CNS Metastasis: The *Blood-Brain Barrier Tsunami* and Watershed

I. Leptomeningeal Cancer

Dedicated to Dan Eilers and Valerie Harper

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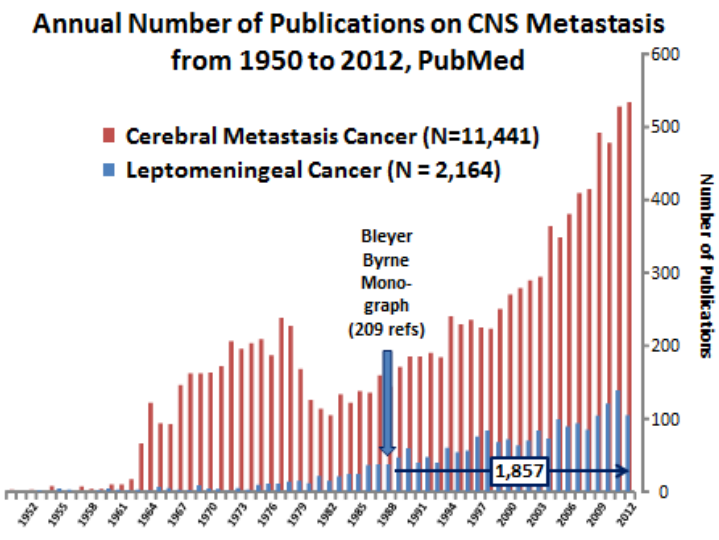
Background Prolongation of survival in patients with cancer that can metastasize to the CNS and our improved capability to detect metastases in the CNS has led to a distinct increase in the incidence and prevalence of patients with CNS metastases and a corresponding public health burden. In addition, for nearly all patients who develop CNS metastases, the expected survival thereafter is not only strikingly abbreviated, but also the subsequent quality of remaining life is usually severely jeopardized. Accordingly, oncologists are now faced with an increasingly acute challenge to prevent and treat CNS metastasis. This report summarizes the burden status and describes the role of the blood-brain barrier with particular reference to the leptomeninges and leptomeningeal cancer (LMC).

Methods The peer-review literature of 209 publications on LMC was reviewed since the publication of *Leptomeningeal Cancer in Leukemia and Solid Tumors* by Bleyer and Byrne in 1988. Also reviewed were CNS management concepts generated during the past half-century by pediatric oncologists in treating acute lymphoblastic leukemia.

Fig. 1



Results During the past three decades, the number of peer-reviewed publications on CNS metastasis increased exponentially (Fig. 1). Those on LMC increased from <5 to >100 per year (ibid). The incidence of LMC has obviously increased in patients with malignancies that have had a propensity to metastasize to the CNS and a substantive increase in survival, but the nation's cancer epidemiology resource, the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute, is deficient in LMC data. Breast cancer, lung carcinoma, acute leukemia and melanoma have been the most affected. Small-cell lung carcinoma, which is one of the most chemotherapy-response types of lung cancer, reached a CNS metastasis rate that now is treated with pre-emptively treated with cranial or craniospinal radioprophylaxis.

Cancers for which systemic therapy is systemically effective does not substantially penetrate the blood-brain barrier, have been particularly affected. Her-2-neu breast cancer is a prime example in that a monoclonal antibody is therapeutic toward systemic disease not does not enter the CNS and has allowed CNS metastases to result in one of the most common sites of relapse or progression. Acute myelogenous and lymphoblastic leukemias are other examples. In turn, successful management of CNS metastases allows systemic cancer to re-manifest itself.

Fig. 2

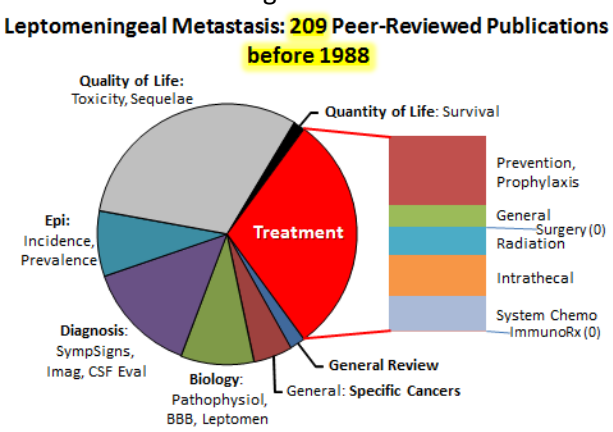
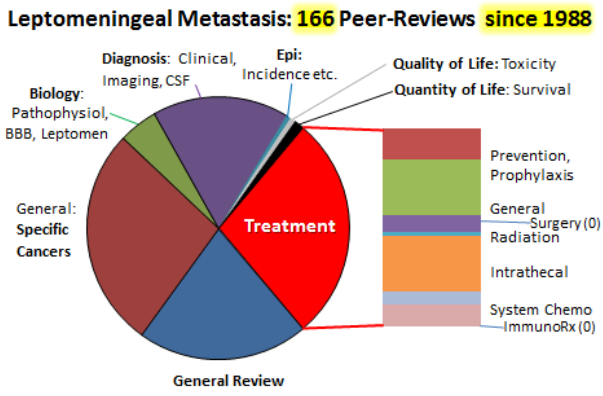
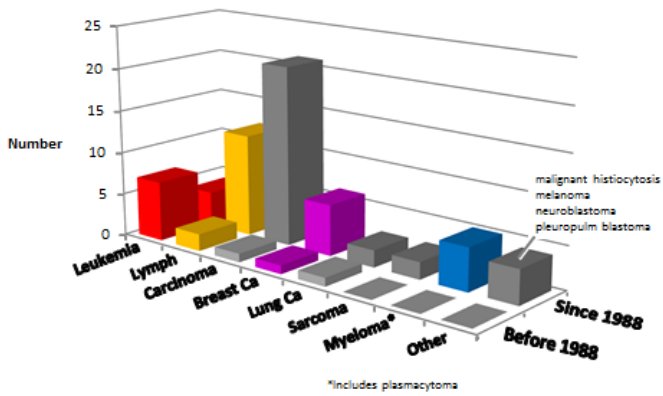


Fig. 3



During the past quarter century, the basic biology of leptomeningeal metastasis and epidemiologic research has gone begging, with relatively few new discoveries in the pathogenesis and biology of LMC (Figs. 2 and 3). The prevalence of LMC has transitioned from leukemia and lymphoma to carcinomas and other solid tumors. Previously unreported, a much greater variety of cancers are now known to cause LMC, including carcinoma of breast, lung, stomach, esophagus, tonsil, larynx, uterine cervix, and ovary, as well as melanoma, Hodgkin lymphoma, pleuropulmonary blastoma, and neuroblastoma (Fig. 4). Diagnostic methodologies still appear to be limiting, as they were 25 years ago. Quality of life studies that once predominated research has essentially disappeared.

Fig. 4



Also relatively lacking are efforts at systemic therapy and radiotherapy. With the exception of leukemia and lymphoma, overall survival has not significantly improved during the past quarter century.

Conclusions The dramatic increase in peer-reviewed publications on LMC has not substantively altered either the brutally short median survival of solid-tumor LM C or the subsequent quality of life. Yet, CNS metastasis has become an increasingly frequent in a growing number of cancers. The "dough-boy" phenomenon noted by pediatric oncologists during the 1970s has become applicable to adults with relevant cancers. Immunotherapy and targeted molecular therapy are promising. When it comes to LMC, the CSF and leptomeninges are a persistent watershed with the blood-brain barrier still very much intact.

Recommendations Translational research of LMC is under-represented in scientific efforts, especially in comparison to other fields of cancer research. SEER's acquisition of LMC data must be improved. Research efforts appear to be overly disease specific instead of biology-based and focused on similarities across cancer such as recently described for luminal breast and ovarian cancer. Quality of life must be more intensively evaluated and researched since QOL is more adversely affected by LMC than most clinical manifestations of cancer. Treatment has underutilized intraCSF therapy, especially intraventricular therapy via an implanted reservoir and ventriculolumbar perfusion. Also lacking are intrathecal radiotherapy, more effective and intensive systemic therapy, and new surgical approaches.