The management of patients with leptomeningeal metastases (LM) is multifaceted and complex. Even with an aggressive approach, therapeutic outcomes are uniformly disappointing. This is because of the relentless growth of the central nervous system (CNS) and/or the systemic cancers, or their lethal complications. Advances in the understanding of the homing of cancer cells to the CNS, and of cancer metastasis in general, and more effective anticancer drugs that are adequately delivered to the CNS and cerebrospinal fluid (CSF) are needed to improve outcomes for patients with LM. These advances may lead to better treatments for this disease and, ultimately, its prevention.

Despite the passing of nearly 140 years since its original description, little progress has been made in improving survival for patients with LM. Hematologic malignancies can result in LM in up to 24% of patients. The most common solid tumors causing LM are breast cancer, lung cancer, and melanoma, with incidences ranging between 5% and 23%. Leptomeningeal metastases risk rises with longer cancer survival.

In the United States, standard treatment for LM includes CSF diversion when indicated, radiation, local intrathecal (refers to intraventricular administration, unless otherwise specified) chemotherapy, and systemic chemotherapy. Recent reviews discuss management of LM. With standard interventions, median survival for patients with LM ranges from 8 to 16 weeks. Roughly 24% to 34% die of LM alone, 22% to 25% die of LM simultaneously with progressive systemic cancer, 19% to 44% die of systemic disease progression, and up to 10% die of other causes.

The incidence of brain metastases (BM) and LM may increase in the near future for at least 2 reasons: (1) longer control of non-CNS cancers may allow for more time for the development of CNS metastases and (2) the use of large-molecule antineoplastic agents with limited CNS and CSF penetration may control systemic disease but leave LM unaffected behind the blood-brain barrier (BBB) and blood-CSF barrier (BCSFB). Paradoxically, the newer large-molecule therapies may improve overall cancer survival while increasing the incidence of CNS metastases. Longer survival and exposure of tumor cells to genotoxic chemotherapy may select for increasingly chemoresistant cell clones, making LM even more resistant to therapy over time.

The Biology of CNS Metastases and LM

Once we understand the biology behind LM, we can develop therapies targeting these biological changes. Metastasis is a cascade of events with multiple cellular and molecular changes. For LM to develop, tumor cells must detach from the primary site, invade a blood or lymphatic vessel, survive vascular transit, adhere to host organ endothelium, invade the host organ, proliferate, and develop a blood supply. Molecular factors implicated in CNS metastases and LM include E-cadherin–catenin complexes, plasmin, urokinase–type plasminogen activator, metallopro-
The delivery of many anticancer drugs from blood to the CNS is limited by the presence of a high permeability barrier. The BBB and BCSFB have a high lipid solubility, pore size, and permeability to molecules of molecular weight less than 600. This may be due to the presence of the P-glycoprotein system, multidrug resistance proteins, and organic and inorganic ion transporters that can mediate efflux of some anticancer drugs away from the brain. 

**Drug Delivery**

The delivery of many anticancer drugs from blood to the brain and from blood to CSF is restricted, for multiple reasons. Drug-related factors include the drug’s level of protein binding and its molecular weight, polarity, and lipid solubility. The BBB and BCSFB have a more relaxed tight junction architecture that correlates with differential diffusion capacities between it and the BBB. Recent work has investigated the effect of P-glycoprotein-modulating drugs on the CSF penetration of some chemotherapies. Tamoxifen, a P-glycoprotein inhibitor, decreased the CSF penetration of paclitaxel, supporting the concept that the pumping direction of P-glycoprotein at the choroid plexus is in the opposite direction to the BBB. The P-glycoprotein system appears to direct natural product toxins away from the brain into the CSF, and when inhibited, lower CSF drug levels are found. Animal models reveal similar findings with the tyrosine kinase inhibitor gefitinib. Its administration results in lower CSF levels and higher brain parenchymal levels of the topoisomerase I inhibitor topotecan.

Table 1 shows the CSF:plasma ratios for some of the drugs studied in humans and rhesus monkeys. A CSF:plasma ratio lower than 0.05 signifies nonspecific leakage of drug. Table 1 shows that many drugs normally achieve CSF:plasma ratios lower than 0.05. However, once LM has arisen, or if radiation is directed to the CNS, leakage of the BCSFB develops, and larger molecules can leak from blood into CSF. Further, some drugs have an intrinsically high CSF:plasma ratio, suggesting their possible utility in treating LM. As the understanding of the BBB and BCSFB advance, we may ultimately be able to facilitate the CNS and CSF penetration of therapeutic molecules, which are now excluded.

**Treatments**

Intrathecal chemotherapies typically used in LM include methotrexate, cytarabine, liposomal cytarabine, and thiopeta. Systemic therapies are usually chosen based on tumor histology, drug penetration into the CSF, and a patient's prior drug exposure.

**Intrathecal Treatments**

Even though intrathecal chemotherapy is widely used in the United States for solid-tumor LM, proof of its benefit has not been established in randomized controlled trials. Randomized controlled trials do suggest modest improvements with long-acting over standard intrathecal chemotherapies, and some retrospective studies suggest intrathecal chemotherapy prolongs survival, but there exists contrary evidence. Recently begun randomized controlled trials, European Organization for Research and Treatment of Cancer 26051, is testing intrathecal liposomal cytarabine vs supportive care in solid-tumor LM.

Intraventricular (as opposed to intralumbar) chemotherapy delivery results in improved CSF drug levels and less interpatient variability of drug distribution. This form of regional chemotherapy has led to effective treatment of occult and overt meningeal leukemia in humans, and based on this success, investigators continue its evaluation in patients with solid tumor, hoping for similar outcomes. Pharmacokinetics of commonly used intrathecal anticancer agents shows that high drug concentrations can be achieved in the CSF and leptomeninges but not deep into the brain. Because of this, intrathecal administration is not effective for bulky disease in the meninges. Further, in solid-tumor LM, intraventricular administration, or the use of sustained-release chemotherapeutic agents if the lumbar route is used, appears to improve treatment outcome.

**Experimental and Newer Agents.** The most promising recently tested cytotoxic and radiotherapeutic agents are presented in Table 2. The topoisomerase inhibitors appear as effective as traditionally used intrathecal agents, and both etoposide and topotecan hydrochloride have little toxicity, so may be useful in combination with other agents or as prophylaxis. A concentration X time study of intrathecal topotecan is open and accruing patients within the Pediatric Brain Tumor Consortium. Because of pain associated with intrathecal administration, mafosfamide requires slow delivery and premedication with steroids and narcotics but may be useful in childhood CNS malignancies to help delay or avoid radiation exposure. Because of almost no toxicity and some efficacy (29% CSF clearance), sodium iodide I 131 (131I) will be further studied in a phase 2 trial with a higher-dose, multiday schedule. For similar reasons, phase 2 studies evaluating serial intrathecal injections of the GD2-targeted monoclonal antibody 131I-3F8, are under way. Early data suggest efficacy in childhood primitive neuroectodermal tumors and neuroblastoma.

**Noncytotoxic Intrathecal Therapies. Immunotherapies.** The CSF space may be excluded from the benefits of the systemic antitumor effects of the immune system, so im-
munotherapeutic approaches to the treatment of LM are theoretically attractive. Unfortunately, immune responses are frequently associated with inflammation. Intrathecal administration of interleukin 2 or interferon alfa both resulted in responses in patients with LM but were also fairly toxic, limiting enthusiasm for further development.88,89

**Rituximab.** Rituximab is a humanized monoclonal antibody against the CD-20 antigen expressed on most B-cell lymphomas. It has been used intravenously since 1997. Cerebrospinal fluid levels of this large molecule (146 kDa) are only 0.1% of the serum level after intravenous administration.77 Several case reports demonstrating safety and possible benefits of intrathecal administration of rituximab led to a recently reported phase 1 study.80 In this study, the maximum tolerated dose of intrathecal rituximab was 25 mg twice weekly (9 doses total). Mean peak CSF concentration 1 hour postdose rose to 472 µg/mL and estimated half-life averaged 34.9 hours. Cytologic responses were seen in 6 of 10 patients; 4 patients experienced a complete response; 2 patients experienced improvement in intraocular lymphoma; and 1 patient's intraparenchymal lymphoma improved. Toxic reactions were limited. Further studies developing this promising therapy are under way. Additionally, a study of intrathecal rituximab combined with intrathecal methotrexate for patients with intraocular or LM lymphoma has been initiated.

**Trastuzumab.** Trastuzumab is a humanized monoclonal antibody that binds to the epidermal growth factor receptor 2 protein, which is overexpressed in 30% of primary breast cancers, as well as some other tumors. Trastuzumab inhibits the growth of tumor cells and mediates antibody-dependent cellular cytotoxicity. A recent study...
The treatment of LM73,74 and exclude intrathecal therapy of response. Based on these results, further study of systemic treatment is under way. Based on the existing reports, capecitabine is now frequently being used in patients with LM or BM secondary to breast cancer, and further prospective study is warranted, possibly in combination with other agents.

**Systemic Treatments**

Numerous reports suggest that systemic therapy improves survival for patients with LM.72,93-100 Some authors feel systemic therapy is the most important part of the treatment of LM73,74 and exclude intrathecal therapy in patients with responsive cancers.99,95,97,101 Agents capable of producing adequate CSF concentrations following systemic administration may benefit patients with LM.

**Methotrexate.** Methotrexate inhibits dihydrofolate reductase and the synthesis of purine nucleotides and thymidylate, interfering with DNA synthesis and repair. At high doses, methotrexate has favorable CSF penetration. A prospective, nonrandomized study comparing intrathecal methotrexate (n = 15) vs high-dose systemic methotrexate (n = 16) in patients with LM produced provocative results. High-dose methotrexate (8 g/m² over 4 hours) resulted in a mean peak concentration of 17.1 µmol/L in the CSF; cytotoxic CSF methotrexate levels remained measurable much longer than with intrathecal dosing. Furthermore, there was higher CSF tumor cell clearance and survival was longer (13.8 months vs 2.3 months, P = .003) in the systemic methotrexate-treated cohort.102 Because of the favorable pharmacokinetics of high-dose methotrexate, further studies in patients with LM are warranted, possibly in combination with other agents.

**Capecitabine.** Capecitabine is a fluoropyrimidine carbamate designed as an oral alternative to 5-fluorouracil. Capecitabine is enzymatically converted to 5-fluorouracil at the tumor site. The increased drug concentration at the tumor site may enhance its antitumor activity and reduce systemic toxicity. Although there is no formal pharmacokinetic data regarding capecitabine’s behavior in the CNS, there are empirical observations of responses to the drug in patients with BM and LM.103,104 Capecitabine has also resulted in responses in a few patients with recurrent BM or LM even after previous capecitabine exposure.104,105 Based on the existing reports, capecitabine is now frequently being used in patients with LM or BM secondary to breast cancer, and further prospective study is under way.

**Temozolomide.** Temozolomide is an orally bioavailable alkylator that reaches CSF levels roughly 20% of those in the serum.11 In a pilot study of oral temozolomide in...
10 patients with LM, the drug was well tolerated, although no responses were seen. Two patients had stable disease through 2 courses (6 weeks receiving therapy, 4 weeks not receiving therapy) but progressed while not receiving treatment, suggesting that continuous treatment might be more efficacious.

**Hormonal Therapies**

There are several case reports of a beneficial contribution of hormonal therapy for patients with LM with hormone-sensitive tumors (breast and prostate cancer). Responses are reported lasting more than 12 months. For patients with LM from hormone-sensitive cancers, hormonal treatment is reasonable to continue or initiate and may provide some activity against the LM.

**Experimental Treatment**

**Pemetrexed.** Pemetrexed, a chemotherapeutic molecule similar to methotrexate, is approved for mesothelioma and non–small cell lung cancer and is active in methotrexate-resistant malignancies. The CSF penetration of pemetrexed was low in an animal model; however, the CSF pharmacokinetics of systemically administered pemetrexed are being evaluated in an ongoing study in patients with LM. The drug is unique from methotrexate in that it is a “multitargeted” antifolate compound acting through several enzyme systems involved in folate metabolism. Pemetrexed gains intracellular access via at least 4 mechanisms, which may increase its activity over methotrexate. Early results demonstrate CSF responses in patients with breast cancer with LM (J. Raizer, MD, written communication, June 22, 2009).

**Bevacizumab.** Bevacizumab is a systemically administered monoclonal antibody directed against VEGF. Bevacizumab is approved for use in colorectal, breast, and non–small cell lung cancers and glioblastoma multiforme. Recent reports have identified elevated VEGF levels in the CSF of the majority of patients with LM due to melanoma or breast or lung cancer. Preliminary data suggest that in LM responders CSF VEGF levels fall and correlate with response. The degree to which bevacizumab penetrates the CSF is unknown but is likely limited. Testing is under way at MD Anderson Cancer Center in patients with LM due to breast and lung cancer and melanoma to determine if systemically administered bevacizumab can affect CSF VEGF levels or impact tumor cells in the CSF.

**Gefitinib.** Gefitinib is a small-molecule tyrosine kinase inhibitor with activity against lung cancers that contain mutations of the epidermal growth factor receptor. Case reports have shown responses in patients with LM from non–small cell lung cancer.

A prospective study evaluating high-dose gefitinib (up to 1250 mg/d) in patients with LM with non–small cell lung cancer and sensitizing epidermal growth factor receptor mutations was recently closed. High doses of gefitinib were used (standard dose, 250 mg/d) attempting to increase CNS and CSF drug levels and improve antitumor effects. Early reports of the clinical, CSF, and imaging outcomes were promising; final results are forthcoming (D. Jackman, MD, written communication, June 22, 2009).

**Combination and Disease-Specific Treatments**

Most reports of intrathecal LM treatments include patients who simultaneously receive systemic agents, and many investigators feel combination intrathecal and systemic therapy improves outcomes. Several planned studies will evaluate the concept of combination therapy, prospectively. Some clinical trials in development include a phase 2 study of intrathecal thiopeta for patients with LM due to primary brain tumors, a phase 2 study of lomustine plus cisplatin plus vincristine sulfate and intrathecal liposomal cytarabine for adults with medulloblastoma and CSF positive for tumor cells, and a phase 1/2 study of oral capecitabine plus liposomal cytarabine in patients with breast cancer with LM (R. Soffietti, MD, written communication, June 27, 2009).

Because of a paucity of available patients, LM studies often accrue multiple primary histologies. This heterogeneity obscures potential efficacy signals. Investigators, with respect to rituximab, gefitinib, and bevacizumab, noted earlier, are beginning to design LM trials with specific histologies in mind.

**EARLY TREATMENT/PREVENTION OPPORTUNITIES**

Prevention strategies similar to those used for children with acute lymphoblastic leukemia or in patients with aggressive lymphoma may become feasible if genetic markers identifying tumors with a propensity to invade the CNS can be identified. High positive predictive value plasma or CSF biomarkers could allow for earlier treatment of LM, possibly affording better tumor control. Early studies suggest CSF VEGF may be useful as a biomarker, but further research is warranted. Until prevention is feasible, or biomarker use is validated, unique clinical scenarios may still hold opportunities for earlier treatment and better outcomes.

**BRAIN METASTASES**

Patients with BM may be at increased risk of developing LM, especially if the BM are located in the posterior fossa (BMPF). Among patients undergoing craniotomy for BMPF, estimates of the risk of developing LM are reported as high as 67%. Recent reports have begun to dissect out the details on the risk of CSF seeding after craniotomy. In a review of 379 patients with BMPF who were treated with either surgical resection or stereotactic radiation, 8.7% developed LM. But, there was a significantly higher risk of LM (14%; rate ratio, 2.45; P = .02) in those patients having a piecemeal resection of their BMPF when compared with either stereotactic radiation or en bloc resection. A follow-up study of 827 patients undergoing craniotomy for supratentorial BM found a similar result, with a hazard ratio of 5.8 (P = .002) comparing piecemeal resection vs stereotactic radiation and a hazard ratio of 2.7 (P = .009) comparing piecemeal re-
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Correspondence: Morris D. Groves, MD, UT MD Anderson Cancer Center, Department of Neuro-Oncology, 1400 Holcombe Blvd, Unit 431, Houston, TX 77030 (mgroves@mdanderson.org).

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REFERENCES

39. Slevin ML, Pliat EM, Ahern GW, Harvey VJ, Johnston A, Lister TA. Effect of


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