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REVIEW ARTICLE

Chemotherapy Delivery Issues in Central Nervous System Malignancy: A Reality Check

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ABSTRACT

Purpose
This review assesses the current state of knowledge regarding preclinical and clinical pharmacology for brain tumor chemotherapy and evaluates relevant brain tumor pharmacology studies before October 2006.

Results
Chemotherapeutic regimens in brain tumor therapy have often emerged from empirical clinical studies with retrospective pharmacologic explanations, rather than prospective trials of rational chemotherapeutic approaches. Brain tumors are largely composed of CNS metastases of systemic cancers. Primary brain tumors, such as glioblastoma multiforme or primary CNS lymphomas, are less common. Few of these tumors have well-defined optimal treatment. Brain tumors are protected from systemic chemotherapy by the blood-brain barrier (BBB) and by intrinsic properties of the tumors. Pharmacologic studies of delivery of conventional chemotherapeutics and novel therapeutics showing actual tumor concentrations and biologic effect are lacking.

Conclusion
In this article, we review drug delivery across the BBB, as well as blood-tumor and –cerebrospinal fluid (CSF) barriers, and mechanisms to increase drug delivery to CNS and CSF tumors. Because of the difficulty in treating CNS tumors, innovative treatments and alternative delivery techniques involving brain/cord capillaries, choroid plexus, and CSF are needed.

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INTRODUCTION

Chemotherapeutic drug concentrations within the CNS depend on multiple factors, including the permeability of the blood-brain barrier (BBB) to the chemotherapeutic agent, the extent to which the drug is actively transported out of the brain, and the drug volume of distribution in the brain parenchyma. Brain distribution incorporates cellular uptake, binding to lipids and proteins, and accumulation in cellular subcompartments and organelles. The BBB limits CNS delivery of many common chemotherapeutic agents.[1,2] The unidirectional transfer coefficient (K_{in}) is a quantitative measure of the ability of a drug to pass from plasma into brain. K_{in} is largely determined by lipid solubility because agents must first dissolve in the lipid membranes of the BBB to cross the BBB by lipid-mediated diffusion. Figure 1 plots K_{in} versus the octanol/water distribution coefficient, a measure of solute lipophilicity.[3] The best-fit regression line for 20 reference permeability markers, which bind minimally to plasma proteins and cross the BBB by passive diffusion, is linear over 5 orders of magnitude (Fig 1). Conversely, K_{in} values for a variety of anticancer drugs fall significantly below the line predicted for BBB passive diffusion. For many agents, the deficit exceeds 3 orders of magnitude (ie, $< 0.1\%$). Factors contributing to poor chemotherapeutic uptake across the BBB include plasma protein binding, solute molecular weight, and active efflux transport.

Plasma protein binding. Many chemotherapeutic agents (eg, chlorambucil, etoposide, melphalan, vincristine, and paclitaxel) bind more than 90% to plasma proteins, which reduces the free fraction of drug in plasma that is available to cross the BBB. K_{in} for these agents is directly proportional to the plasma-free fraction.[4] For chlorambucil, which is 99% bound, protein binding lowers brain uptake by 2 orders of magnitude.

Solute molecular weight. The BBB blocks transvascular leakage of most molecules larger than 180 daltons.[1,2] Many chemotherapeutics exceed 400 daltons of molecular weight (eg, vincristine, vinblastine, paclitaxel, and etoposide).

Active efflux transport. The BBB expresses high levels of drug efflux pumps (eg, P-glycoprotein,

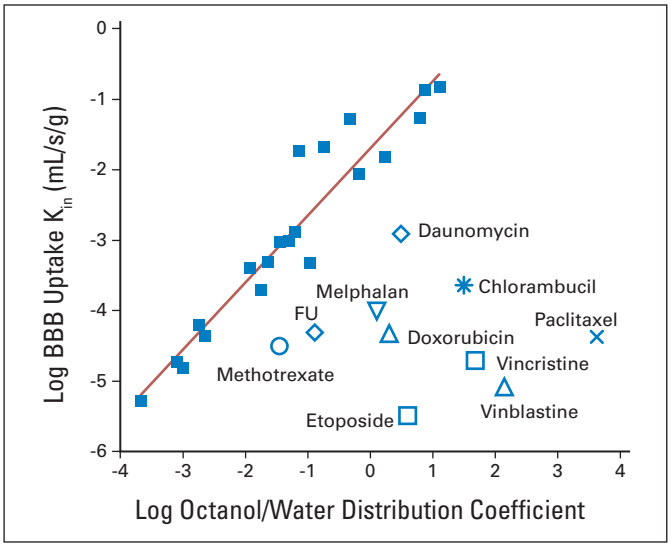

Fig 1. Relationship between blood-brain barrier (BBB) permeability and octanol/water partition coefficient for chemotherapeutic agents. The solid line is the least-squares fit to the data for agents that are not actively taken up by the brain or pumped out by the BBB.[3]

breast cancer–resistance protein, and other multiple drug-resistance transporters), which actively remove chemotherapeutic drugs (eg, paclitaxel, vincristine, vinblastine, doxorubicin, and etoposide) from the brain. Inhibition of active efflux can increase brain uptake K_{in} by two- to 50-fold[5] and may improve the clinical efficacy of substrate drugs.[6] The brain distribution of the tyrosine kinase inhibitor imatinib is reduced by active efflux via P-glycoprotein, which may be implicated in rare cases of CNS relapse in chronic myelogenous leukemia.[7] Delivery of taxanes into the brain may be improved by coadministration of inhibitors of P-glycoprotein; however, this also may enhance neurotoxicity.[8] Patupilone, an epothilone with novel taxane-like microtubule-stabilizing activity, is resistant to P-glycoprotein–mediated efflux of taxanes. This agent penetrates the brain in mouse models and is currently in clinical trials in patients with brain metastases.[9]

The integrity of the BBB can be compromised in brain tumors. New vasculature within the tumor is often disordered and highly permeable, but infiltrating tumor makes use of the existing brain vasculature with a largely intact BBB. The magnitude of tumor vascular permeability varies within tumors both spatially and temporally, with the greatest permeability elevation in tumor core and a relatively intact BBB at the proliferating tumor edge (brain adjacent to tumor).[10]

Drug accumulation in a brain tumor is limited even in the presence of a compromised BBB because of tumor interstitial fluid gradients. Interstitial fluid pressures can be more than 50 mmHg in peritumoral areas compared with 2 mmHg in a normal brain.[11,12] This high-pressure difference reduces diffusion of drugs into tumor tissue and enhances diffusional loss to surrounding brain tissue and out of the cerebrum completely.[11,13] Targeting vascular endothelial growth factor (VEGF) with the monoclonal antibody (mAb) bevacizumab may act to normalize tumor interstitial fluid pressure to increase drug delivery.[14]

CNS PHARMACOKINETICS OF CHEMOTHERAPEUTIC AGENTS

Tissue concentrations of lipophilic agents are predominantly controlled by plasma protein binding, active efflux transport, and drug metabolism. Delivery of water-soluble drugs to brain tumors is more complex, and pharmacokinetic data on this issue are scarce. Table 1 presents the pharmacokinetics of common chemotherapeutic drugs in the brain and in brain tumors.

Drug concentrations in brain tumors can vary by the route of delivery. For etoposide, therapeutic concentrations were found in glioblastomas and astrocytomas after intravenous (IV) delivery, but concentration decreased with increasing distance from the tumor.[23] The etoposide concentration was found to be four times higher after intra-arterial (IA) administration than IV.[22] Route of delivery impacted brain delivery of cisplatin, with IA administration increasing delivery to glioma two-fold compared with IV administration.[18] One study reported results of brain pharmacokinetics of cytarabine, comparing different routes of administration.[20] After IV administration, a diffuse pattern of low drug concentrations was detected throughout the brain.[20] Vincristine and vinblastine penetrate brain tumors poorly despite their high lipid solubility (Fig 1), even after IA administration,[31] because of efflux pumps. Doxorubicin is not detected in the brain after IV injection, but it can penetrate the CNS after IA administration. However, doxorubicin is associated with high rates of neurotoxicity.[21]

Methotrexate is the most widely used hydrophilic chemotherapeutic agent in primary CNS lymphoma (PCNSL), but high doses must be administered to achieve therapeutic drug concentrations in the tumor and surrounding brain. Although one early rat study showed a median brain/serum ratio of 0.2 ± 0.12,[26] other studies show orders of magnitude less methotrexate in brain and tumor.[27] The steady-state between plasma and extracellular fluid of brain tumors is rapidly reached, but it can be modulated by different routes of administration. IV bolus administration increases delivery of methotrexate to brain extracellular fluid by three-fold compared with slow IV infusion.[27] Methotrexate delivery to CNS is enhanced four- to seven-fold when administered IA after osmotic BBB disruption (BBBD) compared with IA administration without BBBD.[32]

Drug concentration can vary by tumor type. In one study, metastatic brain tumors showed 2.5-fold higher paclitaxel concentrations than primary brain tumors.[6] Assessing cisplatin delivery in PCNSL, meningioma, and medulloblastoma, IV cisplatin achieved concentrations in the brain tumor as high as in extra-CNS tumors.[16] In contrast, nontherapeutic concentrations of cisplatin leaked into the resection cavity in gliomas.[16] Factors influencing tumor cisplatin concentrations include calcium levels, the fatty acid composition of the cell membrane, and prior therapies.[16,17] Dexamethasone treatment can decrease the concentration of chemotherapy in the brain around the tumor, without affecting the concentration in the tumor itself.[16,33]

Metabolism can affect drug delivery, retention, and efflux. Studies with busulfan in normal animal brains and in one patient showed rapid uptake into the CNS and then a stable brain/plasma concentration ratio of 0.74.[15] However, the proportion of active metabolites was only 6% in both brain and in plasma.[15] The active metabolite of ifosfamide has been found in both cerebrospinal fluid (CSF)[34] and aqueous humor.[35] Idarubicin has been studied along with its active metabolite, idarubicinol, in brain biopsies of patients with

Table 1. Pharmacokinetics of Drugs in Brain and Brain Tumors

Drug	Reference	Method	Tumor and BAT	Normal Brain
Busulfan	Hassan et al, 1992[15]	In monkeys, one adult with AML without CNS disease: IV administration		Brain:plasma ratio constant at 0.74 ± 0.05 Brain delivery = 20% of administered dose 6% of brain and plasma radioactivity identified as active busulfan
Cisplatin	Stewart et al, 1995[16] and 1994[17]	Human surgical tumor specimen after IV or IA administration	Therapeutic concentration in tumor Higher levels in PCNSL, meningiomas, medulloblastomas Platinum concentration decreased with distance from tumor	
	Nakagawa et al, 1993[18]	Human surgical tumor specimen after IV or IA administration	IA administration increased drug levels by two-fold compared with IV administration in tumor and BAT	
	Straathof et al, 1998[19]	Glioma bearing rats after IV administration	Tumor concentration = 0.76 ± 0.23 μg/g; tumor:plasma ratio = 1.06 BAT concentration = 0.53 ± 0.21 μg/g; BAT:plasma ratio = 0.74	Brain concentration = 0.070 ± 0.012 μg/g; brain:plasma ratio = 0.097
Cytarabine	Groothuis et al, 2000[20]	Healthy rats, one healthy dog after IV or CED delivery		After IV: low concentration throughout brain After CED, high localized concentration Low rate loss constant from brain
Doxorubicin	Neuwelt et al, 1981[21]	Healthy dogs and rats, IV or IA + BBBD		After IV: not detected After BBBD: detected in brain, neurotoxic
Etoposide	Savaraj et al, 1987[22]	In dogs, after IV and IA administration		Brain concentration 4 times higher after IA than IV
	Zucchetti et al, 1991[23]	Human glioblastomas, astrocytomas (100 to 150 mg/m^2 IV)	Tumor concentration > 1 μg/g Not found in peritumoral area Decrease with distance from tumor	
Idarubicin	Boogerd et al, 1999[24]	Human brain metastasis biopsies or malignant glioma, oral	Tumor:plasma ratio = 1.2 to 5.8 Drug level at periphery of tumor > plasma	
Methotrexate	Neuwelt et al, 1984[25]	Rats with glioma, IV ± BBBD	Variable drug levels in tumor and BAT	Increased delivery after BBBD (4 to 7 times)
	Slørdal et al, 1988[26]	Healthy rats, IV		Median brain:serum ratio = 20% ± 12
	Dukic et al, 2000[27]	Rats with glioma, IV + microdyalisis	High intersubject variability Rapid equilibration between tumor and plasma 3 times higher level after IV bolus *v* IV infusion	
Thiotepa	Egorin et al, 1984[28]	Healthy mice, IV		Rapid distribution Brain level = 30% to 50% of plasma Not detected after 1 hour
Topotecan	Straathof et al, 1999[29]	Gliomas-bearing rats after IV administration	Tumor concentration = 96 ± 33 μg/g; tumor:plasma ratio = 0.96 BAT concentration = 13 ± 4.9 μg/g; BAT:plasma ratio = 0.13	Little uptake (20-fold < in tumor)
Vincristine/vinblastine	Greig et al, 1990[30]	Rats with carcinosarcomas	No tumor uptake	No brain uptake
	Boyle et al, 2004[31]	Normal rats and IA in glioblastoma rats	No tumor uptake	No brain uptake

Abbreviations: BAT, brain around tumor; AML, acute myeloid leukemia; IV, intravenous; PCNSL, primary central nervous system lymphoma; IA, intra-arterial; CED, convection-enhanced delivery; BBBD blood-brain barrier disruption.

breast cancer metastasis or malignant glioma.[24] The tumor concentration of idarubicinol was higher than the plasma peak level, but it is unknown if this was due to enhanced metabolism, increased cellular uptake in the tumor, or decreased efflux activity. Systemic metabolism can decrease brain tumor concentrations by decreasing the amount of drug available for delivery. Activation of cytochrome P450 enzymes with antiseizure medications can increase the dose requirement for some chemotherapeutics by two- to three-fold.[36]

Cyclophosphamide is commonly used in the first-line treatment of systemic non-Hodgkin's lymphoma and carcinomas, and it can be used at high doses in intensive chemotherapy before stem cell rescue. As a prodrug, it requires activation by hepatic cytochrome P450 enzymes. However, the active metabolite phosphoramide mustard is difficult to measure. Therefore, pharmacokinetic data from studies using radiolabeled cyclophosphamide are of little value, as the concentration of the active metabolite is not measured.[37] One study measured the alkylating activity of the metabolites of cyclophosphamide and found a brain/plasma concentration ratio of 0.20 in a normal rat brain.[38]

Metabolism of drugs can also limit pharmacologic measurements. Measurement of brain delivery of cytarabine is complicated by its rapid elimination and metabolism to inactive uracil arabinoside. Cisplatin pharmacology studies may be complicated by the difficulty

of differentiating active drug from inactive conjugates or free platinum.[18,39] Rapid distribution of thiotepa, a drug used in high-dose chemotherapy with autologous stem-cell transplantation, was observed in a normal brain, with tissue/plasma concentration ratios of 0.3 to 0.5.[28] Thiotepa was not detected in either the plasma or brain for 1 hour after administration, but this likely reflects its transformation into tepa, the active metabolite of thiotepa, rather than drug efflux.

A number of newer chemotherapeutic agents, such as gemcitabine, docetaxel, pemetrexed, irinotecan, and topotecan, which show promising antitumor activity against systemic tumors, show limited delivery across the BBB because of active efflux transport and plasma protein binding. Topotecan, for example, is a substrate for a multidrug resistance pump,[40] so that although it shows high concentrations in rat glioma, the concentration decreases sharply with increasing distance from the tumor.[29] The tyrosine kinase inhibitor imatinib binds heavily to plasma proteins and is a substrate for active efflux pumps.[41] The second-generation agent lapatinib also is subject to P-glycoprotein-mediated efflux, so may not be effective against brain tumors.[42] Further, downstream targets, such as signal transducer and activator of transcription 3 and histone deacetylase may be promising targets for selective inhibitors that cross the BBB.

The above studies and Table 1 demonstrate that the pharmacokinetics and actual concentrations of only a few of the commonly used chemotherapeutics have been evaluated in the normal brain, brain tumor, and tumor-infiltrated brain around tumor for any of the common CNS tumors (metastases, glioblastoma, and PCNSL). Measurement of the distribution of active drug in and around brain tumors should be a major goal in brain tumor therapy studies. One recent study used microdialysis to more accurately evaluate drug levels in extracellular fluid in high-grade glioma subjects (n = 4) after IV methotrexate (12 g/m^2).[43] Two subjects with the microdialysis probe located within contrast-enhancing tumor had methotrexate peak concentrations in extracellular fluid of 189 $\pm$ 6 μmol/L as compared with only 10.4 $\pm$ 0.4 μmol/L in two patients with the probe located in nonenhancing tissue in proximity to the enhancing tumor.[43] To base new chemotherapeutic combinations for CNS tumors on pharmacokinetic data, studies must take into consideration the impact of tumor type, tumor size and surrounding edema, as well as different doses and schedules of administration.

CNS DELIVERY OF BIOLOGIC AGENTS

New mAb-based therapeutics have had a pronounced impact on the clinical treatment of cancer, as exemplified by approved agents targeting (relatively) tumor-specific cell surface antigens (eg, trastuzumab and rituximab), or tumor vasculature VEGF (bevacizumab). Many others are in late-stage development.[44] To optimize the activity of mAbs, targeted toxins are being developed, in which the mAb carries a toxic payload, such as a radionuclide (^{90}Y ibritumomab tiuxetan), chemotherapeutic, or bacterial toxin to tumor cells.[45] One new approach has been to develop mAb-auristatin conjugates, composed of a potent synthetic antimitotic agent attached to mAb cysteine residues through a proteolytically cleavable linker.[46,47] On antigen engagement and internalization within lysosomal compartments, active auristatin is released intracellularly, leading to cell death. These auristatin conjugates overcame the multidrug resistance phenotype and exerted immunologically specific antitumor activities at fractions of their maximum tolerated doses.[46] Another approach has been the development of fusion proteins consisting of antibody fragments targeting a potent bacterial toxin that kills the tumor cell by inhibiting protein synthesis.[48]

The limitations of brain tumor drug delivery are accentuated for these new biologic therapies, with most mAbs showing minimal transport across the BBB.[49] A study of rituximab immunotherapy in human PCNSL showed no uptake of IV ^{123}I-rituximab in brain[50]; however, clinical responses to rituximab in PCNSL have been reported.[51,52] The long plasma half-life of some of the mAbs and immunoconjugates can lead to a slow leak of these agents, particularly into areas of damaged BBB. One study investigated CSF penetration of trastuzumab in breast cancer brain metastases.[53] The CSF:serum ratio of trastuzumab was 0.0024 in two subjects with relatively intact BBB, 0.0132 in two patients after brain irradiation, and 0.0204 in two patients with meningeal carcinomatosis.[53] Thus, impaired BBB and blood-CSF barrier integrity improved mAb delivery. A case study of ibritumomab tiuxetan (Biogen Idec, Zug, Switzerland) delivery and efficacy in PCNSL is shown in Figure 2. Single photon emission computed tomography imaging showed no uptake of ^{111}In-ibritumomab at 24 hours (Fig 2A) and minimal uptake at 45 hours (Fig 2B, arrow) localized at the lesion detected on magnetic resonance imaging (Fig 2C). A complete response was seen 2 months after administration of ^{90}Y-ibritumomab (Fig 2D), but recurrence was detected at 3 months in the opposite occipital horn with continued complete response at the site of the original tumor (Fig 2E).

Some mAbs may actually improve chemotherapy delivery. Targeting VEGF with bevacizumab may decrease interstitial pressure to allow greater entry of drug into the tumor.[14] The combination of bevacizumab with a new chemotherapeutic agent, irinotecan, commonly used in the treatment of colorectal cancer, has shown promising preliminary results in high-grade gliomas.[54] Antibodies to BBB proteins that translocate across the vascular endothelial cells may be an ideal drug delivery system for the brain. mAbs against the transferrin receptor[55] or the insulin receptor[56] can yield global brain delivery in animal models. Further studies are needed on brain and brain tumor drug availability for targeted agents that are designed to cross the BBB.

DELIVERY OF CHEMOTHERAPY TO THE CSF

The CSF route of drug administration can effectively bypass the BBB and readily access the periventricular and leptomeningeal tissues to treat neoplastic meningitis (NM). Because NM occurs in 5% of all cancer patients, it is imperative to optimize delivery to the meninges of the main chemotherapeutic agents methotrexate, cytarabine, and thiotepa. Compared with intrathecal (IT; subarachnoid) injection, intracerebroventricular (ICV) administration yields better therapeutic levels in CSF with less variability between patients.[57] Both the pharmacokinetic profile of the intra-CSF chemotherapeutic agent and the site of administration influence the outcome for NM.[58] To avoid neurotoxic effects, the dose calculation for chemotherapeutic agents should be normalized for CSF/brain volume rather than body-surface area.[57]

CSF clearance of the lipid-soluble agents is mainly via parenchymal transcapillary diffusion. Thiotepa given ICV is rapidly reabsorbed across the BBB in periventricular brain capillaries; consequently, therapeutic concentrations are not obtained in subarachnoid space of

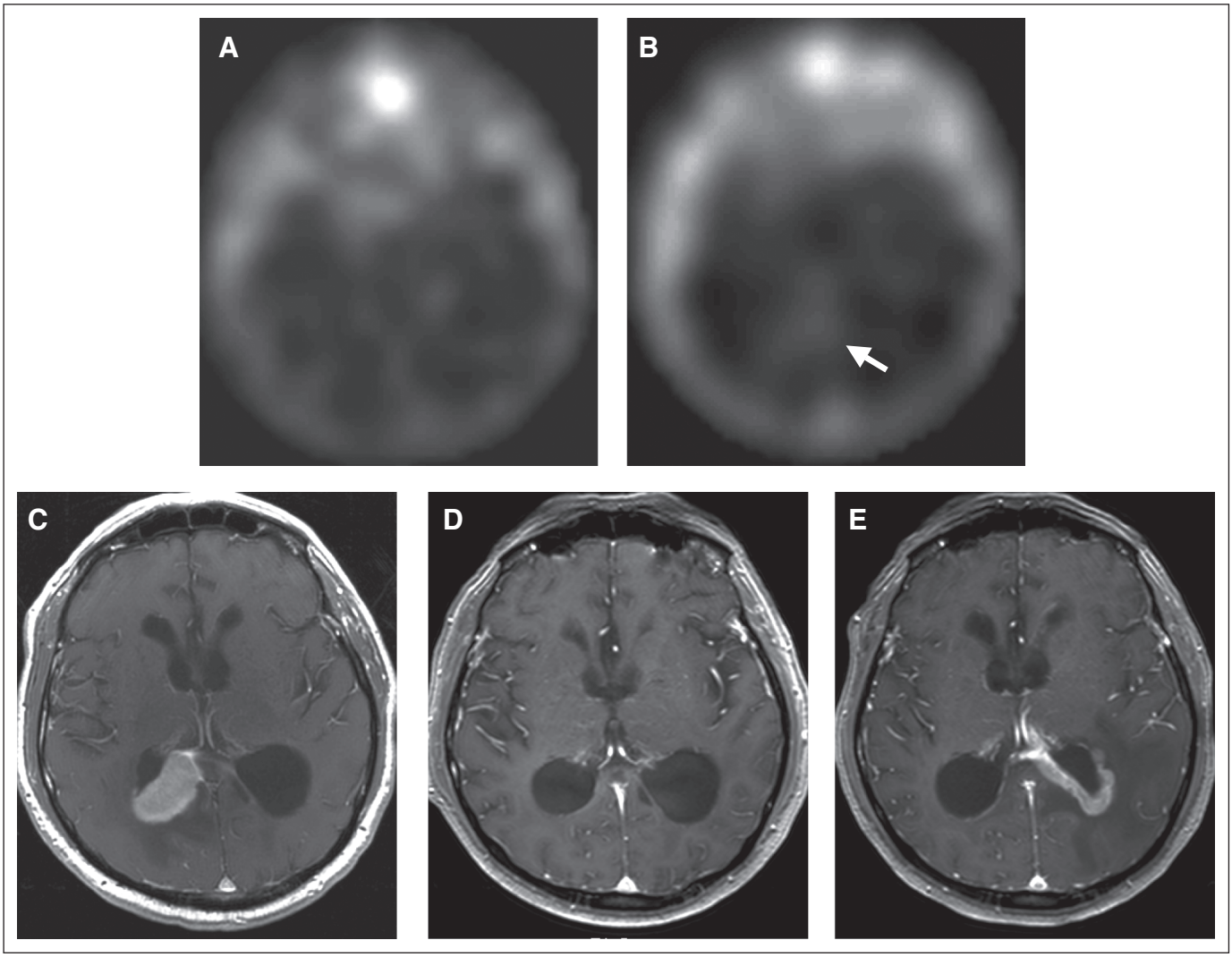

Fig 2. Single photon emission computed tomography brain images 24 (A) and 45 hours (B, arrow shows increased uptake) after ^{111}In-ibritumomab in a subject with primary CNS lymphoma. T1-weighted magnetic resonance images prior to treatment (C) and 2 (D) or 3 months (E) after ^{90}Y-ibritumomab.

the lower cord.[57] Due to thiotepa pharmacokinetics, a higher peak concentration of the active metabolite tepa is found in CSF after IV administration of 5 mg/kg[28] than after CSF administration of the maximally tolerated dose (10 to 15 mg).[57]

For water-soluble agents, the CSF bulk flow or volume transmission[59] is the predominating pharmacokinetic factor. CSF levels of drugs are affected by efflux transporters in choroid plexus[60] and drug-metabolizing enzymes in the choroidal epithelium,[61] but the overriding factor in drug distribution and elimination is CSF bulk flow down the neuroaxis from ventricles to subarachnoid space. ICV-administered methotrexate reaches the lumbar subarachnoid space by 1 hour, and the elimination half-life is 6 $\pm$ 2 hours.[57] A reduction in CSF flow, caused by elevated intracranial pressure, aging, or the carbonic anhydrase inhibitor acetazolamide, increases the elimination half-life and can thus elevate the concentration of therapeutic agent. A slow leak of methotrexate from the CSF to the serum may extend the time frame for high serum levels and thus the need for extended leucovorin rescue.[62]

Consistent with first-order kinetics, the CSF concentrations of water-soluble drugs are proportional to dose. Multiple-dose schedules have been developed to maintain a stable, sustained therapeutic (cytotoxic) concentration in CSF.[57] The ideal regimen avoids the excessive concentrations encountered in single-dose regimens for methotrexate and also produces less neurotoxicity. However, multiple dosing via CSF-indwelling catheters can involve laborious delivery methodologies with potential complication. Liposome encapsulation allows a sustained, gradual release of drugs. The terminal half-life for liposomal cytarabine after a single ICV dose is about 140 hours,[63] at least 30 to 40 times longer than the elimination half-life of methotrexate or cytarabine administered by conventional protocols. A controlled clinical trial has demonstrated that liposomal cytarabine is equally efficacious as free cytarabine for NM.[63] On the negative side, liposomal cytarabine may cause arachnoiditis, leading to deafness or blindness, and requires prophylaxis with systemic glucocorticoids. In solid tumors, clinical studies failed to show improved efficacy in treatment outcome, and in fact, there was no advantage to liposomal cytarabine.[64]

CSF drug concentrations are often used as a surrogate marker of brain tumor drug delivery, but CSF levels of a given drug may vary widely from brain and tumor levels. In periventricular PCNSL,

administration of high-dose IV methotrexate has been used in an attempt to improve delivery across the BBB and blood-CSF barrier.[65] The CSF penetration of IV methotrexate in humans is dose dependent. Cytotoxic CSF levels (greater than 1 μmol/L) were achieved in no subjects at a dose of 0.5 g/m^2, 44% of patients at 2.5 g/m^2, 66% of children treated with 5 g/m^2, and 100% of adults treated with 8 g/m^2 methotrexate.[66-68] Table 2 demonstrates CSF levels after IV administration of several chemotherapeutic agents.

High CSF levels may not translate to improved brain delivery or antitumor efficacy in tumors that affect more than the meninges. In patients with leptomeningeal involvement, the tumor often fills the perivascular Virchow-Robin spaces, decreasing diffusion of the drug through these spaces. ICV and IT methotrexate administration may only achieve therapeutic levels in the superficial 2 to 3 mm of CNS parenchyma beyond the subarachnoid space due to interstitial fluid pressure.[90] The ventriculo-cisternal perfusion system is used to study drug distribution from the CSF into the brain, but even several hours may be too short to accurately assess drug penetration by diffusion and convection into the brain interior.[91] Long-term osmotic pump infusions into the CSF would allow better steady-state assessments.

Combined IT and IV therapy for CNS tumors takes pharmacologic advantage of two distribution pathways (ie, the CSF-brain and the blood-brain interfaces). Combined IT and IV therapy involves a complex array of parameters, pathological and pharmacologic, and not surprisingly has shown failures as well as successes. The number of CSF tumor cells may decrease with therapy, whereas neurologic deficits, particularly of lower cranial nerves, persist or increase due to perivascular tumor infiltration. In Burkitt's lymphoma and acute lymphoblastic leukemia (ALL), combined IV and IT methotrexate achieved therapeutic CSF levels and is regarded as a reasonable option for CNS prophylaxis.[92] Combined methotrexate administration via CSF and blood resulted in favorable long-term neurocognitive outcomes in childhood ALL.[93,94] Finally, in a risk-stratified randomized trial in ALL, a regimen of IT and high-dose IV methotrexate was more effective in preventing CNS relapse than IT methotrexate alone.[95]

New therapeutic strategies for NM include the investigation of agents to enhance cytotoxic potential, minimize neurotoxic effects, and improve pharmacokinetic properties (eg, diaziquone, mafosfamide, etoposide, and topotecan).[57] The choroid plexus is a potentially useful kidney-like target,[91] heretofore underutilized, for more effectively manipulating the concentration of antitumor agents in CSF. An important goal is to be able to supplant the IT infusion aspect of combination regimens with noninvasive pharmacologic manipulation of drug transport across the choroid plexus into the CSF. Finally, it may be feasible to target ligands, which bind specifically to endogenous receptors in the plexus, to funnel antitumor drugs, proteins, and even gene therapeutics for transport into and along the choroid plexus–CSF arachnoid nexus.[91]

METHODS TO INCREASE DELIVERY TO THE CNS AND CSF

Convection-Enhanced Delivery

Interstitial infusion with maintenance of a pressure gradient, known as convection-enhanced delivery (CED), generates bulk fluid flow through the brain interstitium.[96] CED can achieve much higher local levels of chemotherapy in rodent brain than IV administration[20] and is the method of choice for delivery of targeted toxins.[48,97] The volume of distribution of targeted toxins with CED is dependent on the volume and rate of infusion, the agent's molecular weight, concentration, polarity, and avidity for the target antigen, and the viscosity and density of the tissue.[97] The limiting factor for choosing a maximum drug dose and rate of infusion is the onset of neurotoxicity.

Recently, the mechanisms related to failure of the CED technique in human studies as opposed to small animal studies have been investigated.[11] In rat brain tumors, low rates and volumes of infusion led to heterogeneous distribution of toxin. Tumor distribution was homogeneous at higher volumes and infusion rates, but most of the toxin (95%) was localized outside of the tumor mass, in the brain around tumor.[11] High and inconsistent tumor interstitial fluid pressure was a major cause of failure. In brain tumors, areas of normal interstitial pressure where the pressure is 1 to 2 mmHg are interposed with peritumoral areas where interstitial fluid pressures can be 50 mmHg or greater.[11,12] The mixed tissue environment in the tumor-bearing brain can lead to a relatively faster efflux of any drug out of the brain. Thus, treatment failure results from distribution inhomogeneity, high interstitial fluid pressure, and rapid efflux of agent from the injection site. To overcome these issues, increased residence time must be achieved to enhance targeted toxin receptor binding and uptake by the cancerous cells.

Targeted Ultrasound BBB Disruption

A new approach to focal CNS delivery is BBB disruption by MRI-guided focused ultrasound.[98] Consistent vascular leak without tissue damage was achieved by localizing cavitation-generated mechanical stresses to blood vessel walls by IV injection of preformed gas bubbles just before pulsed ultrasound treatment.[99] Histology showed that the low-power ultrasound caused reversible focal opening, which was completely healed within 24 hours. Marker dye extravasation was associated with widening of the tight junctions and active vacuole transport across the endothelial cells.[100] The ultrasound with microbubbles exposures did not cause neuronal damage,[99] apoptosis or ischemia,[101] or long-term vascular damage.[102]

Tests were performed to measure the ability of ultrasound BBB disruption to deliver agents into the brain. A rat brain study showed that the locations of the brain that were exposed to ultrasound showed significantly higher concentrations of liposomal doxorubicin and that clinically relevant levels were reached.[103] In another study, antibodies were delivered into the brain only in the exposed brain locations, and the antibodies stayed functional in the brain binding to their target sites.[104] This opens the door for the use of antibody-based chemotherapeutic agents such as trastuzumab for metastatic brain lesions.

Global Osmotic BBBD

Transient osmotic disruption of the BBB and blood-CSF and blood-tumor barriers can be achieved throughout a vascular circulation by IA infusion of a hyperosmotic agent, usually mannitol.[1,105] Osmotic BBBD reversibly opens the BBB by shrinking the cerebrovascular endothelial cells and opening of the tight junctions between cells.[106] The BBB is opened to chemotherapeutics,[21,107] antibodies,[108,109] and nanoparticles.[110]

Pharmacokinetics in animals showed that vascular permeability to methotrexate was maximal by 15 minutes after infusion of mannitol and returned to preinfusion levels within 2 hours.[1,107] A 10- to 100-fold increase in delivery was measured in intracerebral tumors and tumor-infiltrated brain, comparing IV administration to IA with BBBD.[33,79,107] These studies illustrated differences between CSF and

Table 2. CSF Penetration After Systemic Administration of Chemotherapeutic Agents

Drug	Reference	Subjects (dose)	Results
Busulfan	Vassal et al, 1989[69]	Children with malignant disease, no CNS involvement (16 mg/kg)	CSF:plasma ratio = 0.95 Detectable level in CSF 4 days after therapy
Cisplatin	Jacobs et al 2005[70]	Healthy monkeys (2 mg/m^2 IV)	CSF:plasma ratio of active drug = 0.037
	Nakagawa et al, 1996[71]	IA *v* IV delivery in multiple tumor types	CSF:plasma ratio 15% to 24% in glioma after IA infusion Maximum CSF patient concentration was 0.51 to 1.64 μg/mL, not therapeutic Variable delivery depending on tumor type and route of administration
Cyclophosphamide	Yule et al, 1997[34]	ALL children	No active metabolite in CSF
Cytarabine	Lopez et al, 1985[72]	Patients with CNS or LM metastases	Half-life in CSF > half-life in plasma
	Slevin et al, 1983[73]	Leukemic or NHL patients (1 or 3 g/m^2)	Correlation between CSF concentration and dose CSF:plasma ratio = 0.12
	Scott-Moncrieff et al, 1991[74]	Healthy dogs (600 mg/m^2)	CSF:plasma ratio = 0.58 $\pm$ 0.17; range 0.37 to 0.87 No drug detected in CSF and plasma 8 hours after IV bolus CSF half-life 30% shorter after IV bolus than after 12-hour IV infusion
	DeAngelis et al, 1992[75]	Adult PCNSL patients in CR (3 g/m^2)	Half-life in CSF > half-life in plasma CSF:plasma ratio = 0.12 to 0.14
	Sutoh et al, 2003[76]	Adult AML (1 g/m^2)	Half-life in CSF > half-life in plasma Therapeutic level in CSF in all patients
Etoposide	Savaraj et al, 1987[22]	Healthy dogs (2 mg/kg IV or IA)	CSF concentration peak at one hour Higher concentration at all time points after IA administration
	Zucchetti et al, 1991[23]	Adults with primary brain tumor (100 to 150 mg/m^2 IV)	Never detectable in CSF
	Relling et al, 1996[77]	ALL children with or without CSF infiltration (25 or 50 mg/m^2 orally, or 300 mg/m^2 IV)	Detectable in all CSF samples CSF concentration correlated with plasma concentration and dose Median CSF:plasma ratio = 0.30
Idarubicin	Reid et al, 1990[78]	Leukemic children in relapse	Idarubicinol detected in 20/21 CSF Mean CSF concentration = 0.51 ng/mL; range 0 to 1.05 ng/mL CSF:plasma ratio = 0.04
Ifosfamide	Yule et al 1997[34]	ALL children	Active metabolite detected in CSF with high interpatient variation
Methotrexate	Neuwelt et al, 1980[79]	Healthy dogs, IV or IA with or without BBBD	Brain concentration equivalent to CSF after BBBD No correlation between CSF and brain level for 30% of animals
	Millot et al, 1994[80]	Leukemic children (5 g/m^2 IV)	Correlation between CSF and serum; large interpatient variation CSF level > 1 μmol/L in 66% of cases
	Etinger et al, 1982[81]	Leukemic or NHL children (0.5 or 1.5 g/m^2)	CSF:plasma ratio = 0.01
	Lippens and Winograd, 1988[82]	Leukemic or NHL children (3 g/m^2)	300-fold variation of CSF level, 10-fold variation of plasma level No correlation between plasma and CSF level
	Tetef et al, 2000[83]	Adult cancer patients with or without LM carcinomatosis	Correlation between CSF and plasma concentration Higher CSF level in patients with LM carcinomatosis
	Ballis et al, 2000[84]	Healthy monkeys, IV	Lumbar CSF concentration < fourth ventricle CSF concentration
	Zylber-Katz et al, 2000[85]	PCNSL, IV, or IA with or without BBBD (1.4 to 3.5 g/m^2)	CSF:serum ratio after BBBD was three- to four-fold higher than after IV
Temozolomide	Patel et al 2003[86]	Healthy monkeys	CSF:plasma ratio = 0.33 Peak CSF concentration = 26 $\pm$ 4 μmol/L at 2.5 hours
Thiotepa	Strong et al, 1986[87]	Healthy monkeys	Rapid equilibration between plasma, lumbar, and ventricular concentration after standard IV dose
	Heideman et al, 1989[88]	Children with refractory malignancies	CSF:plasma AUC ratio = 1
Vincristine	Kellie et al, 2002[89]	Leukemic or NHL children with no CNS disease	No measurable concentration in CSF

Abbreviations: CSF, cerebrospinal fluid; IV, intravenous; IA, intra-arterial; ALL, acute lymphoblastic leukemia; LM, leptomeningeal; NHL, non-Hodgkin's lymphoma; PCNSL, primary CNS lymphoma; CR, complete remission; AML, acute myeloid leukemia; BBBD, blood-brain barrier disruption; AUC, area under curve.

brain delivery. After osmotic BBBD, brain levels of methotrexate were consistently elevated, whereas in six animals CSF levels did not increase (Fig 3). The mean levels were the same, but individual CSF levels did not reflect increased brain levels after enhanced delivery.[79]

In humans, BBB permeability to technetium glucoheptonate remained elevated at 2 hours after BBBD, but returned to baseline levels by 4 hours.[111] A pharmacokinetic study demonstrated that CSF/serum methotrexate concentration ratios were elevated by BBBD compared with IV or IA delivery, and the CSF concentration correlated linearly with the degree of barrier disruption (Fig 4).[85]

A concern with the use of BBBD is the potential for neurotoxicity from the high concentrations of chemotherapy delivered to the normal brain. Chemotherapeutics, such as doxorubicin, cisplatin, and taxanes, cause neurotoxicity with BBBD, even though they are well tolerated systemically.[112] Drugs found to be safe with BBBD include methotrexate, carboplatin, etoposide phosphate, cyclophosphamide, melphalan, mAbs, and immunoconjugates. Concurrent cranial irradiation enhanced the neurotoxicity of some chemotherapy agents delivered with BBBD in rat models.[113] With methotrexate, extended leucovorin rescue may be necessary to prevent neurotoxicity.[62] The BBBD technique itself is not neurotoxic. Overdisruption and cerebral edema rarely occur in humans because the mannitol infusion rate can be closely adjusted to match blood flow.

Osmotic BBBD is used clinically to enhance chemotherapy delivery in brain tumor patients at nine centers across the United States,

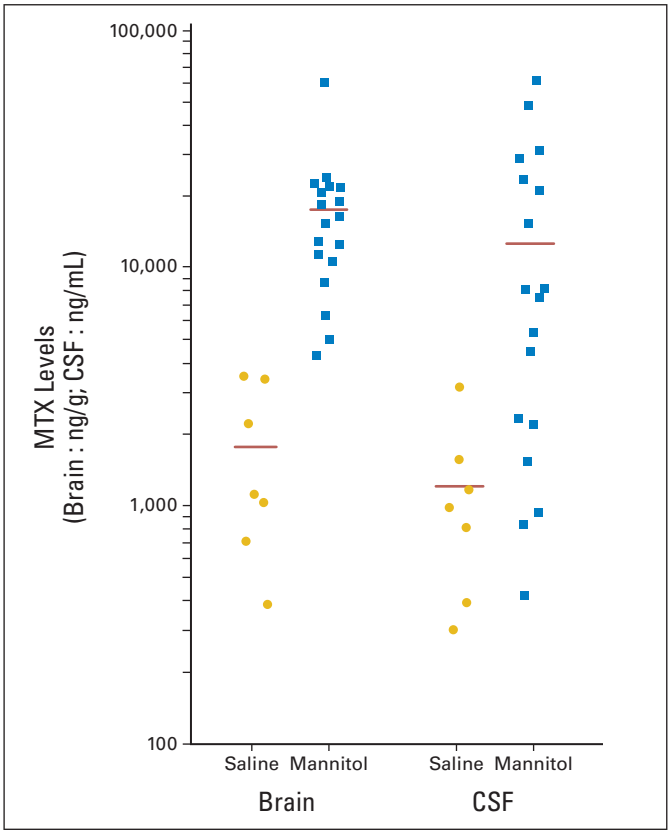

Fig 3. Comparison of methotrexate levels in brain and cerebrospinal fluid (CSF). Methotrexate (MTX) was administered to dogs after infusion of saline or mannitol to open the blood-brain barrier (BBB). Horizontal lines represent the mean MTX values for each group (adapted[79]).

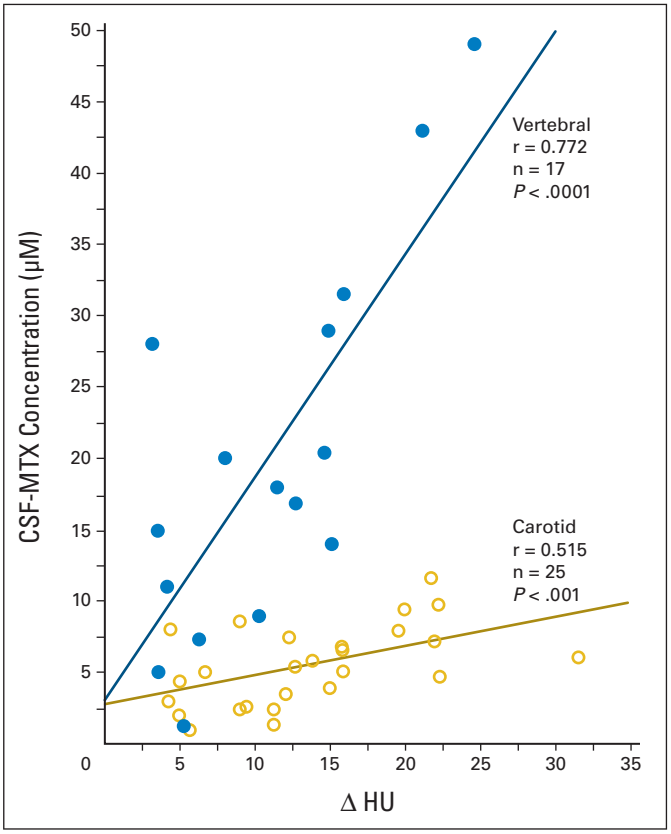

Fig 4. The degree of osmotic blood-brain barrier disruption (BBBD), expressed as the difference in Hounsfield units between the disrupted and undisrupted brain regions on computed tomography images, correlated with ventricular cerebrospinal fluid (CSF) metotrexate concentrations measured 10 minutes after intra-arterial administration following BBBD (adapted[85]).

Canada, and Israel.[1,114-117] To date, almost 6,000 BBBD procedures in 515 patients have been performed, with low morbidity and mortality. Toxicities in patients treated with IA chemotherapy in conjunction with BBBD were generally manageable. No cases of dementia were recorded in a study with 74 PCNSL patients.[116]

It is hypothesized that enhanced delivery correlates with improved efficacy. In rats, BBBD delivery of a clinically relevant chemotherapy regimen was effective in a rat intracerebral lung cancer xenograft model.[118] BBBD delivery of a tumor-specific mAb-doxorubicin immunoconjugate significantly increased antitumor efficacy compared with IV or IA administration without BBBD.[109]

The effect of BBBD on efficacy has been more difficult to quantify in humans. BBBD chemotherapy in chemoresponsive tumors, such as PCNSL, germ cell tumors, and primitive neuroectodermal tumors, compared favorably with published case series of conventional chemotherapies.[114-116] Randomized phase III trials of BBBD have not been performed due to the rarity of specific intracerebral tumor types and the need for multidisciplinary expertise. In PCNSL phase II studies, a significant difference was found when comparing patients treated with BBBD chemotherapy with or without prior whole-brain radiotherapy.[119] These studies suggested that BBBD delivery of chemotherapy produced long-term remissions with acceptable morbidity and mortality and preservation of cognitive function.

In conclusion, chemotherapy for brain tumors often uses drugs and regimens that are poorly supported by pharmacokinetic and pharmacodynamic data. Many preclinical studies are difficult to translate into clinical practice because different doses and treatment regimens were tested in animal models that incompletely represent the range of human tumors. Drug delivery is complicated by the presence of the BBB and the variability of BBB and blood-tumor barrier permeability depending on tumor type, size, location, and prior treatments. The need for a greater understanding of the pharmacology of CNS drug delivery should prompt additional translational research to correct the gaps in pharmacokinetic information. In vivo microdialysis with concomitant CSF and serum measurements of pharmacologically active drug may be the best route to accurately assess both pharmacokinetics and dynamics in animal models and clinical trials.

The key to successful chemotherapy of brain tumors is drug delivery to the tumor-infiltrated brain around the tumor and the individual tumor cells and micrometastases distant from the main tumor mass. Conventional drug administration regimens often result in low levels of drug delivery to brain tumors; therefore, innovative treatments and alternative delivery techniques are needed. The choroid plexus can be exploited—directly via modification of its bidirectional epithelial transport mechanisms and indirectly by way of pharmacologic alteration of bulk CSF formation and flow—to enhance the delivery of chemotherapeutic drugs in the CNS. CED and focused ultrasound can improve local delivery, whereas osmotic BBBD gives global delivery throughout a cerebral circulation. Optimization of delivery techniques combined with quality pharmacokinetic studies will improve our use of the promising new drugs and biologic agents in the pipeline for brain tumor therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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