Understanding brain penetrance of anticancer drugs

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Abstract. This paper explicates the impact of tumor capillary permeability for glioma WHO grades 2 to 4 on brain-penetrant drug entry and distribution within the tumor and the brain adjacent to tumor (leading edge). In addition, we consider the distribution of non-brain penetrant drugs and how, in some cases, large molecular weight drugs might achieve good distribution into tumor and brain adjacent to tumor.

Introduction and problem. Here we assess some pharmacological and pharmaceutical mantras that have been guiding principles for early drug development during the past decades. The 50 years of clinical and research experience of one of the authors (VAL) concentrated on developing therapies for treating infiltrative primary CNS tumors. Additionally, preclinical pharmacokinetic research focused on the permeation of drugs from blood to brain, tumor, and nerve as well as diffusion within brain and distribution of drugs in the cerebrospinal fluid (CSF).

Infiltrative gliomas of the brain and spinal cord are divided into three main histological groups based on their histology and molecular genetics: Astrocytoma, oligodendroglioma, and ependymoma tumors. These tumors are also classified by increasing malignancy from World Health Organization (WHO) grade 2 to grade 3 (anaplastic phenotype) and grade 4 (glioblastoma) tumors. Characteristically, these tumors infiltrate (invade) brain and spinal cord parenchyma, typically along white matter tracts. The tumors putatively stimulate establishing new capillaries that are more permeable (leaky) than normal brain capillaries. This is accomplished by opening tight junctions between adjacent capillary endothelial cells, forming breaks and fenestra within them, and/or improperly formed capillary endothelial cells. New vessel formation (neovascularization) putatively parallels the increasing malignant phenotype of infiltrative gliomas. Therefore, tumor cells of lower phenotypic malignancy may invade adjacent brain and spinal cord without stimulating neovascularization. Consequently, some infiltrative
tumor cells may “hide” behind intact portions of the blood-brain barrier (BBB). This concept is the basis for the mantra that if an anticancer drug is to be effective against infiltrative gliomas it must be brain penetrant\textsuperscript{1-15}.

A difficulty with this dogma of the importance of using anticancer drugs that easily cross the BBB is, however, the lack of challenge implicit in the fact that outside of alkylating agents, no new anticancer drugs have received regulatory approval for the treatment of gliomas\textsuperscript{16} except for bevacizumab for glioblastoma (GBM). Bevacizumab was approved by the FDA for the treatment of GBM but with no clear evidence of an improvement in overall survival (OS)\textsuperscript{17}. Secondarily, this concept of using only drugs that can traverse the BBB is challenged by re-examining our understanding of brain and tumor permeability and how this different perspective might change our view of regional drug distribution in glial tumors.

While many scientists believe the restriction to passive diffusion of drug through the BBB is an absolute restriction, the authors’ hypothesis in this paper is that passive permeability is quantitative and what is considered to be the BBB rather signifies a level of restriction of movement of standard chemicals and drugs that appears to be promulgated by physical measures of molecular size, lipophilicity, and polarity\textsuperscript{6,8,18}. In addition, because of the presence of efflux pumps in endothelial cells, sometimes drug properties are further optimized to decrease efflux of the drug by transporters to increase drug concentrations in the brain.

The relationship between permeability in brain and intracerebral tumor is predictable, with poorly permeant drug molecules distributing by diffusion in tumor more than in brain\textsuperscript{6,19}. In
contrast, distribution of drugs with high brain permeability is governed to a greater degree by blood flow and, in most cases, distribution is better in brain than tumor. Figure 1 depicts how standard molecules and anticancer drugs have historically behaved in rodent brain and intracerebral (IC) rodent tumors. This composite plot shows median transfer constant, $K_i (\approx K_{\text{trans}})$, with error bars for these compounds in normal brain and IC tumors. $K_i$ values were calculated from capillary permeability, $P$, measurements. Figure 1 nicely informs the relationship between brain and tumor $K_i$, and the error bars show wide variation in $K_i$ resulting from tumor heterogeneity. These relationships appear as would be expected by thermodynamic concepts.

Tumor cell permeability. In addition to capillary permeability increasing with malignancy, tumor cells diverge from the differentiated phenotype and increase in size, change surface area to volume relationships, lose pathway and membrane integrity, and become more permeable (leaky) to ions and, therefore, water movement. This intuitive conclusion, borne of viewing tumors cells under the microscope and in culture, has not been well-studied in its sequential physiological entirety, although studies to date support the fact that glioma cells may not behave normally to ion fluxes. One of the consequences of large and leaky tumor cells in the brain is to exaggerate the size of the ECS by extracellular radiolabeled tracers (e.g., inulin, creatine, urea) that distribute in many leaky tumor cells compared to normal brain parenchyma producing an ECS that is a combination of extracellular and intracellular water.

Neuroimaging insights. Clinicians have used many neuroimaging techniques [radionuclide scan, computed tomography (CT) scan, magnetic resonance imaging (MRI)] to follow the
growth of high-grade gliomas in the brain. Much of the value of these techniques is based on the observation that some IV contrast agents preferentially permeated tumor vessels and leaked into the surrounding tumor extracellular fluid (ECF). In 1980, we modeled the consequence of a breakdown of the blood-tumor “barrier” compared to the highly-restricted BBB, which demonstrated visualization of contrast after approximately 0.004% of brain capillary surface area was damaged or open to contrast leaking from capillary blood into tumor. Surprisingly, this seemingly minuscule leakage of contrast is sufficient for clinicians to differentiate tumor compared to brain with radionuclide, CT, and MRI scans. Clinically, many low- and mid-grade gliomas are reported as showing “no contrast enhancement”. However useful that standard is for clinicians, adherence to this position is likely unhelpful to those seeking to create new drug treatments for glioma patients, and may also be erroneous.

Careful quantitative MRI studies in patients with varying degrees of glioma malignancy show that capillary permeability, greater than defined by the intact BBB, intensifies with increasing glioma tumor malignancy grade from astrocytoma to glioblastoma. In these MRI studies, the volume transfer coefficient, $K_{trans}$, of gadolinium (Gd) contrast was used to approximate capillary permeability. $K_{trans}$ is directly related to capillary permeability, $P$, when adjusted for blood flow and capillary surface area using the following equation:

$$K_{trans} = F \left(1-e^{-(P \cdot S/F)}\right),$$

(1)

where $P =$ permeability coefficient, cm$^2$/sec; $S =$ capillary surface area, cm$^2$; and $F =$ blood flow, mL/g/min. Therefore, $K_{trans}$, uncorrected for capillary surface area and tissue blood volume is reported commonly in units of min$^{-1}$, whereas brain capillary permeability, that considers
capillary surface area and blood volume, is reported in units of cm/sec. From equation 1, it can be deduced that for non-blood-flow-limited compounds, $K^{\text{trans}} \approx P.S$.

Examining the relationship of $K^{\text{trans}}$ to Gd-contrast in different glioma tumor grades and evaluating the significance of these values to drug penetration into different grades of glioma is a useful point of discussion. Investigations using $K^{\text{trans}}$ computed from Gd-contrast MRI in different grades of gliomas is collated in Table 1 together with estimates of tumor extracellular fluid (ECF) volume, $V_e$. Looking at Table 1, it is apparent that some values, especially for $V_e$ are suspect since $V_e$ should, at the very least, exceed 0.19, a normal value for brain ECF, which has been determined to be about 0.17-0.20 in mammalian brain. The most reliable values for tumor $V_e$ from Table 1 appear to be those of Zhang and colleagues. These values of 0.27 to 0.40 were experimentally determined in intracerebral rodent tumor models and depend on the extent of necrosis and integrity of tumor cells. From that perspective, $V_e$ values of 0.03, 0.07, and 0.12 in Table 1 are likely underestimates and might indicate experimental error.

From the perspective of drug penetrance in infiltrative gliomas (WHO grade 2-4) in the brain, we can conclude that most glial tumors will manifest less restriction compared to the BBB of normal brain white matter. For normal brain, Zhang and colleagues used Gd-contrast to define the $K^{\text{trans}}$ of normal BBB as $4 \times 10^{-3}$ min$^{-1}$, similar to $8 \times 10^{-4}$ min$^{-1}$, the value for sucrose Levin and colleagues measured in capillary permeability coefficient, $P$, studies. Thus, on average, grade 2 gliomas will have a 10-fold higher permeability and $K^{\text{trans}}$ over brain; anaplastic gliomas about a 30-fold increase; and glioblastoma, more than a 40-fold increase in $K^{\text{trans}}$ and permeability.
Insights from regional drug modeling. It is useful in drug development theorizing to consider the consequences of these $K^{\text{trans}}$ values for infiltrative gliomas with respect to drug penetration and attainment of drug levels in low- and mid-grade glioma tumor cells. One obvious conclusion is that access to anticancer agents will have fewer constraints on molecular size and charge in any of these tumors than would be predicted by standard models of brain penetrance. Drug molecules will, therefore, distribute faster and, to a greater extent, because of capillary leakage. Looking at brain immediately adjacent to the tumor (BAT) as well tumor cells further away from the tumor that might be hiding behind an intact BBB, it is likely that drugs will not have much trouble reaching the BAT. Drug penetration into the BAT will, however, be influenced by how the tumor grows and whether it is expansile and compresses adjacent brain or is infiltrative and does not produce a lot of compression and edema. In the former case, the growth of an expansile intracerebral (IC) 9L tumor resulted in lower permeability to $^{14}$C-urea and $^{22}$Na in the BAT that was, in some instances even lower then more normal brain. In comparable studies, Groothuis and colleagues studied $^{14}$C-aminoisobutyric acid (AIB) in the IC RG-2 rat glioma model and found that the AIB transfer constant fell markedly in the BAT. Agarwal and colleagues studied erlotinib, a small lipophilic drug (393 MW, log P 2.7), and found, in IC U87 tumors in rats, that the tissue/plasma ratio in BAT was considerably lower in BAT than in tumor, but similar as in normal brain. Thus, these studies all support the concept that high permeability in IC tumors drops significantly at BAT and might fall lower than in normal brain or not depending on the size of the IC tumor, the pressure it exerts on surrounding brain and the physical characteristics of the substance (drug) studied, all factors to be carefully considered during the drug development process.
A similar relationship can be seen using Gd-contrast MRI and sequential voxel measurements $K^{\text{trans}}$ in patients. Figure 2 shows the fall off, from tumor into normal brain white matter, of $K^{\text{trans}}$ values in a patient with a high-grade glioma. It can be appreciated from these measurements that $K^{\text{trans}}$ can drop 100-fold from about 0.10 min$^{-1}$ to about 0.001 min$^{-1}$ over several mm from the enhancing tumor. The obvious and practical consequence of these studies is that for many drugs, there will be a significant reduction in drug penetration and drug level in the BAT compared to in the tumor itself.

Additionally, it appears that a drug, with less than optimal BBB penetration might also achieve adequate penetration into tumor and surrounding brain under particular conditions. This counterintuitive conclusion was based on studies with DFMO (eflornithine, α-difluoromethylornithine). $^{14}$C-DFMO had a brain capillary permeability coefficient, $P$, of $3.9 \times 10^{-7}$ cm/s and a $K_i$ of $2.6 \times 10^{-3}$ min$^{-1}$, constants implying that DFMO could have significant limitation in capillary to brain penetrance. Because DFMO showed activity in IC rodent tumors and was not appreciably biotransformed, experiments were designed to better understand regional tumor pharmacokinetics of DFMO in a treatment environment. Rats with an intracerebral 9L tumor were tethered with a soft harness and infused with intravenous $^{14}$C-DFMO and unlabeled DFMO to maintain a constant blood level of DFMO. After 1 to 4 days, animals were euthanized to measure tissue/plasma ratios in brain adjacent to and distant from IC 9L tumors. This was accomplished using a specially designed blade set to cut serial 0.75 mm sections from frozen brain slabs. The results showed that between days 1 to 4, the $^{14}$C-DFMO...
BAT/plasma and brain/plasma levels could reach 0.5 to 1.5 at 4.5 to 5 mm from the edge of the tumor (Figure 3).

What allowed the attainment of a brain/plasma ratio of about 1 for $^{14}$C-DFMO and to what extent does it reflect free drug? The brain/plasma ratio of free drug levels, devoid of protein binding in plasma and tissue (e.g., brain), are used as one measure of drug brain penetration, so a ratio of ~1 would infer either high drug penetration $^{35,36}$, or marked tissue binding. Since DFMO is not appreciably biotransformed, has low plasma clearance (~2.1 mL/min/kg), has a volume of distribution, $V_d$, ~0.5, and it can be given chronically for days to weeks with acceptable systemic toxicity $^{37-39}$ it is expected that the brain/plasma and BAT/plasma of ~1 reflects distribution in BAT and brain. This construct raised questions because the physicochemical features of DFMO are not common to other anticancer drugs and DFMO may represent a unique case: a small molecule (~182 Da) that is highly polar in physiological solutions, does not appreciably bind to plasma proteins, and irreversibly and specifically binds to its target. These characteristics might explain why DFMO appears to diffuse across more leaky (higher permeability) tumor cerebral endothelial cell junctions and then diffuses in brain ECF.

In addition to diffusion, it is conceivable that some L-DFMO might be transported into the brain like L-ornithine using a cationic amino acid transporter 1 (CAT1) $^{40}$, however, we think it unlikely to contribute significantly to the movement of DFMO across the BBB or into infiltrating tumor for the following reasons: 1) the CAT1 L-ornithine transporter is a shuttle transporter and only L-DFMO would be expected to be transported by this carrier as DFMO is a mixture of D- and L-DFMO enantiomers; 2) the previously determined capillary permeability coefficient for
DFMO was consistent with passive movement of a molecule of the size and polarity of DFMO \(^8,33\); and 3) L-ornithine transport follows Michaelis-Menten kinetics in CAT1 with half-saturation of 50-100 \(\mu\)M \(^40\) orders of magnitude lower than typical plasma levels of DFMO. These observations, in aggregate, suggest that the impact of CAT1 on BBB and rat 9L tumor passage of D/L-DFMO would be negligible compared to diffusion.

It can be hypothesized from DFMO experiments that a drug with limited brain penetrance can distribute well in IC tumor, BAT, and even distant brain if the drug has certain physical and pharmacological traits. These attributes are: 1) very high tumor cell binding specificity; 2) little in the way of non-targeted binding; 3) low plasma clearance; and 4) ability to maintain a therapeutic plasma level over days to weeks. Unfortunately, not many anticancer drugs have the requisite characteristics and toxicity profile to take advantage of this approach. Theoretically, and under appropriate condition, large molecule prodrugs might also achieve adequate distribution within an infiltrating CNS tumor without being brain penetrant. As counterintuitive as the concept might be, antibody drug conjugates (ADC) might achieve sufficient drug dosing to the leading edge of an infiltrating glioma. Like the DFMO example, select attributes listed earlier along with little non-targeted protein (albumin or cells) binding and a drug conjugate that does not leave the ADC until it is within tumor cells would allow penetration of drug into infiltrating tumor and its leading edge. The ability of the ADC to deposit a cytotoxic drug preferentially in tumor cells would further enhance specificity over mere cell surface target binding. To expand this consideration, it is instructive to consider \(^{111}\)In-ABT-806 and its clinical ADC, ABT-414, which is in clinical trials for glioblastoma.
Studies with $^{111}$In-ABT-806, a chimeric monoclonal antibody to EGFR epitopes found in amplified EGFR, successfully penetrated intracerebral U87 rodent tumors and $^{111}$In-ch806 was observed to penetrate a human anaplastic astrocytoma tumor with an apparent increase in lesion size from day 3 to day 7 after IV dosing. The same group did PK studies and found mean $t_{1/2\alpha} = 10$ h, $t_{1/2\beta} = 5.9$ days, $V_1$, mL, of 3400 mL, and $CL = 30$ mL/hr, for $^{111}$In-ch806. In other human PK studies, ABT414 had terminal plasma $t_1/2$ of approximately 9 days. Furthermore, ABT-414 was found to have 7-fold higher affinity binding to amplified EGFR epitopes C271A and C283A (0.067 nmol/L) and EGFRvIII (0.059 nmol/L) compared to wild-type EGFR (0.461 nmol/L). Thus, ABT-414 with low clearance, high binding to unique tumor EGFR epitopes, sustained plasma levels for days, and a stable cytotoxic conjugate might also be an example of a drug able to achieve effective levels in infiltrative CNS tumors yet lacking brain penetrant features of small molecules. Further study, using radiolabeled drug and quantitative imaging, will be needed to validate this ADC as a valid exception to the brain penetrant imperative for drugs to treat infiltrative CNS tumors.

Earlier drug modeling in brain and experimental IC tumors provides additional insight into the impact of variation in tumor permeability, allowing the steady-state exposure integral for drugs of varying permeability. Figure 4 recapitulates prior models comparing hypothetical drug exposure integral ($AUC_P$) in IC tumors to four different $P$ differing by a factor of 10. It is generally accepted that $P$ in the $10^{-7}$ cm/sec range reflects a high restriction to brain entry and $P$ in the $10^{-6}$ range, moderate restriction, whereas $P$ of $10^{-5}$ and $10^{-4}$ reflect unrestricted brain penetrance. In Figure 4A, if we use an average IC tumor blood flow of 0.3 mL/g/min, cell/ECF ($f$ ratio) at 1, and set the ECF drug $t_1/2$ at 15 or 180 minutes we see that with a $t_1/2$ of 15 minutes and
\( P = 3 \times 10^{-7} \text{ cm/sec (} K_{\text{trans}} = 0.002 \text{ min}^{-1} \) that AUC\(_D\) = 0.07, but that AUC\(_D\) increases dramatically to 0.43, 0.82, and 0.86 when \( P \) increases to \( 3 \times 10^{-6}, 3 \times 10^{-5}, \) and \( 3 \times 10^{-4} \text{ cm/sec, respectively. If } \frac{t_{1/2}}{t} = 180 \text{ minutes, then the relationship still holds with AUC\(_D\) at 0.09 when } P \text{ is } 3 \times 10^{-7} \text{ and increasing to 0.50 when } P \text{ is } 3 \times 10^{-6} \text{ and 0.85 when } P \text{ increases to } 3 \times 10^{-5} \text{ cm/sec. The effect of ECF } t_{1/2} \text{ increasing 12-fold to 180 minutes has a negligible effect on AUC\(_D\), which only increases from 0.82 to 0.85.}

Figure 4B and Table 2 show the effect of increased drug partitioning (cell/ECF), \( f \), by holding drug ECF \( t_{1/2} \) constant at 180 minutes and varying \( f \) from 0.5 to 4.0. Here, AUC\(_D\) varies insignificantly starting at low value of 0.09-0.10 at \( P = 3 \times 10^{-7} \text{ escalating to 0.50-0.48 at } P = 3 \times 10^{-6} \) and increasing further at \( 3 \times 10^{-5} \) (0.85 to 0.84). This change dramatically shows the impact of \( P \) and the modest effect of an 8-fold increase in \( f \). As in the prior example, shown in Figure 4A, there is a marked increase (72%) between AUC\(_D\) at \( 3 \times 10^{-6} \text{ and } 3 \times 10^{-5} \text{ and, thus, an even greater change compared } P = 3 \times 10^{-7} \text{ cm/sec.}

From these analyses, it is expected that cumulative anticancer drug penetration (AUC\(_D\)) even for a low-grade glioma with a BBB restricted drug, would be about 5-fold higher than expected based on the analyses of \( P \) for normal brain. For example, if we use blood flow of 0.5 \text{ mL/g/min} we see that AUC\(_D\) increases with increasing \( P \) of \( 3 \times 10^{-7} \text{ cm/sec from a low AUC\(_D\) of 0.15 to 0.62 at } 3 \times 10^{-6} \text{ and to a high of about 0.91 at } 3 \times 10^{-5}, \text{ supporting the belief that brain penetrant reversible inhibitor drugs need to be in the } P \text{ range of } 10^{-5} \text{ to } 10^{-4} \text{ cm/sec to be optimal to cross the intact BBB, although, for IC tumors, it would appear that all anticancer drugs would behave as though their effective } P \text{ would be equal to or greater than } 3 \times 10^{-6} \text{ cm/sec (} K_{\text{trans}} = 0.02 \text{ min}^{-1} \).
Conclusions. The primary conclusion that can be drawn from the observations presented here is that while the physical parameters that define brain penetrant drugs are generally applicable for infiltrative primary CNS cancers, there is at least one setting in which drugs of limited brain permeation might find purchase as effective chemotherapies. That setting is narrowly defined by the following parameters: low plasma clearance, very low plasma protein binding, ability to sustain plasma drug levels for days to weeks with little systemic toxicity, and target binding that is irreversible. This may not be the only situation that will successfully deviate from the historic brain penetrance mantra as others utilizing carriers, endocytosis mechanisms, and novel nanotechnologies may also succeed.

Lastly, one penetrance topic has not been addressed: Drug penetration from the ECF into its target at the tumor cell membrane, cytosol, and/or nucleus. Typically, permeability increases at both the capillary level and the tumor cell membrane with increasing malignancy so one presumes that most drugs will be able to diffuse across tumor cell membranes into the cytoplasm and eventually across the nuclear plasmalemmal as well. These studies are usually not easily conducted, but from those that have been done in the past, we know that there is a great deal of heterogeneity in drug binding to cellular targets and target effects.

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Table 1. Collation of Gd-contrast transfer constant, $K_{\text{trans}}$, and tumor extracellular space, $V_e$, for different grades of glioma.

*Study was limited to oligodendroglioma tumors.

Table 2. Values from Figure 4B for total drug exposure (AUC$_D$) are listed below for blood flow, $F$, 0.3 and 0.5 ml/g/min, ECF $t_{1/2} = 180$ min, and for $f$ from 0.5 to 4.

References


**Figure 1.** This plot of capillary transfer constant, $K_i$, in rat brain and intracerebral 9L tumor is for 16 radiolabeled and purified compounds studied between 1975 and 1981 \(^6,8,20\) and originally published in *Fundamental of Cancer Chemotherapy* in 1987 \(^19\). The dashed line has a slope of unity and is not a fit for the data. The radiolabeled compounds on the graph are: 1, HOH; 2, NaCl; 3, urea; 4, glycerol; 5, creatinine; 6, 5-fluorouracil; 7, dianhydrogalactitol; 8, galactitol; 9, misonidazole; 10, procarbazine; 11, DFMO (eflornithine); 12, dibromodulcitol; 13, sucrose; 14, epipodophyllotoxin; 15, bleomycin; and 16, inulin. The outside of blue box defines the $K_{\text{trans}}$ ($\sim K_i$) for gadolinium contrast in brain \(^26\).

**Figure 2.** MRI of a high-grade glioma after a rapid injection of Gd-contrast showing acquired $K_{\text{trans}}$ values obtained in sequential voxels in the enhancing tumor and then shows a decrease in $K_{\text{trans}}$ values as the Gd-contrast permeates and/or diffuses into the adjacent “normal” white matter. A) Post-contrast T1-weighted image. B) Quantitative map of $K_{\text{trans}}$. C-D) Line plots illustrating linear and log10 measurements of $K_{\text{trans}}$ as a function of distance through an area of solid contrast enhancing tumor into adjacent “normal” white matter (pink line in “A”). E-F) Additional line plot (green line in “A”) illustrating linear and log10 measures of $K_{\text{trans}}$ as a function of distance including regions of central (macroscopic) necrosis, solid enhancing tumor, and adjacent “normal” white matter.

**Figure 3.** \(^{14}\)C-DFMO tissue/plasma levels from intracerebral 9L rat tumor to brain adjacent to tumor to normal brain at intervals of 0.75 mm. Intravenous infusion of \(^{14}\)C-DFMO and label-free
DFMO maintained a near constant blood level over 1, 2, 3, and 4 days prior to euthanizing rats and measuring tissue/plasma levels\textsuperscript{33}.

**Figure 4.** This graph shows, for a well-mixed model, the total exposure dose as a function of tumor blood flow, capillary permeability coefficient ($P$), intracellular/extracellular drug ($f$ ratio), and extracellular drug half-life (ECF $t_{1/2}$). The values of extracellular fluid, ECF, diffusion coefficient, $D_e = 3 \times 10^{-6}$ cm$^2$/sec; extracellular fluid volume, $V_e = 0.27$; capillary surface/blood flow, $SF = 750$ min/cm; and average capillary radius, $r = 9.5 \times 10^{-4}$ cm, are typical values for a variety of brain tumor models\textsuperscript{9}. In 4A we set $f = 1$, $P = 3 \times 10^{-7}$, $3 \times 10^{-6}$, $3 \times 10^{-5}$, and $3 \times 10^{-4}$ cm/sec, and intracellular drug $t_{1/2} = 5$ min, and ECF drug $t_{1/2} = 15$ min (solid lines) or 180 min (dashed lines). Average brain blood flow, $F$, is 0.5 mL/gm/min and IC tumor $F$ about 0.3 mL/g/min\textsuperscript{9}. In 4B we set $f = 0.5$ (dotted lines), 1 (solid lines), and 4 (dashed lines) and ECF drug $t_{1/2} = 180$ min.
Table 1. Collation of Gd-contrast transfer constant, $K^{\text{trans}}$, and tumor extracellular space, $V_e$, for different grades of glioma.

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*Study was limited to oligodendroglioma tumors.
Table 2. Values from Figure 4B for total drug exposure (AUC$_D$) are listed below for blood flow, $F$, 0.3 and 0.5 ml/g/min, ECF $t_{1/2}$ = 180 min, and for $f$ from 0.5 to 4.

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