

The Science of Prevention: Novel Strategies for and New Insights Into Central Nervous System Prophylaxis in Patients With Cancer

An unanticipated consequence of recent successes in the treatment of non-central nervous system (CNS) malignancies has been a steady increase in the frequency of brain and spinal fluid relapse. This pattern has been well-documented in patients with breast cancer, small cell and non-small cell lung cancer, and non-Hodgkin lymphoma (NHL) and may well emerge in other common (colorectal cancer) and less common (melanoma) tumor types. Unfortunately, the treatments available for brain metastases and neoplastic meningitis have not evolved as quickly as those for non-CNS disease. In general, these are limited to cranial irradiation of various types, intracerebrospinal fluid (CSF) chemotherapy with a very few available agents, and an even shorter list of systemically administered drugs with good CNS penetrance. In general, treatment of CNS relapse, regardless of the underlying malignancy, has been only modestly successful because of the restricted access of some drugs to the CNS, because of resistance of the CNS metastases to available therapies, and because the risk of treatment-related CNS toxicity imposes limits on the aggressiveness of therapy. For all of these reasons, interest in preventing CNS metastases, ie, CNS prophylaxis, has become an increasing focus of basic and clinical research.

In 2007, an international symposium attended by some of the world's leading neurologists, hematologists, oncologists, and basic scientists was convened to discuss the scientific underpinnings of CNS prophylaxis and their implementation in clinical practice. This supplement provides an updated overview of their presentations, and the discussions they engendered. The opening article reviews both the history and the current therapeutic state-of-the-art in the two diseases—childhood acute lymphoblastic leukemia and very aggressive NHL—in which CSF prophylaxis has been an unmitigated success. This and subsequent articles review the evidence for and against CSF prophylaxis in other forms of NHL, in a variety of solid tumors, and in malignant primary brain tumors, both those where intra-CSF chemo-

therapy and craniospinal irradiation are commonplace (medulloblastoma) and those where such interventions are not currently part of standard care. Along the way, articles review the challenges inherent in diagnosing and treating neoplastic meningitis, the persuasiveness of the stem cell theory of gliomagenesis and how this theory suggests that intra-CSF chemotherapy should be part of initial therapy for patients with malignant gliomas, and novel strategies for exploiting the anatomy, physiology, and molecular biology of the choroid plexus, the CSF, and its pathways to treat and to prevent CNS metastases. In each article, detailed descriptions of state-of-the-art treatment protocols are presented, critical gaps in our knowledge are revealed, and, often, detailed proposals for urgently needed clinical and translational research studies are presented. The supplement concludes, appropriately, with an article that reviews the challenges encountered when conducting such clinical and translational studies, describes the statistical principles that underlie persuasive clinical research in this and all fields of oncology, and provides concrete strategies for addressing these challenges.

As of this writing, the problems of CNS metastases and relapse of malignant primary brain tumors remain among the most intractable in all of oncology. The hope of each of the contributors is that this supplement will serve as a comprehensive review of the field and provide guidance to clinicians as they contemplate the techniques and the role of CNS prophylaxis in their patients. In addition, we hope that this supplement will provide a starting point and an incentive for clinical and basic researchers, so that, when *Seminars in Oncology* revisits this field in the not-too-distant future, the dramatic advances that have been made will be apparent to all—especially to our patients.

Michael Glantz, MD
Penn State Hershey Medical Center
Hershey, PA

Lawrence Recht, MD
Stanford University School of Medicine
Stanford, CA
Guest Editors

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