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.

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.\(^1\) 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.\(^2\) 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.\(^5\) 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,
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. Etoposide concentration was found to be four times higher after intra-arterial (IA) administration than IV. Route of delivery impacted brain delivery of cisplatin, with IA administration increasing delivery to gliona two-fold compared with IV administration. One study reported results of brain pharmacokinetics of cytarabine, comparing different routes of administration. After IV administration, a diffuse pattern of low drug concentrations was detected throughout the brain. Vincristine and vinblastine penetrate brain tumors poorly despite their high lipid solubility (Fig 1), even after IA administration, 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.

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. Methotrexate delivery to CNS is enhanced four- to seven-fold when administered IA after osmotic BBB disruption (BBBD) compared with IA administration without BBBD.

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

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. However, the proportion of active metabolites was only 6% in both brain and in plasma. The active metabolite of ifosfamide has been found in both cerebrospinal fluid (CSF) and aqueous humor. Idarubicin has been studied along with its active metabolite, idarubicinol, in brain biopsies of patients with
breast cancer metastasis or malignant glioma. 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 increasing the amount of drug available for delivery. Activation 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 phosphoramid 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. One study measured the alkylation activity of the metabolites of cyclophosphamide and found a brain/plasma concentration ratio of 0.20 in a normal rat brain.

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

### Table 1. Pharmacokinetics of Drugs in Brain and Brain Tumors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>Method</th>
<th>Tumor and BAT</th>
<th>Normal Brain</th>
</tr>
</thead>
</table>
| Busulfan   | Hassan et al, 1992<sup>15</sup> | 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, 1996<sup>16</sup> and 1994<sup>17</sup> | Human surgical tumor specimens 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<sup>18</sup> | Human surgical tumor specimens 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<sup>19</sup> | 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 | |
| Cytarabine | Groothuis et al, 2000<sup>20</sup> | 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<sup>21</sup> | Healthy dogs and rats, IV or IA + BBBD | Brain concentration 4 times higher after IA than IV | |
| Etoposide  | Savaraj et al, 1987<sup>22</sup> | In dogs, after IV and IA administration | Brain level at periphery of tumor  
High intersubject variability  
Rapid equilibration between tumor and plasma  
Variable drug levels in tumor and BAT  
Increased delivery after BBBD (4 to 7 times)  
Drug level at periphery of tumor | |
|           | Zucchetti et al, 1991<sup>23</sup> | Human glioblastomas, astrocytomas (100 to 150 mg/m<sup>2</sup> IV) | Tumor concentration > 1 µg/mL  
Decrease with distance from tumor | |
|           | Boogerd et al, 1999<sup>24</sup> | 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<sup>25</sup> | Rats with glioma, IV ≥ BBBD | Increased delivery after BBBD (4 to 7 times)  
Increased delivery after CED (4 to 7 times)  
Median brain:serum ratio = 20% ± 12 | |
|           | Slordal et al, 1988<sup>26</sup> | Healthy rats, IV | Variable drug levels in tumor and BAT | |
|           | Dukic et al, 2000<sup>27</sup> | Rats with glioma, IV + microdialysis | Variable drug levels in tumor and BAT  
Increased delivery after BBBD (4 to 7 times)  
Median brain:serum ratio = 20% ± 12 | |
| Thiotepa   | Egorin et al, 1984<sup>28</sup> | Healthy mice, IV | Rapid distribution  
Rapid equilibration between tumor and plasma  
Increased delivery after BBBD (4 to 7 times)  
Median brain:serum ratio = 20% ± 12 | |
| Topotecan  | Straathof et al, 1999<sup>29</sup> | Gliomas-bearing rats after IV administration | Little uptake (20-fold < in tumor) | |
| Vincristine/ vinblastine | Greig et al, 1990<sup>30</sup> | Rats with carcinomas | No tumor uptake | |
|           | Boyle et al, 2004<sup>31</sup> | Normal rats and IA in glioblastoma rats | No tumor 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.
of differentiating active drug from inactive conjugates or free platinum. 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. 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, so that although it shows high concentrations in rat glioma, the concentration decreases sharply with increasing distance from the tumor. The tyrosine kinase inhibitor imatinib binds heavily to plasma proteins and is a substrate for active efflux pumps. The second-generation agent lapatinib also is subject to P-glycoprotein-mediated efflux, so may not be effective against brain tumors. 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/m2). Two subjects with the microdialysis probe located within contrast-enhancing tumor had methotrexate peak concentrations in extracellular fluid of 189 ± 6 μmol/L as compared with only 10.4 ± 0.4 μmol/L in two patients with the probe located in nonenhancing tissue in proximity to the enhancing tumor. 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.

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 thiopeta. Compared with intrathecal (IT; subarachnoid) injection, intracerebroventricular (ICV) administration yields better therapeutic levels in CSF with less variability between patients. Both the pharmacokinetic profile of the intra-CSF chemotherapeutic agent and the site of administration influence the outcome for NM. To avoid neurotoxic effects, the dose calculation for chemotherapeutic agents should be normalized for CSF/brain volume rather than body-surface area.

CSF clearance of the lipid-soluble agents is mainly via parenchymal transcapillary diffusion. Thiopeta given ICV is rapidly reabsorbed across the BBB in periventricular brain capillaries; consequently, therapeutic concentrations are not obtained in subarachnoid space of
Due to thiotepa pharmacokinetics, a higher peak concentration of the active metabolite tepa is found in CSF after IV administration of 5 mg/kg than after CSF administration of the maximally tolerated dose (10 to 15 mg).

For water-soluble agents, the CSF bulk flow or volume transmission is the predominating pharmacokinetic factor. CSF levels of drugs are affected by efflux transporters in choroid plexus and drug-metabolizing enzymes in the choroidal epithelium, 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 ± 2 hours. 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.

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. 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, 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. 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.

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.\textsuperscript{65} The CSF penetration of IV methotrexate in humans is dose dependent. Cytotoxic CSF levels (greater than 1 \textmu mol/L) were achieved in no subjects at a dose of 0.5 g/m\textsuperscript{2}, 44\% of patients at 2.5 g/m\textsuperscript{2}, 66\% of children treated with 5 g/m\textsuperscript{2}, and 100\% of adults treated with 8 g/m\textsuperscript{2} methotrexate.\textsuperscript{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. IV 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.\textsuperscript{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.\textsuperscript{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 in children treated with 5 g/m\textsuperscript{2}, and 100\% of adults treated with 8 g/m\textsuperscript{2} methotrexate.\textsuperscript{66-68} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{100} The ultrasound with microbubbles exposures did not cause neuronal damage,\textsuperscript{99} apoptosis or ischemia,\textsuperscript{101} or long-term vascular damage.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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-tumor barriers can be achieved throughout a vascular circulation by IA infusion of a hyperosmotic agent, usually mannitol.\textsuperscript{1,105} Osmotic BBBD reversibly opens the BBB by shrinking the cerebrovascular endothelial cells and opening of the tight junctions between cells.\textsuperscript{106} The BBB is opened to chemotherapeutics,\textsuperscript{11,107} antibodies,\textsuperscript{108,109} and nanoparticles.\textsuperscript{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.\textsuperscript{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.\textsuperscript{33,79,107} These studies illustrated differences between CSF and
<table>
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<th>Drug</th>
<th>Reference</th>
<th>Subjects (dose)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulfan</td>
<td>Vassal et al, 1989&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Children with malignant disease, no CNS involvement (16 mg/kg)</td>
<td>CSF:plasma ratio = 0.95 Detectable level in CSF 4 days after therapy</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Jacobs et al 2005&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Healthy monkeys (2 mg/m² IV)</td>
<td>CSF:plasma ratio of active drug = 0.037</td>
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<tr>
<td></td>
<td>Nakagawa et al, 1996&lt;sup&gt;31&lt;/sup&gt;</td>
<td>IA v IV delivery in multiple tumor types</td>
<td>CSF:plasma ratio 15% to 24% in glioma after IA infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum CSF patient concentration was 0.51 to 1.64 µg/mL, not therapeutic</td>
<td>Variable delivery depending on tumor type and route of administration</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Yule et al, 1997&lt;sup&gt;34&lt;/sup&gt;</td>
<td>ALL children</td>
<td>No active metabolite in CSF</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Lopez et al, 1985&lt;sup&gt;72&lt;/sup&gt;</td>
<td>Patients with CNS or LM metastases</td>
<td>Half-life in CSF &gt; half-life in plasma</td>
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<td></td>
<td>Slevin et al, 1983&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Leukemic or NHL patients (1 or 3 g/m²)</td>
<td>Correlation between CSF concentration and dose</td>
</tr>
<tr>
<td></td>
<td>Scott-Moncrieff et al, 1991&lt;sup&gt;74&lt;/sup&gt;</td>
<td>Healthy dogs (600 mg/m²)</td>
<td>CSF:plasma ratio = 0.12</td>
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<tr>
<td></td>
<td>DeAngelis et al, 1992&lt;sup&gt;75&lt;/sup&gt;</td>
<td>Adult PCNSL patients in CR (3 g/m²)</td>
<td>CSF:plasma ratio = 0.58 ± 0.17; range 0.37 to 0.87</td>
</tr>
<tr>
<td></td>
<td>Sutoh et al, 2003&lt;sup&gt;76&lt;/sup&gt;</td>
<td>Adult AML (1 g/m²)</td>
<td>No drug detected in CSF and plasma 8 hours after IV bolus</td>
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<tr>
<td></td>
<td></td>
<td>Half-life in CSF &gt; half-life in plasma</td>
<td>CSF:plasma ratio = 0.12 to 0.14</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Savaraj et al, 1987&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Healthy dogs (2 mg/kg IV or IA)</td>
<td>Half-life in CSF &gt; half-life in plasma</td>
</tr>
<tr>
<td></td>
<td>Zucchetti et al, 1991&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Adults with primary brain tumor (100 to 150 mg/m² IV)</td>
<td>Therapeutic level in CSF in all patients</td>
</tr>
<tr>
<td></td>
<td>Relling et al, 1996&lt;sup&gt;77&lt;/sup&gt;</td>
<td>ALL children with or without CSF infiltration (25 or 50 mg/m² orally, or 300 mg/m² IV)</td>
<td>CSF concentration peak at one hour Higher concentration at all time points after IA administration Never detectable in CSF Detectable in all CSF samples CSF concentration correlated with plasma concentration and dose Median CSF:plasma ratio = 0.30</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>Reid et al, 1990&lt;sup&gt;78&lt;/sup&gt;</td>
<td>Leukemic children in relapse</td>
<td>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</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Yule et al 1997&lt;sup&gt;34&lt;/sup&gt;</td>
<td>ALL children</td>
<td>Active metabolite detected in CSF with high interpatient variation</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Neuvelt et al, 1980&lt;sup&gt;79&lt;/sup&gt;</td>
<td>Healthy dogs, IV or IA with or without BBBD</td>
<td>Brain concentration equivalent to CSF BBBD</td>
</tr>
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<td></td>
<td>Millot et al, 1994&lt;sup&gt;80&lt;/sup&gt;</td>
<td>Leukemic children (5 g/m³ IV)</td>
<td>No correlation between CSF and brain level for 30% of animals</td>
</tr>
<tr>
<td></td>
<td>Etinger et al, 1982&lt;sup&gt;81&lt;/sup&gt;</td>
<td>Leukemic or NHL children (0.5 or 1.5 g/m³)</td>
<td>Correlation between CSF and serum; large interpatient variation</td>
</tr>
<tr>
<td></td>
<td>Lippens and Winograd, 1985&lt;sup&gt;82&lt;/sup&gt;</td>
<td>Leukemic or NHL children (3 g/m³)</td>
<td>CSF:plasma ratio = 0.01</td>
</tr>
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<td></td>
<td>Tetef et al, 2000&lt;sup&gt;83&lt;/sup&gt;</td>
<td>Adult cancer patients with or without LM carcinomatosis</td>
<td>300-fold variation of CSF level, 10-fold variation of plasma level</td>
</tr>
<tr>
<td></td>
<td>Ballis et al, 2000&lt;sup&gt;84&lt;/sup&gt;</td>
<td>Healthy monkeys, IV</td>
<td>No correlation between plasma and CSF level</td>
</tr>
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<td></td>
<td>Zylber-Katz et al, 2000&lt;sup&gt;85&lt;/sup&gt;</td>
<td>PCNSL, IV, or IA with or without BBBD (1.4 to 3.5 g/m³)</td>
<td>Correlation between CSF and plasma concentration</td>
</tr>
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<td></td>
<td></td>
<td>Higher CSF level in patients with LM carcinomatosis</td>
<td>Lumbar CSF concentration &lt; fourth ventricle CSF concentration</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>Patel et al 2003&lt;sup&gt;86&lt;/sup&gt;</td>
<td>Healthy monkeys</td>
<td>CSF:serum ratio after BBBD was three- to four-fold higher than after IV</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>Strong et al, 1988&lt;sup&gt;87&lt;/sup&gt;</td>
<td>Healthy monkeys</td>
<td>Peak CSF concentration = 26 ± 4 µmol/L at 2.5 hours</td>
</tr>
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<td></td>
<td></td>
<td>Rapid equilibration between plasma, lumbar, and ventricular concentration after standard IV dose</td>
<td>CSF:plasma AUC ratio = 1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Kellie et al, 2002&lt;sup&gt;88&lt;/sup&gt;</td>
<td>Leukemic or NHL children with no CNS disease</td>
<td>No measurable concentration in CSF</td>
</tr>
</tbody>
</table>

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.\textsuperscript{79}

In humans, BBB permeability to technetium glucoheptonate remained elevated at 2 hours after BBBD, but returned to baseline levels by 4 hours.\textsuperscript{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).\textsuperscript{115}

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.\textsuperscript{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.\textsuperscript{113} With methotrexate, extended leucovorin rescue may be necessary to prevent neurotoxicity.\textsuperscript{62} The BBBD technique itself is not neurotoxic. Overdisruption and cerebral edema rarely occur in humans because the mannitol infusion rate can be closely matched to match blood flow.

Osmotic BBBD is used clinically to enhance chemotherapy delivery in brain tumor patients at nine centers across the United States, Canada, and Israel.\textsuperscript{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.\textsuperscript{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.\textsuperscript{118} BBBD delivery of a tumor-specific mAb-doxorubicin immunoconjugate significantly increased antitumor efficacy compared with IV or IA administration without BBBD.\textsuperscript{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.\textsuperscript{114,118} 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.\textsuperscript{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.

REFERENCES

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