

Treatment Modalities for Leptomeningeal Metastases

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Secondary involvement of the leptomeninges represents an infrequent but devastating (and nearly always fatal) complication of solid tumors, hematologic malignancies (both leukemia and lymphoma), and primary brain tumors. Clinical suspicion of neoplastic meningitis (NM) may be raised by the appearance of multivariate neurological symptoms; however, a definitive diagnosis is often difficult to obtain. Improved treatments for primary malignancies and advances in diagnostic imaging technology have led to an apparent increase in the number of patients diagnosed with NM. Unfortunately, therapeutic options remain limited, particularly for patients with chemoresistant tumors. Optimized treatment remains controversial and may rely upon a combination of chemotherapy (intrathecal and/or intravenous) and concurrent focal radiotherapy. This review discusses the advantages and disadvantages of intra-cerebrospinal fluid (CSF) versus systemic strategies for treating NM. Clinical trial evidence is presented for the different treatment modalities. In addition, the therapeutic potential of intra-CSF therapy for cancer prophylaxis is discussed. Earlier diagnosis and more aggressive preventive treatment regimens may provide substantial increases in survival and favorably affect quality of life. Additional data from large-scale, well-controlled trials are required to more accurately assess the efficacy of intra-CSF versus systemic treatment in NM. Future treatment options using novel targets for intra-CSF therapy will be addressed as well.

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Metastatic spread of tumor cells to the leptomeninges of the central nervous system (CNS) is a severe complication of cancer that is usually associated with late stages of disease progression.¹ Malignant cells are disseminated within the cerebrospinal fluid (CSF) and replicate at various sites within the CNS. CSF is contained in the cerebral ventricles and in the subarachnoid space found between the pia mater and arachnoid leptomeningeal membranes, enveloping the brain and spinal cord. Cancer cells that penetrate into the CSF can form secondary deposits in the leptomeninges throughout the neu-

roaxis.^{2,3} Neoplastic meningitis (NM) is estimated to occur in 3% to 8% of all patients with cancer; however, as therapies improve and enable patients with cancer to live longer, this incidence appears to be increasing.¹ Due to the rapid pace of diagnostic and therapeutic advancements, malignant infiltration of the leptomeninges by systemic cancer is being recognized with increasing frequency.

Leptomeningeal metastasis of malignant cells is associated with high morbidity and mortality rates. The median survival of patients with untreated cancer with NM is 4 to 6 weeks. For these patients, death generally occurs because of progressive neurologic dysfunction.¹ Treatment is intended to improve or stabilize neurologic status, maintain neurologic quality of life (QoL), and prolong survival.⁴ Although fixed neurologic deficits are rarely improved with treatment, the progression of neurologic deterioration may be halted in some patients, and median survival can be increased to 4 to 6 months. Numerous prognostic factors for survival and response have been suggested, but many remain controversial. It is commonly accepted that poor prognosis is associated with low performance status (using validated QoL assessment instruments such as the Karnofsky Performance Scale [KPS]), multiple fixed neurologic deficits, the presence of bulky CNS disease,

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coexistent encephalopathy, and CSF flow abnormalities demonstrated by radionuclide ventriculography. Ideally, CNS cancers should be diagnosed in the early stages of disease to prevent progression of disabling neurologic deficits.¹

Current treatment strategies for leptomeningeal metastasis include radiation therapy (RT), systemic therapy, intra-CSF therapy (ie, intrathecal), and combination therapy. Systemic chemotherapy often is associated with difficulties in achieving and maintaining cytotoxic CSF concentrations.⁴ However, the use of high doses has, to a certain extent, resulted in cytotoxic concentrations in the CSF. Intra-CSF therapy has shown efficacy in the treatment of CNS cancers and may have potential for the prophylactic treatment of such cancers.⁴ Four main agents are currently used for intra-CSF therapy: methotrexate (MTX), thiotepa, cytarabine, and liposomal cytarabine.⁴ This review will discuss the efficacy and safety of the various treatment modalities and compare their advantages and disadvantages. Future medications may exploit novel points of entry to the CSF. A final discussion will highlight how the choroid plexus may represent a new transport interface for CNS cancer treatment and how it may enhance our prospects for targeted CSF drug delivery.⁵

INTRA-CSF CHEMOTHERAPY: ROUTES OF DELIVERY

Chemotherapies are required to achieve and maintain a therapeutic concentration at the target site for a sufficient amount of time in order to be efficacious.⁶ Most chemotherapies produce a pharmacologic response in a dose-dependent manner. Historically, chemotherapy has been delivered to the CNS via systemic intravenous (IV) routes or via direct intra-CSF injection. A major challenge associated with systemic therapy, which relies on the circulatory system for drug delivery to the CNS, lies in the ability to penetrate the blood-brain barrier (BBB) and blood-CSF barrier.⁷ Collectively, these barrier systems serve to maintain brain homeostasis by restricting the uncontrolled diffusion of blood-borne chemicals into the CNS parenchyma. Only a few chemotherapeutic agents have achieved cytotoxic intra-CSF concentrations after IV administration without reaching toxic levels systemically. High-dose IV deliveries of MTX, thiotepa, and cytarabine have been used effectively to treat CNS cancers; however, systemic toxicity remains an important concern.⁸⁻¹¹

The therapeutic or cytotoxic concentration required for MTX efficacy has been estimated at 3×10^{-6} mol/L; however, considerable debate persists regarding the absolute effective concentration.¹² Concentrations as low as 1×10^{-8} mol/L have been shown to produce substantial tumor-cell death, depending on the duration of exposure.¹³ A study by Shapiro et al¹⁰ found that IV injection of 50 mg MTX resulted in sub-cytotoxic

concentrations of drug in the ventricular CSF (peak serum concentration 2×10^{-5} mol/L; peak ventricular concentration $\leq 0.06\%$ of serum). IV infusion over 24 hours with a 10-fold higher dose (0.5 g/m^2) achieved greater CSF penetration but still did not achieve cytotoxic concentrations (mean serum concentration 2×10^{-5} mol/L; mean ventricular concentration 6×10^{-7} mol/L). This study confirmed that CNS permeability is limited following single-dose systemic IV administration of MTX; even with higher dose infusions, therapeutic concentrations in the CSF are rarely achieved. However, this early study used a lower dose of MTX than has been reported more recently, and concentrations were quantified following a single IV bolus. The precise amount of MTX that constitutes high-dose delivery is not clearly defined in the literature.¹⁴ Doses greater than 3 g/m^2 are used most often with the intent of delivering high-dose systemic therapy.

In a study by Glantz et al⁹ investigating the efficacy of high-dose IV MTX therapy (delivered by 4-hour continuous IV infusion at a dose of 8 g/m^2) for patients ($N = 16$) with nonleukemic leptomeningeal cancer, MTX concentrations in the CSF on average remained greater than 1×10^{-6} mol/L for 48 hours and greater than 1×10^{-7} mol/L for 93.3 hours. A retrospective comparison of cytologic and clinical response was made with a reference group of 15 patients who were treated with standard intrathecal MTX therapy during the same time interval (results compiled from Shapiro et al,¹⁰ Strother et al,¹⁵ and Bleyer et al¹⁶). Intrathecal MTX was administered at a dose of 12 mg, two doses per week during a 4-week period. Cytologic response was considered to be complete clearing of tumor cells from the CSF 1 month after initiation of treatment. Clinical response was assessed through neurologic examination at 1 month using the KPS (improved = improved KPS score and improvement in disease-related signs and symptoms; stable = unchanged or improved KPS score and no change in signs and symptoms; all other patients were considered to have progressed). Improved and stable patients were considered clinical responders. Cytologic and clinical responses were seen in 81% of patients treated with high-dose MTX. These response rates compared favorably with the rates of cytologic and clinical response (60% and 47%, respectively) seen in the group of patients who received intrathecal MTX therapy in the study by Glantz et al.⁹

Several studies also have demonstrated that therapeutic levels in the CSF may be achieved following systemic administration of high-dose unencapsulated cytarabine.¹⁷⁻²⁰ However, the measurement of unencapsulated cytarabine in the CSF is complicated by its rapid elimination and metabolism.²¹ Overall, systemic chemotherapy offers several potential advantages over direct CSF delivery methods. In particular, the necessity of lumbar punctures and surgery (eg, Ommaya reservoir) and

their associated complications are avoided.²² In addition, patients with an obstruction to normal CSF flow can be treated without correction of the flow abnormality and more uniform drug distribution may be achieved. Furthermore, because the drug reaches leptomeningeal tumor deposits through their systemic vascular supply, bulky disease may respond to treatment.²²

Direct intra-CSF injection of chemotherapeutic agents by either lumbar puncture or intraventricular Ommaya reservoir offers an alternative to systemic administration with the advantages of selective compartmentalized delivery and a lower propensity for systemic toxicity.^{4,6} The efficacy of intra-CSF therapy is limited by the ability of drug to penetrate surrounding parenchyma. Preclinical evidence demonstrated that tritiated (³H) MTX administered into the ventricles (of New Zealand white rabbits) via an Ommaya reservoir penetrates tissue in the grey matter adjacent to the CSF.²³ Similar distribution patterns have been reported following both lumbar and ventricular administration of cytarabine and MTX.²⁴ Mathematical modeling studies in various brain compartments following intra-CSF administration via lumbar puncture injection or Ommaya reservoir have expanded our understanding of drug flow dynamics and penetration.²⁵⁻²⁷ These models may offer some predictive guidelines for drug diffusion characteristics and can be useful in helping clinicians understand potential parameters limiting CSF drug distribution. They also may guide future drug design strategies.

Blasberg et al²⁶ constructed a model of MTX flow dynamics following intraventricular administration and found that movement of drug to the basal cistern and ventricle is very rapid, while movement to the lumbar sac is much slower. This model suggested that MTX concentrations continued to rise in periventricular tissues at 48 hours following administration. When the additive effects of capillary permeability and drug metabolism were incorporated into the model (half-life was set at ≤ 6 hours), the rise of MTX at 48 hours was no longer predicted, and the duration of cytotoxic levels in the tissue was reduced from 48 hours to 24 hours.²⁶ The authors postulated that MTX most likely reaches the subarachnoid space, producing a "second source" of drug after it returns to the ventricle. When the 6-hour estimated half-life was included in the modeling, MTX at 8, 24, and 48 hours did not penetrate tissue or produce adequate cytotoxic tissue levels. On the basis of these results, the authors suggest six primary limiting factors of CSF drug delivery to CNS tissue (Table 1).

The method by which drugs are administered directly into the CNS may affect distribution. For example, Shapiro et al¹⁰ compared the kinetics and distribution of MTX when administered via lumbar puncture or Ommaya reservoir. The authors concluded that intra-CSF therapy via Ommaya reservoir produced the most

Table 1. Factors Limiting Drug Delivery to Brain Tissue After Intrathecal Drug Administration²⁶

1. Drug distribution between CSF compartments, where the lumbar sac has a longer delay than the cistern and ventricle
2. CSF clearance of drug
3. Apparent diffusion constant of drug through brain ECF
4. Distance between opposing CSF surfaces
5. Half-lives of drug in brain ECF: metabolism and transcapillary drug loss
6. CNS and systemic toxicity of drug

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; ECF, extracellular fluid.

consistent and durable cytotoxic levels of MTX in the CSF. In this study, MTX injection via lumbar puncture did not produce reliable CSF drug levels and occasionally resulted in epidural and subdural leakage.¹⁰ Similarly, another study concluded that intraventricular MTX is significantly more effective against CNS leukemia than identical therapy given via lumbar puncture.²⁸ In contrast, evidence suggests that liposomal cytarabine achieves uniform distribution throughout the neuroaxis when given either via lumbar puncture or Ommaya reservoir.²⁹⁻³¹ Liposomal cytarabine has a unique pharmacokinetic profile with a ventricle half-life of 130 hours (administered via lumbar puncture) to 141 hours (administered intraventricularly), which was considerably longer than unencapsulated cytarabine (2 hours) or MTX (8 to 15 hours).³²⁻³⁴ In general, the preferred route of intra-CSF chemotherapy is through the intraventricular Ommaya reservoir, which exploits CSF bulk flow for more reliable and uniform delivery of drug throughout the neuroaxis.³⁵

A number of early- and late-stage risk factors and potential complications associated with intra-CSF therapy exist. Early complications may include surgical complications (eg, misplacement of intraventricular catheters, mechanical dysfunction, risk of hemorrhage or CSF leaks into the peritoneum) and inflammatory reactions (eg, transient chemical meningitis that is manifested by fever, headache, nausea, vomiting, and photophobia).³⁶ Late complications may include necrotizing leukoencephalopathy that may be progressive and fatal.^{37,38} Clinical sequelae of leukoencephalopathy include confusion, somnolence or irritability, ataxia, dementia, and tremor.²³ An important risk factor for intra-CSF therapy complications is CSF flow obstruction.^{35,39}

Abnormal CSF flow is commonly reported in patients with bulky leptomeningeal cancer.^{35,40,41} Among patients with NM from solid tumors, CSF flow obstructions have been reported to occur in $\geq 30\%$ of pa-

tients.^{35,40,42} CSF flow abnormalities can impede adequate distribution of intra-CSF drugs to all disease areas and may therefore constitute one reason for treatment failure.³⁵ Non-uniform drug distribution secondary to CSF flow obstruction has important implications for the evaluation of therapeutic approaches, as it may confound proper and realistic evaluation of a medication's efficacy.^{40,42} CSF blocks occur most commonly at the base of the skull, in the spinal canal, and over the cerebral convexities.³⁵ Neurotoxicity also may result due to a high drug accumulation in unimpeded CSF compartments.³⁵ Radionuclide studies using either indium 111-DTPA or technetium 99m macro-aggregated albumin are routinely used to assess CSF flow dynamics.^{40,43,44} Involved-field radiotherapy is currently the treatment of choice for patients with a CSF flow block and is effective in 50% of patients with intracranial CSF obstruction and in 35% of patients with spinal subarachnoid CSF obstruction.^{4,44} Correction of CSF flow obstruction by radiotherapy has been shown to result in significant improvements in response and survival.^{35,42}

INTRA-CSF PROPHYLAXIS

There is a genuine need for prospective trials investigating novel therapeutic strategies and interventions for patients with CNS metastases. Early diagnosis is critically important, because patients who present with few or no neurological deficits and a low CNS tumor burden commonly achieve improved treatment response and survival rates.⁴ Patients at high risk for NM may be ideal candidates for prophylactic intervention. Factors that put patients with lymphoma at high risk include a raised lactate dehydrogenase level; a low serum albumin level; age <60 years; involvement of the testis, breast, or bone marrow; and more than two extranodal disease sites.⁴⁴ Optimally, NM should be diagnosed in the early stages of disease to prevent progression of disabling neurologic deficits and to increase the potential for successful prophylactic intervention. Potential advantages of prophylaxis for solid tumor metastases to the leptomeninges needs to include: minimal disease setting, minimal CSF flow abnormalities, and the absence of acquired drug resistance. Conversely, obstacles to effective prophylaxis include the high risk of associated toxicity and the fact that intervention often occurs in late-stage, widely disseminated systemic cancer. Furthermore, CNS metastases are rarely the single site of relapse, and patients with late-stage cancer often possess a higher degree of chemoresistance because of prior exposure to treatment regimens.^{39,45}

There are currently no randomized studies investigating chemotherapeutic drug delivery for established NM in patients with solid tumors. The lack of controlled data for the successful treatment of leptomeningeal disease has impeded the implementation of prophylactic measures. However, prophylaxis offers significant potential advantages and has been used successfully in other disease settings. For example, antibiotics have been used in the prophylaxis of infection of postoperative wounds and surgical site infections.⁴⁶ Clear guidelines have been established for the prophylactic use of antibiotics.^{46,47} Antibiotic prophylaxis is indicated in situations where the risk of infection substantially outweighs the risk of potential adverse events from antibiotic use.⁴⁶ Guidelines taken from prophylaxis in other disease models could form the basis for a new model of intra-CSF prophylaxis in patients with solid-tumor NM.

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SOLID-TUMOR NM: THERAPEUTIC POTENTIAL OF INTRA-CSF DRUG DELIVERY

The availability of safe and effective chemotherapies with sustained intra-CSF pharmacokinetics is an obvious prerequisite for the initiation of prophylactic therapy. Currently, there is no high-level evidence that intra-CSF chemotherapy provides clear benefit to patients with NM from solid tumors. Intra-CSF therapy and local radiotherapy have become the standard of care on the basis of success with the treatment of specific cancers (not necessarily solid tumors), including leukemia, lymphoma, and breast cancer.⁴⁸⁻⁵¹ Shapiro et al⁴⁸ conducted a study in patients receiving intraventricular MTX and/or cytarabine via Ommaya reservoir, either with or without CNS irradiation. The longest median survival among patients with solid tumors was 5 months for patients with breast cancer with CNS metastases. The majority of these patients received combined MTX/cytarabine therapy with additional focal CNS irradiation. Other studies have reported variable mean survival times ranging from 5 weeks to 3 months.^{8,52,53} Prognosis and survival time depend upon a variety of factors, including primary tumor type, disease stage, and patient characteristics (eg, age). Disease- and patient-related factors may figure more prominently in prognosis and survival than specific factors related to the mode of therapeutic intervention.

Several studies suggest that there may not be any added benefit, in terms of prognosis or survival, to intra-CSF versus systemic therapy for NM from solid tumors.^{29,37,54-58} It bears noting that several of these studies suffer from limitations such as: being underpowered to detect significant differences between groups, the failure to randomize patients to intraventricular or lumbar puncture administration, not choosing clinically meaningful end points, and the appropriateness of intrathecal dosing and frequency.

There are many factors that may account for a poor response to intra-CSF chemotherapy in NM from solid tumors. These include a low degree of chemosensitiv-

ity of solid tumors, a small spectrum of available therapies,⁴⁵ poor diffusion of chemotherapeutic drugs, inadequate penetration into the bulky tumor,^{23,24} and a high degree of tumor chemoresistance.⁴⁵ Enhanced penetration through systemic drug delivery is partially supported by the outcome of several non-randomized studies.^{8,54,55} Chemotherapeutic response (measured by clinical assessment and survival) was improved with combined systemic and intra-CSF therapy versus no systemic therapy in two separate studies.^{8,54} In addition, two retrospective studies of patients with breast cancer showed similar survival but reduced toxicity with systemic versus intra-CSF therapy.^{54,55} In contrast, a more recent retrospective study of patients with breast cancer highlighted the importance of CSF clearance in clinical outcome in these patients.⁵⁹ This study reported significant improvements in median survival ($P < .003$) and clinical improvement in patients receiving intrathecal MTX whose CSF was clear of abnormal cells compared with those patients whose CSF did not stabilize.

A randomized study conducted by Boogerd et al⁵⁸ also provides support for the concept that standard systemic chemotherapy with RT, in the absence of intra-CSF therapy, may be a feasible treatment option for NM secondary to breast cancer. In this study, treatment differed only in the inclusion or exclusion of intraventricular chemotherapy. Patients with breast cancer were randomized to receive either intra-CSF MTX with appropriate systemic chemotherapy (not defined but based on previous treatment, hormone receptor status, and patient condition), and, if necessary, radiation therapy to relevant sites ($n = 17$), or they received essentially the same therapeutic regimen but without intra-CSF MTX ($n = 18$). Analysis of the intent-to-treat population revealed that a higher proportion of patients receiving systemic therapy without intra-CSF therapy exhibited neurological improvement and/or stabilization (67% [12/18] *v* 59% [10/17]; $P =$ not significant [NS]) and slower time to neurologic progression compared with patients receiving intra-CSF therapy (overall median 24 weeks *v* 23 weeks, respectively; $P =$ NS). The median survival was not significantly different between groups (18 *v* 30 weeks, respectively; $P = .32$). Likewise, the 1-year survival did not differ significantly between groups (18% *v* 32%, respectively; $P =$ NS) (Figure 1).⁵⁸ Overall, treatment-related neurologic complications and toxicities (including headache, lethargy, cognitive impairment, and delayed leukoencephalopathy) were significantly higher for the group that received intra-CSF therapy (47% *v* 6%; $P = .0072$). This study concluded that the addition of intraventricular chemotherapy to systemic therapy and involved field radiotherapy in patients with NM from breast cancer does not lead to improved neurological response or survival but instead may be associated with increased treatment-related toxicity.⁵⁸

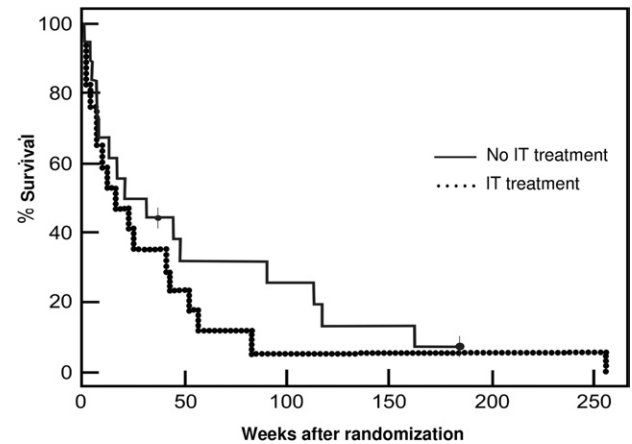


Figure 1. The effect of intrathecal chemotherapy on the survival of patients with leptomeningeal metastasis from breast cancer. Survival curves are given for the intraventricular treatment (IT) group versus the no-IT group. At 1 year, estimated survival was 18% ($\pm 9\%$ [SE]) for the IT arm and 32% ($\pm 12\%$) for the no-IT arm ($P = .32$, log-rank test). Median survival was 18.3 weeks (± 6.7) in the IT arm and 30.3 weeks (± 10.9) weeks in the no-IT arm ($P =$ NS). Reprinted with permission.⁵⁸ Copyright © 2004 Elsevier Ltd.

Large-scale, randomized studies are warranted to provide further evidence of the benefit, or lack thereof, of intra-CSF treatment in NM from solid tumors. In an attempt to address this important issue, the European Organization for Research and Treatment of Cancer (EORTC) 26051 trial is investigating the benefit of intra-CSF liposomal cytarabine in patients with NM from breast cancer and lung cancer. Liposomal cytarabine was chosen, as it confers a number of benefits over unencapsulated cytarabine and MTX, including sustained release of cytarabine and therefore a less frequent dosing schedule;⁶⁰ even distribution of cytotoxic concentrations throughout the neuroaxis when delivered via lumbar puncture or Ommaya reservoir;⁶¹ and prolonged progression-free survival.²⁹ Patients diagnosed by cytologic examination and/or magnetic resonance imaging and without CSF flow blockade are randomized to receive a combination of both radiation therapy and appropriate primary chemotherapy ($n = 47$) or radiation therapy, chemotherapy, and intra-CSF liposomal cytarabine ($n = 47$). Patients are stratified according to tumor type (eg, breast cancer or lung cancer), KPS score, and institution. The primary end points are neurological progression-free survival and overall safety profile. Secondary end points include survival, improvement of signs and symptoms, and QoL (assessed using the EORTC QLQ-C30 and the Brain Module 20).

A number of potentially confounding variables associated with evaluating the efficacy of intra-CSF therapies warrant careful consideration. Apart from CSF

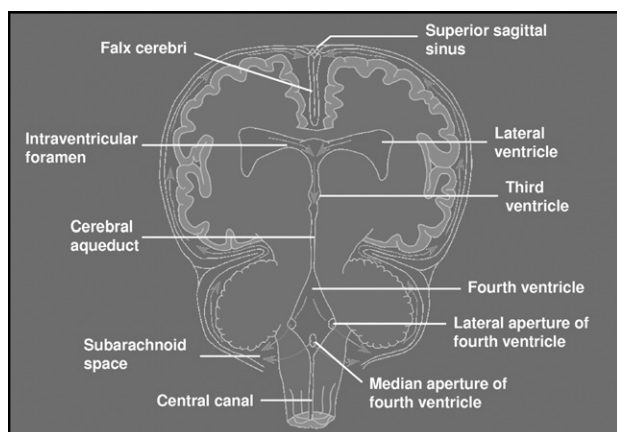


Figure 2. Cerebrospinal fluid (CSF) production and circulation depicted on a coronal brain section of the posterior central nervous system (CNS). CSF originates from the choroid plexi of the lateral and third ventricles and flows downward through the narrow cerebral aqueduct (arrows). It then empties into the fourth ventricle and is driven downward around the spinal cord (subarachnoid space) and upward over the convexities of the cerebral hemispheres. CSF flows outward into the venous blood of the superior sagittal sinus and also into the lymphatic system of the eye and nose.^{5,62}

flow abnormalities or obstructions,³⁵ the differential chemosensitivity of various types of solid tumors also can complicate analysis of the results.⁴⁵ As discussed above, abnormal flow affects the distribution of drug and, consequently, restricts access of the drug to the tumor tissue.³⁵ To alleviate any doubt that intra-CSF therapy has the opportunity to be effective, it is recommended to include patients with flow abnormalities but to provide radiation therapy to remove the abnormality before randomization. To avoid a potentially spurious evaluation, it also is recommended that solid-tumor NM with a high propensity for developing treatment resistance over time (eg, melanoma) be excluded from analyses. In addition, the method chosen for quantifying outcome measures must be carefully considered. For example, the EORTC 26051 trial uses neurologic progression-free survival as a primary end point and allows clinicians to measure this outcome in an unblinded manner. Because this methodology may introduce unintended bias, an outside masked source for measuring clinical outcome and the use of prospectively defined objective criteria are recommended to govern the quantification process.

NOVEL MODALITIES FOR INTRA-CSF CANCER THERAPY AND PREVENTION—EXPLOITING THE CHOROID PLEXUS

CSF flow has a profound impact on cerebral metabolism.^{5,62} CSF flow, volume, and pressure are regulated and maintained by transport processes at barrier inter-

faces.⁵ There are two principal interfaces that act in this capacity: the BBB and the blood-CSF barrier. The cells forming these virtually impenetrable barriers are endothelial and epithelial, respectively, which are joined by tight junctions that restrict free passage of water-soluble molecules and cells.⁵ The BBB interface transports glucose, amino acids, free fatty acids, and peptides, whereas the blood-CSF epithelial interface transports growth factors, vitamins, and hormones.⁶³

The blood-CSF barrier is widely distributed and, with its wide array of transporters, may represent an efficient alternate route for chemotherapeutic drug entry into the CNS.⁵ This barrier is composed of the choroid plexus and the arachnoid membrane.⁶⁴ Representing the primary site of CSF production, the choroid plexus is composed of a rich capillary bed, pia mater, and epithelial cells.⁷ Drugs that penetrate the lateral ventricle choroid plexus are conducted downstream by CSF bulk flow in the ventricular system and are thereby brought into contact with all regions of the brain (Figure 2).^{5,62} Although it accounts for only 0.2% of brain weight, the choroid plexus is necessary for adequate nutrition and function of the brain.⁵ Additional functions of the choroid plexus include renal regulation, hepatic metabolism, immune cell trafficking, endocrine regulation, maintenance of osmotic balance, and regulation of trophic factors (Table 2).^{5,7}

The choroid plexus comprises a heterogeneous population of cells and a diverse complement of cellular proteins.⁵ Strategies for targeted delivery of pharmaceutical agents to the CSF could conceivably harness the unique choroid plexus cellular mechanisms involved in: (1) the transport of anti-tumor agents between the blood and CSF (eg, prolactin receptor localized in the blood-CSF barrier but not the BBB)⁶⁵; (2) the Na⁺/ascorbate cotransporter that is unique to

Table 2. Versatile Functions of the Choroid Plexus^{5,7}

Function	Example
Renal regulation	pH and ion regulation
Hepatic metabolism	P450 metabolism
Immune-cell trafficking	Antigen-presenting cells; leukocyte-trafficking regulation
Endocrine regulation	AVP, ANP, volume regulation
Maintenance of osmotic balance	NaKCl cotransport
Regulation of trophic factors	Vitamins, growth factors

Abbreviations: AVP, arginine vasopressin; ANP, atrial natriuretic peptide.

the blood-CSF barrier⁶⁶; (3) viruses that readily infect the choroid plexus epithelium⁶⁷⁻⁶⁹; or (4) leukocyte traffic across the choroid plexus.⁷⁰⁻⁷² In principle, researchers could also develop strategies to prevent access of tumor cells into the CSF by blocking choroid plexus cell-surface markers to which tumor cells are attracted.^{69,73} Exploitation of the multivariate functions of the choroid plexus has potential for the development of novel approaches to CSF-targeted chemotherapy.

CONCLUSION

Intra-CSF therapy holds significant promise for the treatment and prevention of NM from both solid and hematologic tumors. There is a paucity of data from rigorously controlled trials investigating the efficacy and safety of intra-CSF therapies for solid-tumor NM. Randomized and well-controlled trials may provide support for the use of available intra-CSF therapies in patient populations with solid-tumor NM. A combination of both systemic, intra-CSF, and—in the case of bulky tumors—RT could be employed both to treat the primary tumor and to prevent neoplasms from entering the CSF. New therapies and regimens may be developed that target novel CSF entry points; the choroid plexus may represent one such therapeutic opportunity.

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