentially, a very useful ancillary outcome measure, if prospectively defined and determined by examiners blinded to treatment status.

Ultimately, the literature permits a few conclusions. As a current diagnostic gold standard, CSF cytological examination, performed in a standardized and rigorous way, seems to be optimum. Additional study of ancillary diagnostic techniques, particularly MR imaging and molecular biological markers of CSF malignancy, should be pursued. As an ideal outcome measure, no single criterion is adequate. A combination of the results of CSF cytological examination and scoring on a standardized neurological examination or measure of performance is probably the best currently available strategy, but substantial room for improvement remains. This combined endpoint should be supplemented by at least three secondary measurements: quality of life, survival, and relation of death to neoplastic meningitis. In the end, the strongest conclusion justified by this literature review is that 100 years of study have yielded relatively few answers and underscore the need for additional well-designed prospective trials focusing on diagnosis and comparing various outcomes, including those of interest to patients who suffer from the disease as well as those who attempt to treat it.

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