Commentary (Gilbert): Carcinomatous Meningitis: It Does Not Have to Be a Death Sentence

By Mark R. Gilbert, MD

The title of the article by Dr. Stephen Sagar, "Carcinomatous Meningitis: It Does Not Have to Be a Death Sentence" is very provocative. Most oncology specialists consider leptomeningeal dissemination of cancer as an indication of end-stage disease, particularly in patients with solid malignancies. More than 70% of patients found to have neoplastic meningitis have evidence of concurrent progressive systemic disease.[1] Although neoplastic meningitis is thought to have less of an impact on survival in patients with lymphomas or leukemias, the presence of tumor cells in the cerebrospinal fluid (CSF) of these patients significantly complicates the treatment regimen.

Guarded Optimism

Reported outcomes support the grim prognosis associated with the leptomeningeal spread of cancer. Untreated, the median survival of patients with neoplastic meningitis is 1 month, and for patients with disease that is refractory to treatment, only 2 months. Overall, median survival is approximately 6 months, with some variability based on the type of primary tumor—the prognosis is better with lymphoma (10 to 12 months) but much worse with malignant melanoma (4 months).[2]

What, therefore, accounts for the optimism suggested by the title of Dr. Sagar’s article? He emphasizes that, although overall survival is poor, a subgroup of patients achieve prolonged control of the tumor in the CSF and maintain their quality of life. Furthermore, he supports the contention that new treatment approaches will expand on this promise in the near future. I agree with this optimism and support the idea that, currently, although only a small percentage of patients experience a prolonged benefit from treatment of neoplastic meningitis, patients with good performance status and limited or controlled systemic disease should be strongly considered for treatment. I would add to this discussion by delineating some of the reasons why outcome is generally poor for this disease.

Factors Affecting Prognosis

First, the diagnosis of neoplastic meningitis is often delayed. The symptoms may be nonspecific (eg, lethargy or mild confusion) and may be attributed to ongoing cancer treatments or the effects of analgesics.[1] Occasionally, patients are diagnosed with multiple brain metastases, when the actual underlying pathogenesis is not hematogenous dissemination of cancer, but rather, malignant cells in the CSF forming tumor nodules in brain sulci or infiltrating brain parenchyma via Virchow-Robin spaces. Early diagnosis when tumor burden is limited will be a key factor in improving response to treatment. Extensive, nodular disease in the leptomeninges changes the treatment approach. Chemotherapy delivered directly into the CSF cannot diffuse into tumor nodules; hence, only the free-floating or thin layers of tumor will be adequately treated. Bulky disease also results in abnormalities in CSF flow, thus altering the delivery of agents administered directly into the CSF. Some compartments—for example, the lateral ventricles—may have prolonged exposure to the agent with a marked increase in neurotoxicity, whereas other regions may not receive adequate concentrations of drug.[3] The existence of these "sanctuary sites" may cause some treatment failures.
Finally, only a small number of available agents can be administered directly into the CSF, markedly limiting treatment options.

**Unique Opportunity to Monitor Treatment Effects**

The question, therefore, remains: Why maintain an enthusiasm for treatment when faced with all of these potential hurdles? The answer is provided in Dr. Sagar’s discussion. Neoplastic meningitis provides a unique opportunity to directly examine the effects of new treatment strategies on individual tumor cells. This capability has been exploited in the development of treatment for the leukemias, where blast cells in peripheral blood can be routinely sampled and treatment effects directly monitored. Similar strategies for solid tumors require multiple biopsies—an invasive and often impractical solution.

The free-floating cells in the CSF present a unique opportunity to instill treatment agents directly into the fluid, then perform serial samplings and analyze the effects of treatment on the tumor. This strategy can be readily applied to gene therapies, immunotherapies, and the rapidly expanding field of signal transduction inhibitors.[4,5] This method also represents an extremely powerful treatment paradigm with the capability of directly monitoring efficacy on a molecular level. Examining the molecular effects of treatment such as changes in cytology or normalization of CSF protein and glucose can augment traditional measures of response. Failure to achieve the desired change would be an early indication of resistance to treatment and would warrant a change in strategy while limiting disease progression.

**Remaining Issues**

Other issues limiting treatment success remain, but most of these can be addressed. Early diagnosis requires a heightened level of suspicion among clinicians and will likely evolve as treatments for neoplastic meningitis improve and early recognition translates into improved survival. Effectively managing patients with bulky disease or compartmentalization of CSF flow continues to be important, particularly as available treatments improve. Ineffective delivery of treatment may ultimately be the success-limiting step. Established treatment paradigms deal with these issues and ensure that the delivery of treatment is maximized for most patients.[6]

**Conclusions**

In conclusion, Dr. Sagar’s title, while not outlandish, may be premature. Continuing improvements in the treatment of systemic cancers suggest that, as in leukemia, the CSF may be a major sanctuary site and a predominant reason for treatment failures in the future. The early history of leukemia treatment was notable for complete systemic remission, followed by failures with relapse in the CSF. Recognizing this problem with prompt and anticipatory treatment (ie, prophylaxis) markedly changed the outcome of leukemia treatment.[7] A similar situation may exist for neoplastic meningitis from solid tumors. Indeed, the dismal prognosis that accompanies disseminated disease may improve greatly with the application of current knowledge regarding tumor biology and cancer treatments.

**References:**


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